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Theme: Obesity

Articles

Made in Belgium

Paediatric Cochrane Corner

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Société Belge de Pédiatrie

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Editorial

Dear colleagues,

2020 has been a very special year and we hope that 2021 will bring us to better horizons.

In our editorial of September, we announced that Prof. Samy Cadranel had decided to retire from his role as editor-in-chief of the *Belgian Journal of Paediatrics*. Together with the entire editorial board we paid tribute to his creativity, his intelligence, his diplomacy and his joviality.

On October 8th 2020, before the September edition arrived in your mailboxes, we learned that Professor Cadranel passed away. In addition to an outstanding editor-in-chief, we lose a passionate paediatrician and a friend. Thank you Samy for everything you gave to the journal and to our group. One more time, we express our deep sorrow to Mrs Cadranel and Samy's family. In this issue we publish an In Memoriam on behalf of the board of the BVK/SBP and an Obituary on behalf of the ESPGHAN family.

The corona-virus vaccine is knocking on our door. Paediatricians have always been major players in vaccination. Although children have less risk of severe COVID-19 forms and will probably be included later in the vaccination program, we are convinced that pediatricians will play an important role in reassuring and informing parents and families. We hope that the progressive campaign in Belgium and all around the world will help us to return to normal life and to reexperience the joy of being together, with family, friends and colleagues. In this Holiday Season and before a new (we hope, an ultimate) effort, this is our wish for all of us.

The core content of the BJP issue is devoted to the theme " Obesity in childhood". It was coordinated by Joseph Vinckx (KULeuven) and Marie-Christine Lebrethon (ULg). We thank our guest editors for their very dedicated commitment and all the authors for their remarkable contributions. The causes and consequences of this pathology are reviewed with a particular focus on genetic forms, exposure to bisphenol A and pre and postnatal determinants. The therapeutic approaches of obesity are also discussed. The specificities of inpatient, outpatient as well as bariatric surgery in children are detailed by our Belgian experts . As suggested on our cover designated exclusively by Serge Ernst for the journal, we are sure you will enjoy it !

In addition to these theme articles, we are also pleased to publish clinical cases that were reported by young colleagues in training: recurrent acute event in an infant, hypopharyngeal perforation presenting as progressive pneumonia and pneumomediastinum and rare presentation of congenital spinal dermal sinus.

Larger series or studies are also published in this issue. A survey analyses the alcohol consumption by minors in Flemish youth movement. Two cases of arteriovenous malformations illustrate the management of these pathologies in the paediatric population. A retrospective study focuses on the complications of umbilical venous catheter. Finally, the paediatric residency payment gap is illustrated by a cross-sectional study in Flanders.

Our *"Made in Belgium"* section summarizes the PhD thesis of Giorgia Bucciol from UZLeuven. She unravels the genetic cause of life-treatening infections in children.

At a time when a same virus causes slight fever in some but acute respiratory distress in others, we hope you will appreciate the importance of her work.

The *"Paediatric Cochrane Corner"* comments on the systemic treatments for eczema.

Every cloud has a silver lining… this year gave us the opportunity to modernize and to improve the journal. The editorial board has grown with several dynamic and enthusiastic members from the different Belgian Universities. Many of you submitted interesting papers that enhanced the scientific quality of BJP. A new website dedicated to the journal will be online soon. As a novelty, we offer the possibility to submit audioslides as a digital enhancement to a manuscript (e.g. Raes M et al, BJP 2020; 22(3): 138-144) In March 2021, a new electronic management system will be proposed to facilitate the submission and peer-review. We will keep you informed !

On behalf of the entire editorial board, we wish you much reading pleasure and happy New Year 2021 !

Christophe Chantrain and Marc Raes, editors-in-chief

Erratum

Article: *Raes M et al. Epidemiology of invasive meningococcal disease in Belgium and implications for use of meningococcal vaccines in children and adolescents. BJP 2020; 22(3): 138 - 144*

Correction on page 141 :
"MenACWY vaccination is recommended by the Superior Health Council in children aged 15 months instead of 13-15 months".

Uw vragen of commentaar
Vos questions ou commentaires

BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE
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Obituary for Samy Cadranel

Samy, a great friend to many of us, left us on October 8th, 2020. Unfortunately, he had to accept one thing he had never accepted before: to lose a battle. Some of his favorite citations, "Quousque tandem?" and "courage, lets' go for it", perfectly illustrate his enormous willingness to bring everything to a good end. All but one. The crab inside him, as he called it, did win the struggle. In December last year, Samy reached the age of 80. Many will remember him still being very active and in good shape at the event organized for the celebration of his last birthday. In the name of ESPGHAN, we send his family our most sincere condolences.

We know Samy in ESPGHAN as the best diplomatic person, the bridge builder. Born in Tanger (Morocco), high school in Congo, university in Brussels: a citizen of the world. Sometimes we wondered which language he did not speak. His Facebook page mentions English, French, Italian, Spanish, Portuguese, Dutch, Tshiluba. He had such an incredibly creative mind. The 112 papers listed in Pubmed do not even begin to fairly summarize his contribution to science. He participated in the discovery of Campylobacyter jejuni. His unit was involved in many trials on hepatitis and ROTA vaccines. He was also involved in discovering novel culture methods of Giardia lamblia, and last but not least he was from the very beginning heavily involved in the Helicobacter pylori story. He was the first to describe nodular gastritis in children in 1979. He also developed protocols on caustic ingestions which are now used worldwide. He was a founding member of the European helicobacter Study Group and received the European Helicobacter study group Marshall and Warren award for achievements in gastroenterology and microbiology in Dublin 2011. He was also active in many other scientific societies. He loved to chat and to teach and was always happy to share his global encyclopedic knowledge.

Samy trained many of us as well as pediatricians from Belgium and abroad. He was capable of maintaining close personal friendships with all his former fellows, a manifestation of a mutual longstanding esteem. Once you met Samy, you were his friend for life. He could talk with you with similar expertise about politics, economy, religion, history or cuisine. He invited you to voice your opinion while he shared his. He was one of these are true free thinking people, with similar weight for "free" and "thinking".

He was the first paediatric gastroenterologist in Belgium, a pioneer in endoscopy, and created the Belgian Paediatric Gastro group in 1982. Samy remained active at all levels. The last 10 years, he invested a lot of energy in the Belgian Society of Paediatrics and especially the development of the Belgian Journal of Paediatrics.

ESPGHAN had a special place in his heart. He co-organized the 7th Annual Meeting in 1975, and organized, in collaboration with the Belgium Gastro Group, the 25th Annual Meeting. He was among the visionary leaders that first thought of the World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. He has also always been very active in all endoscopy activities. He participated in many Summer Schools. During his ESPGHAN Presidency, the society was opened to young members and the JPGN contracts with the publisher were finalized. As said before, collaboration was his number one priority: as a consequence, he was involved behind the scenes in the organization of the First World Congress in 2000. He remained very active in ESPGHAN and was still a member of the Ethics Committee.

We and the entire ESPGHAN family will miss Samy and his ever positive stimulating creative spirit. But the ESPGHAN logo, his creation, will forever remind us of him.

Patrick Bontems, Carlo Di Lorenzo, Michelle Scaillon, Stephanie Van Biervliet, Yvan Vandenplas

Save The Date

RBC disorder day 25/02/2021 Virtual

9h-9.10h	welcome	A.Vanderfaeillie, V. Labarque
9.10-9.20h	Introduction (Eurobloodnet)	B. Gulbis
Morning session 1: Research in sickle cell disease physiopathology		
9.20-9.40h	Update of the Belgian sickle cell registry	Sarah Wambacq, HUDERF
9.40-10h	Ophthalmologic problems in sickle cell	Arianda Begu, St Pierre/HUDERF
10-10.30h	Hepatic problems in sickle cell	Sliman Allali, Hopital Necker, Paris, France
10.30-11h	Nephrotic problems in sickle cell	Christiana Adebayo, KUL
11h-11.15h:	Coffee break	
Morning session 2: red blood cell disorders (other than sickle cell)		
11.15-11.45h	Phenotypic and genotypic spectra off BLackfan-Diamond	Pierre-Emmanuel Gleizes, European DBA consortium
11.45-12.15	Hemolytic anemia due to Pyruvate kinase deficiency	Anne.Lambiliotte, Lille, France
12.15-12.35h	Anemies hémolytiques	Ann sophie Adam, L-hub, St Plerre
12.35-14h:	Lunch break	
Afternoon session 1: treatment in sickle cell disease		
14-14.30h	DREP-Haplo protocol	Nathalie Dhedin, France
14.30-14.50h	Problems during surgery	Adèle Therer, Huderf
14.50-15.10h	Management of priapisme	Thierry Roumeguere, Erasme
15.10-15.30h :	coffee break	
Afternoon session 2: patient oriented talks		
15.30-15.50h	Covid 19 in hematologic patients	MA Azerad, Liège
15.50-16.10	Neonatal sickle cell screening in BXL and Liège	B. Gulbis, O. Ketelsleghers, Liège
16.10-17h	Discussion general	MA Azerad, A; Vanderfaeillie

In Memoriam

SAMY CADRANEL

On October 8th, 2020, Prof Dr Samy Cadranel left our world.

Scientists, colleagues, students, parents, children, but especially friends and his close family were overwhelmed with sadness. They looked back with gratitude, appreciation and respect on a man with multiple lives, a healer, a professor, a friend, a (grand) father, a husband, full of attention, inspiration and love for many of them.

His spontaneity, his diplomacy, his creativity, his dynamism, his sense of humor, his warm conviviality, his inexhaustible anecdotes will always remain with us.

For several decades he was one of the architects of Paediatrics in Belgium not only through his scientific work, his clinical activities, his countless discourses, but also as a stimulating, ever enthusiastic and tireless board member within the BVK / SBP and as editor-in-chief of the BJP. His constructive attitude and innovative ideas have supported and influenced many, not least the youngsters, in the development of their career and the pursuit of their profession.

Samy also played an essential role in the 70-80ies in the field of research in paediatric infectious diseases; he participated actively with the team of Prof JP Butzler (VUB) to the discovery of major ubiquitous infective agents of the gastrointestinal tract such as C Jejuni and Helicobacter.

In addition, Samy had a skill hidden to many of his colleagues: during many years he negociated with the big pharmas and the food industry in the name of the BSP allowing our society to obtain fundings for research and for the organization of the BSP annual congress. Thanks to Samy, research grants have been regularly distributed to Paediatricians and trainees in Paediatrics.

All he undertook was characterized with efficacy, creativity, generosity and panache.

It was an honor and privilege for many of us to have known and worked with him.

We have lost not only a brilliant master of Paediatrics, but also a master of life wisdom.

We will fill the void in our hearts with memories of a warm-hearted, passionate and highly erudite personality.

We share the grief of the family and convey our feelings of sincere and deep compassion especially to Mrs. Cadranel, the children and the grandchildren

Thanks, Samy!

on behalf of the board of the BVK / SBP and all Belgian paediatricians and trainees in pediatrics

Marc Raes
President BVK/SBP

Philippe Lepage
Past-president BVK/SBP

Ben je kind, jongere, ouder of werk je met kinderen en jongeren

&

tijdens Covid-19 op zoek naar een balans tussen ...

informatie voor kinderen en jongeren over Covid-19

...

je veilig en goed in je vel voelen

een bundeling van organisaties die je ondersteunen tijdens Covid-19

...

...

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...

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Theme

Obesity

Editorial

Dear colleagues,

My co-editor, myself and all the participants of this issue on childhood obesity hope that you and your family are in good health and that the workload is doable.

The last months I thought a lot about the motto of the biennale in Venice in 2019, which is also a Chinese (sic) proverb: "may you live in interesting times", where interesting stands for fascinating, but also difficult, challenging!

Why in these "interesting times" of Covid 19 pandemic make an issue on childhood obesity?

First of all, there is a simple reason: that decision was made before the pandemic spread around the world.

But there is another reason: among medical staff there is a great concern about the collateral damage of Covid 19, meaning that whole groups of patients, amongst also patients with obesity, do not get the attention that they need. Long before this pandemic, obesity was already a pandemic and one of the most lifethreatening according to the WHO. The difference with other pandemics is in its multiplicity and chronicity. Besides that, the lockdown itself has its influence on our lifestyle. For a lot of people, especially children, it seems like prolonged holidays en we know that gaining weight occurs more during holidays than during schooltime. There is also more home cooking, but is this always healthier than outdoor eating (in lower income families with the possibility of even lesser income or loosing jobs)? And what about stress and anxiety which often leads to sweet and fatty snacks or comfort food. Finally, the stay-at-home orders limit physical activity.

Yet there is still an other reason, one that is not so obvious and maybe of less importance for children, but still. Patients with obesity are at the highest risk, when they get infected with Coronavirus. There are three explanations for this. First of all, they suffer from a lot of complications like diabetes, hypertension and cardiovascular disease, but there is also often a mechanical problem with insufficient ventilation and difficulties in artificial ventilation and other procedures. Finally, obesity is a chronic inflammation with an impact on acute inflammation, meaning: patients with obesity are susceptible for infections, more complications, slower healing and lesser response to treatment.

That brings us to the next and capital question: why an issue on obesity, regardless of the Covid 19 pandemic?

Well in my experience there are still a lot of colleagues who seem to have a problem or let us say might feel uncomfortable with obesity: is this a real disease (and therefore do we have to threat it, at what age do we start and how), the approach is frustrating (you have low results), what are the complications (a lot more than you might think and influencing a lot of other diseases) and so one.

These preoccupations often lead to another problem, in particular that of stigmatization with a loss of "person first language", even in medical professions. Therefore I would make a plea here that from now one we only talk about "children with obesity" and no longer about obese or even worse" fat children".

Just like for Covid19, insight in a disease - and obesity is a real disease - is important to get motivated to deal with it in a good way. "When you don't understand the rules, you cannot play the game".

And that it is important to do something about it shows the prevalence of obesity worldwide and also in Belgium. Like I mentioned before: obesity is also a worldwide pandemic. Almost one third of the world population or more than 2 billion persons have to deal with overweight or obesity. In Belgium, according to the 2018 rapport of Sciensano, 19% of the 2-18 years old has a weight above the normal range for age and gender and almost 6% of them suffers from obesity. Although these numbers seem to stabilize over the last two decades, the prevalence in the early childhood group (2-4 years) is still increasing and amounts now almost to 12% obesity!

These numbers emphasize the need of early prevention: that means not only from chilhood on, but even earlier (the first 1000 days: pregnancy until the age of two) and even of more importance: pregestational prevention. Otherwise we are creating an offspring, that is not only burdend by parental lifestyle and genetics, but also epigenetics. At this moment, the life expectancy in the USA is already stable or even decreasing.

So in this issue you can find everything you always wanted to know about childhood obesity - at least I hope - and a lot more.

Some of the finest Belgium specialists in obesity have contributed to this issue . The first article is about common causes and consequences of obesity, followed by an article about genetics and one about a specific endocrine disruptor. The relationship between sleep and obesity is highlighted in the next article. Then we have one on broad, social prevention, one on early prevention and one on secondary prevention, while avoiding stigmatization . Outpatient and inpatient treatment are discussed in three articles and finally there is an opinion about bariatric surgery.

My colleague, doctor Lebrethon, and I hope you can appreciate their work and wish you a nice reading.

Joseph Vinckx, also on behalf of Marie-Christine Lebrethon

Guest editors

Causes and consequences of childhood obesity

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Keywords

obesity, childhood, aetiology, comorbidity

Abstract

Obesity is a dynamic disease of complex aetiology and multifactorial character. The interaction of genetic factors of each individual and its association with perinatal, environmental, dietary, and psychosocial factors constitute a common pathway for the development of childhood obesity. Obesity in childhood is known to track strongly into adulthood, especially in those children with a severe form of obesity and/or a clear family history. The two most important modifiable risk factors for childhood obesity are dietary factors and low physical activity. Others are sleep deprivation, early adiposity rebound, drugs, socio-economic status, and in rare cases endocrine- and hypothalamic disorders. Early diagnosis and appropriate management and/or treatment are key words. As in adults, paediatric overweight and obesity are linked to a higher risk of co-morbidities. These comorbidities affect almost every organ system. However, in children these obesity-related co-morbidities will significantly impact (mental)health in their future lives. Hormonal and cardiovascular alterations include insulin resistance, high levels of low-density lipoprotein cholesterol, hypertension, non-alcoholic fatty liver disease, metabolic syndrome, alterations of the microbiome, cancer and alterations of the reproductive system. Structural problems include obstructive sleep apnoea syndrome, enuresis nocturna, musculoskeletal and orthopedic complications. Finally, children with obesity experience a lower health-related quality of life compared to children with normal weight.

Introduction

Obesity is a dynamic disease of complex aetiology and multifactorial character. The interaction of genetic factors of each individual and its association with perinatal, environmental, dietary, and psycho-social factors constitute a common pathway for the development of childhood obesity (1). The positive energy balance resulting from high caloric intake and low energy expenditure constitutes one of the main primary causes of obesity. Genetical predisposition makes individuals more susceptible for this energy imbalance. Obesity in childhood is known to track strongly into adulthood, especially in those children with a severe form of obesity and/or a clear family history (2). As in adults, paediatric overweight and obesity are linked to a higher risk of co-morbidities. However, in children these obesity-related co-morbidities will significantly impact (mental)health in their future lives (3).

Risk factors and aetiology

The etiological factors for childhood obesity are extremely complex. We begin to understand that countless genetical and environmental factors interact with one of the multiple aspects of a child's metabolism. Early childhood examples are: intra-uterine programming, birth size, breast-feeding status, and catch-up growth, but many other risk factors and etiologies have only been recently discovered (4). Mothers with present obesity before conception have increased odds of 264% of having overweight children (5). Another example are children with an 'early adiposity rebound', they are at higher risk of developing obesity later in life (6). Increasing evidence suggests that numerous neuroendocrine peptides and cytokines, which are secreted mostly from adipose tissue, play a role in both short and long term energy balance, metabolism and inflammatory response in humans (7). Different models estimate that environmental factors have an impact of 20 up to 50% on a child's bodyweight. Certain factors are modifiable, others are important not to miss. In the next part, a summary of the most important factors is listed (8).

The two most important and well-known risk factors for childhood obesity are dietary factors and low physical activity (9). Dietary factors not only include increased use of sugar-sweetened beverages, unhealthy snacks and inadequate consumption of fruits and vegetables, but also irregular eating patterns (e.g. skipping breakfast), large portions and foods with a high glycaemic index have an influence. Dietary behaviour strongly correlates with parents' eating habits and nutritional knowledge (10). The same linearity can be seen in low physical activity of parents and their children. Not only a sedentary lifestyle is an obesity risk factor, also the fairly new phenomenon of 'screen time' shows of his influence. Nowadays there is more than only the evening television time, smartphones with social media and countless video channels, tablets, PlayStation and many other electronics ask our (sedentary) attention. Furthermore, the presence of a television in a child's bedroom has been shown to be directly related to childhood obesity (11). In Belgium, more than half of the adolescents between 10 and 17 years old spent too much time in front of screens (12). There are no uniform guidelines about how much time a child could spent in front of a screen. In general, younger children should spent less time in front of screen than adolescents. Toddlers should spent a maximum of half an hour a day on electronic devices, adolescents a maximum of three hours (12)). Another risk factor that is frequently overlooked is sleep deprivation (13). Alterations in ghrelin and leptin concentrations are believed to be the leading mechanism. However, sleep deprivation also plays a role in increased insulin resistance. Next to these pathophysiological pathways, sleep deprivation stimulates unhealthy eating patterns and lowers levels of physical activity. As mentioned above, an 'early adiposity rebound' significantly increases the risk of developing obesity in later life (14). Children reach their lowest BMI (Body Mass Index) at the age of 6. After that point they experience a steady BMI increase, known as adiposity rebound. However, children who experience the adiposity rebound at younger ages (i.e., an '*early adiposity rebound*') are at higher risk of developing obesity. Furthermore it's important to remember that certain medical drugs can be associated with weight gain and obesity (15). In children, the most frequently prescribed pharmacological agents related to weight gain are antipsychotics (e.g. aripiprazole or risperidone), antiepileptic drugs (e.g. valproic acid), antidepressants, corticoids and insulin.

Paediatric obesity may, in a minority of the cases, be the result of certain *endocrine disorders.* Examples are hypothyroidism, Cushing disease, growth hormone deficiency and pseudohypoparathyroidism type 1a. These conditions are rare and account for less than 1% of children and adolescents with obesity (9). Compared to common causes of obesity, these conditions are usually associated with a delay in length growth, hypogonadism and/or other atypical clinical features. Another rare entity in obesity are acquired *hypothalamic disorders* (16). These can be present secondary to tumours (particularly after treatment of craniopharyngioma, or in the presence of a diencephalic tumour), brain irradiation, cranial trauma or inflammatory diseases affecting the hypothalamus and may lead to obesity in affected children. Additionally, some monogenetic disorders are also associated with pronounced childhood obesity (e.g. Prader-Willi syndrome, *MC4R* gene mutation, Bardet Biedl syndrome…) (9). Although these endocrine, hypothalamic and monogenetic disorders are rare, they have to be kept in mind as a possible cause of obesity.

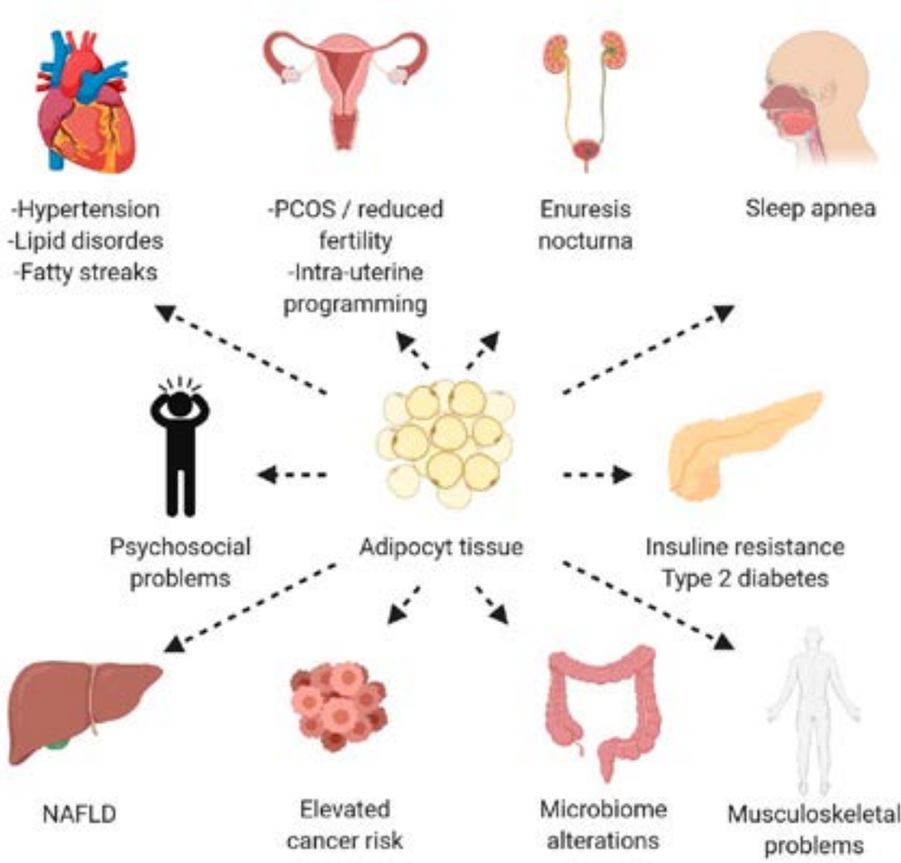
Co-morbidities and consequences of obesity in children

Population studies show that if a child has obesity before puberty, he or she will have up to 70% chance of being obese in their adult life. The higher the body mass index as a child, the higher the risk of obesity in adulthood (17). Importantly, about one quarter of children and adolescents with obesity may already present with one or more comorbidities. These comorbidities affect almost every organ system (Fig 1). Clinicians should carefully examine medical- and family histories and laboratory assessments of overweight children to identify existing risk factors and comorbidities. Early diagnosis and appropriate management and/or treatment are key words (3). In the next paragraphs, an overview of the most important comorbidities is listed.

Hormonal and cardiovascular alterations include insulin resistance, changed lipid levels, non-alcoholic fatty liver disease (NAFLD), hypertension and reproductive alterations. Visceral and intramyocellular lipid accumulation, as seen in obesity, contributes to a pro-inflammatory state and leads to insulin resistance. Later in life, this insulin resistance can eventually lead to pre-diabetes and, ultimately, type 2 diabetes. In addition, blood levels of lipids are altered in children with obesity. Almost 1 out of 3 children with obesity are presenting with borderline-high or high levels of low-density lipoprotein (LDL) cholesterol (18). Levels of high-density lipoprotein cholesterol or HDL cholesterol are lowered in 1 out of 6 children with obesity. Moreover, 50% of children with obesity <10 years old present fatty streaks, the first stage of atherosclerosis (19). This percentage rises up to 70% in adolescents with obesity. Hypertension affects up to 1 in every 4 children with obesity (20). Non-alcoholic fatty liver disease (NAFLD) occurs in 0.7% to 38% of children with obesity (range depending on diagnostic methods, age, sex and ethnicity), with higher prevalence in older children (21,22). NAFLD is usually asymptomatic and may be accidentally found by liver ultrasound or upon abnormal transaminase levels in blood. NAFLD is nowadays the most common cause of liver disease in children.

The clustering of abdominal obesity with hypertension, hyperglycemia and -triglyceridemia with decreased HDL-cholesterol is known as the metabolic syndrome (MetS). Although different definitions of the MetS in children exist, the underlying mechanism consists of insulin resistance and inflammation

Figure 1: *Influences of childhood obesity on different organ systems.*



arising from an accumulation of free fatty acids in liver, adipocytes, skeletal muscles and pancreas. Its prevalence, as defined by the International Diabetes Federation in overweight and children with obesity, ranges from 16% to 44% depending of different studies (23). The MetS is a major risk factor for cardiovascular disease and type 2 diabetes in adulthood. A special entity of hypertension is the pseudotumor cerebri. For some unclear reason, children with obesity are at higher risk of this form of idiopathic intracranial hypertension. Acanthosis nigricans, a marker of insulin resistance, is a common finding in children with obesity. Other skin abnormalities include intertrigo, striae, acnea, and hidradenitis suppurativa (3).

Hormonal alterations also influence the reproductive system. Girls with obesity may present with a precocious puberty and are also at higher risk of suffering from polycystic ovary syndrome (PCOS), which can lead to decreased fertility. In the case of boys, obesity may be associated with either a precocious or a delayed puberty onset (24).

A recently discovered entity in the obesity landscape is the influence of the microbiome on childhood obesity (9, 25). Overweight is associated with a dysbiosis in the gut's bacterial composition. Lower levels of bacterial diversity are seen in overweight adults. New insights in cancer pathophysiology show a positive correlation between overweight and cancer (26). Obesity leads to increased secretion of adipokines and proinflammatory cytokines such as interferon-γ (IFN-γ), interleukin 6 (IL-6), and tumour necrosis factor-α (TNF-α), which promotes an infiltration of inflammatory immune cells into adipose tissue. This pro-inflammatory state then promotes carcinogenesis.

Structural problems because of overweight are sleep disordered breathing with obstructive sleep apnea syndrome (OSAS), enuresis nocturna and orthopedic complications. OSAS occurs in around 41% of children with obesity and in 19% of children with overweight (27). Estimations show that every 1 kg/m^2 increase in BMI beyond the mean for age and gender leads to a 12% increase in the risk of suffering from OSAS. OSAS itself is associated with a higher cardiovascular risk profile and poor school performances. The risk of enuresis nocturna is a 6-fold higher in overweight children compared to children with a normal body weight (28). The prevalence of enuresis nocturna in children with obesity ≥6 years old is above 10% which decreases to 5% by the age of 10. Because of their overweight, children with obesity have more musculoskeletal and orthopedic complications (e.g. genu valgum, hyperlordosis, bilateral slipped capital femoral epiphysis) (9). These complications may contribute to the impaired physical and psychosocial functioning and eventually evolve to long-term or chronic conditions into adulthood. Furthermore, overweight children have a lower threshold of exercise dyspnea and, by consequence, may have negative feelings towards exercising and participating in social activities that involve physical activity.

Finally, the psychological part of obesity cannot, may not be neglected. Most children and adolescents with overweight or obesity have problems with their psychosocial functioning and experience a lower health-related quality of life compared to children with normal weight (29). Children with obesity often present with lower self-esteem, lower sense of well-being and higher rates of depression (29). They may also suffer bullying and judgmental behaviors from their environment, which further contributes to isolation, impaired social relationships and poor school performance (29).

Conclusion

The aetiology of obesity is multifactorial and complex through the interaction of genetic, perinatal, environmental, dietary, and psychosocial factors. Childhood obesity is associated with several comorbidities having a negative impact on different body systems and favour higher mortality in early adult life, mainly due to cardiovascular events.

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Genetic forms of obesity

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Keywords

paediatric, obesity, genetic

Abstract

Obesity is a complex multifactorial disease. A combination of genetic susceptibility and a permissive environment starting in utero and extending through childhood and adolescent is usually evoked as causal factors. Genetic forms of obesity are rare and have usually an early onset. They may be categorized as monogenic and as syndromic forms. In this paper, we focus on the diagnosis of the genetic causes of obesity. Firstly, we aim to provide to the clinician basic principles for the diagnosis of genetic forms of obesity to give them the opportunity to quickly identify those forms. Secondly, we present the most frequent syndromic form of obesity, the Prader-Willi syndrome, and finally, we describe the other forms of genetic obesity (monogenic and other syndromic).

Introduction

Multiple factors contribute to the development of paediatric obesity. A combination of genetic susceptibility and a permissive environment starting in utero and extending through childhood and adolescent is usually evoked as causal factors.

A polygenic predisposition to obesity where a large number of genes variants contribute in a cumulative way to body mass index (BMI) exists in almost all patients suffering from obesity, as demonstrated by twin studies and studies in adoptees (1). Heritability explains about 70-80% of the BMI variation between subjects (1). A meta-analysis of genome-wide association study of childhood body mass index has revealed many genetic loci associated with childhood BMI or adiposity (2). However, the effect of those identified single-nucleotide polymorphisms (SNPs) are small: an increase in body weight around 500 to 1000g has been reported per risk allele.

Rare chromosomal abnormalities and/or highly penetrant genetic mutations have described in approximatively 7% of patients with extreme paediatric obesity (3). Genetic forms of obesity are rare and have usually an early onset. They may be categorized as monogenic forms when only one gene is affected and obesity is the most predominant symptom of the clinical picture and as syndromic forms when several genes may be affected (4). In this case, obesity is only a part of the clinical picture and is often associated with dysmorphic features, neurodevelopmental delay or other organs dysfunction/malformations.

In this paper, we focus on the diagnosis of the genetic causes of obesity. Firstly, we aim to provide to the clinician basic principles for the diagnosis of genetic forms of obesity to give them the opportunity to quickly identify those forms. Secondly, we present the most frequent syndromic form of obesity, the Prader-Willi syndrome (PWS), and finally, we describe the other forms of genetic obesity (monogenic and other syndromic). For the management and future therapeutic possibilities of genetic forms of obesity, readers are invited to consult the BASO guidelines.

When do we need to perform a genetic analyse?

It is crucial that patients with genetic forms of obesity are properly identified and promptly referred to a specialist. A correct and early diagnosis also helps the family and caregivers in the management of their child and provides valuable information for genetic counselling.

In all cases where a genetic form of obesity is suspected, clinicians should obtain a careful family history to identify potential consanguineous relationships, a history of severe obesity or bariatric surgery in the family and the ethnic origin of the child. However, clinicians should consider *de novo* mutations if both parents/relatives are of normal weight.

Genetic testing should be performed in patients with early onset obesity (before 5 years of age) or with clinical features such as developmental delay and mental retardation, short or very tall stature, red hair, polydactyly, facial dimorphism, epilepsy, deafness, multiple hormonal insufficiencies, recurrent infections, diarrhoea or with a family history of extreme obesity (3).

We focus on a diagnostic approach that proves useful in the clinical practice: based on age of onset of obesity and on clinical features.

1. Based on age of onset

Monogenic forms of obesity are normally associated with a very early age of onset of obesity—see section "Other genetic forms of obesity" later in this paper. Consequently, the presence of morbid obesity in the first months of life (i.e. before the first 12–18 months of age) should trigger indication for a specific genetic test to detect potential deficiencies in genes responsible for monogenic forms of obesity. The typical panel of genes used in Belgium to test for monogenic forms of obesity includes *MC4R, MC3R, LEP, LEPR, PCSK1, POMC, SIM1* and *NTRK2*.

If weight gain and/or obesity start after the third year of age, together with a development of hyperphagia around the age of 5–6 years, patients should be investigated for additional signs of PWS, such as a history of hypotonia and poor suck in the neonatal and infancy periods or a delay in psychomotor development. When a suspicion of PWS exists, a specific methylation genetic test should be performed—see section "Prader-Willi syndrome (PWS)" in this paper.

2. Based on clinical features

In patients with syndromic forms of obesity, obesity is only a part of the whole clinical picture. These patients often show multiple clinical features, which should be used to diagnose these syndromic forms of obesity (see Table 3 for the most relevant clinical features).

The presence of a developmental delay is a first step to classify and identify certain syndromic forms of obesity. Besides the presence or absence of developmental delay, distinct clinical features should be used to make a differential diagnosis since they are typical in patients suffering from certain syndromes, e.g. retinal dystrophy and other visual alterations (Bardet-Biedl and Alström syndromes; tubby bipartite transcription factor (TUB) deficiency) or key skeletal defects (Albright hereditary osteodystrophy).

Extreme hyperphagia may suggest a disruption of the hypothalamic pathways involved in the regulation of energy balance. History of food-seeking behavior, searching for/stealing food, waking at night to find food, eating food others leave behind should prompt genetic investigation but neurological or psychological causes should be excluded where the history is short.

Prader-Willi syndrome:

1. Description

1.1. Prevalence and first description of the disease

PWS is a genetic disorder that affects one in every 15,000–30,000 births (5). The syndrome, which is clinically and genetically heterogeneous, was first mentioned by John Langdon Down in 1864 (6). However, it was described in detail by Andrea Prader, Heinrich Willi and Alexis Labhart in 1956, based on the clinical characteristics present in nine children examined (7). The description of signs and symptoms was expanded in the following decades, including behavioral and medical problems described in the 1970s and 80s. In 1987, a pivotal study showed that nutritional control helps extend life expectancy of PWS patients (8). Of note, PWS was the first described human disorder to be related to genomic imprinting and to be caused by uniparental disomy.

1.2. Etiology

PWS is caused by the loss of expression of paternally expressed genes from the 15q11.2-q12 region. This may result from several genetic aberrations that are normally non-inheritable: a paternal deletion of 15q11-q13, a maternal uniparental disomy of chromosome 15, an imprinting defect, or (less frequently) a translocation of the paternal chromosome 15. The minimal genetic lesion associated with severe hyperphagia and obesity in PWS contains a cluster of noncoding small nucleolar RNAs (snoRNAs): the *SNORD116* gene cluster (9, 10).

1.3. Clinical presentation

PWS affects multiple organ systems and is clinically heterogeneous, with complex signs and symptoms that evolve over life. The severe hypotonia at birth, which contributes to suckling and swallowing problems and delayed psychomotor development, partially improves with age. Many patients with PWS present characteristic facial features (narrow forehead, almond-shaped eyes, thin upper lip and down-turned mouth) and very small hands and feet. After this initial phase, more evident signs appear: hyperphagia and absence of satiety often leading to severe obesity in affected children as young as 2–3 years of age. The situation may deteriorate quickly without adequate outside controls; obesity is a major factor influencing morbidity and mortality in these patients. Other associated endocrine abnormalities contribute to the clinical picture of short stature due to a growth hormone deficiency and incomplete pubertal development. The degree of cognitive dysfunction varies widely from one child to another, and it is linked to learning disabilities and impaired speech and language development that may be aggravated further by psychological and behavioral troubles.

In the following sections, we will describe key features of PWS. Some other problems that patients with PWS face (scoliosis, thick saliva, skin picking, etc.) will not be described here.

Hypotonia, developmental delay and the natural history of obesity in PWS

PWS has been classically described as having two phases: 1) poor feeding and frequent failure to thrive and 2) onset of hyperphagia leading to obesity. Recently, this has been expanded to the characterization of four main nutritional phases (with several subphases) in PWS patients (Table 1) (11).

Table 1. Nutritional phases in patients with Prader-Willi syndrome (11).

Phase and onset age		Typical features
Phase 1		Poor feeding and frequent failure to thrive
Subphase (0–9 months)	1a	Infants are hypotonic and not obese. Hypotonia (muscle weakness) contributes to the feeding problems and to a delayed motor development
Subphase (9–25 months)	1b	There is no feeding difficulties anymore, and the child grows appropriately along the growth curve. Appetite is normal
Phase 2		Onset of hyperphagia leading to obesity
Subphase (2.1–4.5 years)	2a	Weight starts crossing the growth curve centile lines, but there is no increase in appetite. If calories are not restricted, the child will become obese
Subphase (4.5–8 years)	2b	Weight increases, together with an increased appetite and interest in food. If allowed to eat what they want, child will become obese. At this stage, however, children can still feel satiated and will stop eating voluntarily.
Phase 3 (8 years–adulthood)		Hyperphagia and altered (decreased) feeling of satiety. Constant and obsessive food-seeking behavior; patients maintain hidden food storages and negotiate with parents and other caregivers about obtaining more food. If left untreated, hyperphagia can easily develop into obesity
Phase 4 (adulthood)		Appetite can fluctuate in this phase, but there is a noticeable improvement in control of appetite compared to when patient was younger. The onset of this phase is very variable and may never happen in some (most?) patients.

Hypotonia persists through the whole life of patients with PWS and it contributes to the feeding problems typical in the first year of life (phase 1a). However, high unacylated ghrelin levels in infants with PWS also support the concept of anorexia in the early phases of the disease (12).

Hyperphagia emerges as one of the most representative features of PWS during the nutritional phases 2b and 3 (as early as ages 4.5 through adolescence and adulthood). A switch to a relative deficit of unacylated ghrelin is thought to be responsible for the development of this hyperphagia. Due to an altered feeling of satiety, patients develop an insatiable appetite that prompts them to constantly seek for food; if left untreated, this behavior can quickly develop into obesity that mostly presents as subcutaneous fat. Other factors contributing to weight gain are the lower level of physical activity that PWS patients often show (due to their hypotonia), their lower metabolic rate and their abnormally high

percentage of fat in their body composition. Consequently, dietary restriction, physical activity and behavior management are fundamental in preventing and managing obesity in PWS.

Co-morbidities typically related to overweight and obesity are certainly present in many patients with PWS, including diabetes mellitus, metabolic syndrome, obstructive sleep apnoea syndrome, respiratory insufficiency and cardiovascular diseases.

Social abilities, learning and psychiatric problems

In patients with PWS, a developmental delay is frequently observed in the motor, intellectual, language and psychosocial domains. Hypotonia is a contributing factor to the observed delayed motor development in many patients. Most patients show also learning disabilities of diverse degrees.

Children with PWS are often described as affectionate, happy and compliant. However, mood swings and behavior difficulties may appear over time. This includes temper tantrums, stubbornness, rigidity, susceptibility to frustration especially about food, argumentativeness and repetitive thoughts and behaviors. Social skills are often impaired. True psychosis occurs only in a minority of older adolescent and young adult patients, but they usually respond well to treatment. In later years, depression may result when self-image issues emerge, particularly over the conflict between the drive for independence and the need for disease management[13].

Endocrine abnormalities

Typical endocrine abnormalities seen in PWS patients include (13):

- Lower number and volume of oxytocin (OXT) neurons in the paraventricular nucleus of the hypothalamus
- Growth hormone deficiency in around 80% of the patients
- Mixed (primary and central) hypogonadism in >60% of patients (boys and girls); puberty is rarely completed although precocious breast development is often seen (makorin ring finger protein 3 [*MKRN3*], a gene of precocious puberty, is located in the PWS region)
- Premature adrenarche
- Cryptorchidism in 80%–90% of patients
- Hypothyroidism in 20%–80% of patients
- Central adrenal insufficiency in 10%–60% of patients
- Type 2 diabetes in approximately 25% of adult patients (if obese)

The dysregulation of the hypothalamic function is a key feature in PWS, and it is manifested as a range of disorders in several organ systems: insufficient growth and short stature, hypogonadism, delayed or absent puberty, problems in temperature regulation, abnormal body composition (high percentage of fat, although mostly subcutaneous), lower metabolic rate, insufficient feeling of satiety, inadequate stress/social response, and higher pain threshold.

Oxytocin is a neuropeptide that plays an important role in modulating social interactions and mother–infant bonding. Quantitative neuroanatomical studies of post-mortem human hypothalamic tissue from patients with Prader–Willi syndrome (PWS) have demonstrated a reduced number and volume of OXT neurons in the paraventricular nucleus in comparison with controls (14). Similarly, an alteration in the OXT system was described in PWS mouse models (15). Interestingly, a single OXT injection before the first 5 hours of life rescued 100% of the new-born *MAGEL2* knock-out (KO) mice from early death by restoring normal sucking activity (15). The *MAGEL2* KO mouse is now considered a mouse model for PWS and autism spectrum disorder (ASD) because truncated mutations in the *MAGEL2* gene have been reported in some patients with ASD (16). Restricted production of mature OXT despite normal prohormone production was detected specifically in the hypothalamus of the *MAGEL2* KO pups. Altogether, these data suggest that OXT is involved in the pathophysiology of PWS and ASD. A 7-day intranasal oxytocin administration in infants with Prader–Willi syndrome has been reported well tolerated and improving sucking/swallowing, social skills, and mother–infant interactions. Changes in brain connectivity of superior orbitofrontal cortex correlated with clinical improvements (17).

Higher mortality risk

Patients with PWS have an increased risk of death. On the one hand, sudden or unexplained deaths are more frequent in the population with PWS—the reason for this is debated, but respiratory causes seem to play a role in most of these deaths (13, 18). On the other hand, PWS patients may show fewer or no symptoms of disease at all, which may make some illnesses not recognizable by caregivers or by the patients themselves until very late stages. In addition, the pain threshold in PWS patients is higher than in the rest of the population, which might mask signs and symptoms of certain diseases or complications after surgical procedures.

2. Diagnosis

An early diagnosis of PWS is critical for an effective long-term management of the patient and a better quality of life of their families. If there is suspicion of PWS due to clinical features, a specific genetic test should be performed as a first-line test as soon as possible. This test, based on DNA methylation of the affected region of the chromosome 15, allows the diagnosis of 99% of the cases and serves as differential diagnosis between PWS and Angelman syndrome. A proposal of age-specific clinical criteria that should trigger recommendation for PWS genetic testing are presented in Table 2 (19, 20).

Table 2: Suggested criteria to recommend genetic testing for PWS (19).

Age (years)	Criteria to recommend Prader-Willi syndrome specific genetic testing
0–2	Unexplained hypotonia and poor suck
2–6	Hypotonia with history of poor suck and concomitant global developmental delay
6–12	Hypotonia (or history of hypotonia with poor suck), global developmental delay and excessive eating (with central obesity if uncontrolled)
13 and above	Cognitive impairment, excessive eating (with central obesity if uncontrolled), hypogonadotropic hypogonadism and/ or characteristic behavior problems (e.g. temper tantrums, compulsive-like behaviors)

PWS, Prader-Willi syndrome.

Once the diagnosis of PWS is confirmed by the DNA methylation test, it is essential to further characterize the responsible genetic mechanism in order to implement appropriate management (e.g. early management of psychiatric disorders which are more severe in case of maternal uniparental disomy) and to provide genetic counselling (21). To this end, other genetic methods are needed:

- A fluorescence in situ hybridization (FISH) analysis of a sample from the patient allows to detect deletions of the q11-q13 region of chromosome 15, but it does not recognize parental chromosomes. A positive FISH result together with a very clear clinical presentation of PWS brings sufficient confirmation of PWS diagnosis. However, a negative FISH result is not enough to discard PWS but requires further investigations to avoid a false negative. Of note, since high-resolution karyotype detects only 60% of interstitial chromosomal deletions, it is now replaced by FISH.
- In the absence of deletions detected by FISH, an analysis of DNA polymorphisms (and if needed, DNA sequence) in the patient and his/her parents will distinguish between maternal uniparental disomy and rare cases of defects in parental genomic imprint mechanisms, which lead to loss of expression of genes carried by the paternal chromosome (1% of the cases).

Families with a child with PWS can undergo prenatal screening during subsequent pregnancies. Since the genetic anomaly causing PWS is sporadic, the probability of having another affected baby is <1%.

Due to the complexity of PWS, the management of these patients requires a multidisciplinary approach. PWS is a rare disease, so it is advised to assign a paediatric endocrinologist with experience in PWS for the treatment of the affected child. Even though PWS is an incurable genetic disease, it is possible to treat its symptoms and associated disorders. The multidisciplinary care aims to reduce morbidity and to improve the quality of life of patients and their families at all ages. Beside the well-described benefit of Growth Hormone treatment in those patients, other treatments such as oxytocin and unacylated ghrelin analogue are promising (17, 22, and 23).

Other genetic forms of obesity:

Besides PWS, many other genetic forms of obesity have been described so far (either syndromic or monogenic) thanks to the development of highly precise genetic tools in the past years, which has contributed to the identification of numerous genes directly influencing obesity. Table 3 presents the most well-known genetic forms of obesity (excluding PWS, which has been exhaustively presented above) and it summarizes the genetic cause, clinical features, and age of onset and prevalence of each condition. Of note, we have classified the conditions by the presence or absence of developmental delay, which is an additional key feature used for diagnosis.

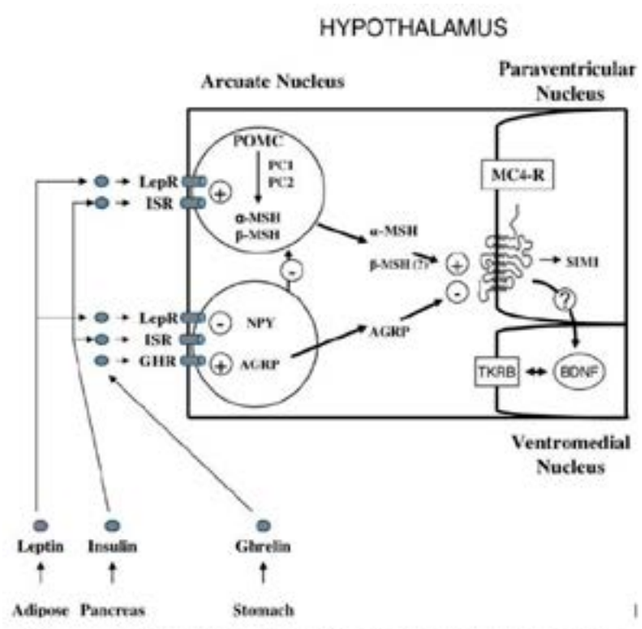
Monogenic forms of obesity are linked to single mutations of genes that are involved in appetite regulation. Food intake is regulated through the brain-gut axis, where the hypothalamic leptin-melanocortin pathway has a central role in energy balance regulation (Figure 1). As a first step in the appetite regulation process, peripheral signals related to food intake or metabolic status, such as glucose, cholecystokinin, glucagon-like peptide, insulin, ghrelin, leptin, adiponectin and cortisol are produced in several organs. These signals eventually arrive to the central nervous system and are integrated in the hypothalamus through a series of key molecules involved. Specifically, the activation of leptin, insulin and ghrelin receptors in different sets of neurons in the hypothalamus leads to the production of pro-opiomelanocortin (POMC) and agouti-related peptide (AGRP). POMC is then converted into melanocyte stimulating hormone (MSH) by the enzymes proconvertase 1 (PC1) and proconvertase 2 (PC2). Both MSH and AGRP are released and bind to the melanocortin 4 receptor (MC4R) in another region of the hypothalamus, but each molecule triggers opposite effects: while MSH reduces appetite, AGRP increases it. Other regulators of the leptin-melanocortin pathway that contribute to appetite regulation are: single-minded 1 (SIM1), brain-derived neurotropic factor (BDNF), tropomyosin-related kinase B (TrkB) and SH2B adaptor protein 1 (SH2B1).

When some of these molecules involved in appetite regulation and energy expenditure are affected in a person, the resulting dysfunction in the system may lead to hyperphagia, weight gain and obesity at a very early age (often in the first months of life), which we refer to as a "monogenic" form of obesity. Deficiencies in the following molecules (and genes) have been described as monogenic forms of obesity: leptin (LEP), leptin receptor (LEPR), POMC, MC4R, PC1, SIM1, SH2B1, BDNF, and TrkB (Table 3). Of note, some of these molecules control many other physiological processes besides appetite regulation—as a result, other metabolic and endocrine alterations can be present. As a consequence, even if very early obesity is the key diagnostic feature of these monogenic form of obesity, they may be associated with alterations in several organ systems, for example endocrine disorders, developmental delay and/or neurocognitive alterations. Examples of monogenic forms of obesity associated with developmental delay are BDNF, SIM1, TrkB and TUB deficiencies (Table 3) (4).

Besides the genes linked to the leptin-melanocortin pathway, other genes and chromosomal regions have been related to genetic forms of obesity that present a broader spectrum of clinical features involving several organs and systems (with obesity being just one of the many clinical features observed). These forms of obesity are frequently referred to as "syndromic". That is the case for Albright hereditary osteodystrophy (pseudohypoparathyroidism phenotype Ia), Bardet-Biedl syndrome, Cohen syndrome and Alström syndrome. The genetic cause, clinical features, age of onset and prevalence of these conditions are detailed in Table 3.

As presented earlier in this paper, the diagnosis of monogenic and syndromic forms of obesity is based on the age of onset, clinical presentation, familial history and specific genetic testing.

Figure 1: Diagram of the leptin-melanocortin pathway (4).



α-MSH, α-melanocyte stimulating hormone; β-MSH, β- melanocyte stimulating hormone; AGRP, agouti-related peptide; BDNF, brain-derived neurotrophic factor; GHR, ghrelin receptor; ISR, insulin receptor; LepR, leptin receptor; MC4-R, melanocortin-4 receptor; NPY, neuropeptide Y; PC1, proconvertase 1; PC2, proconvertase 2; POMC, pro-opiomelanocortin; SIM1, single-minded 1; TrkB, tropomyosin-related kinase B (BDNF receptor). (Reproduced from the BASO guidelines with permission).

Conclusion:

With the increasing access to high precision diagnostic tools for genetic investigation, numerous genes influencing the phenotype have been identified, especially in early onset severe obesity. As childhood obesity is highly prevalent in our population, it is imperative to define the place of genetic analysis in the management of childhood obesity. Early onset severe obesity or specific clinical features are the key clues that indicate a genetic testing. The diagnosis of a genetic form of obesity can help children and their families to whom genetic counselling can be provided and can inform management and specific pharmacological treatment (e.g. leptin and setmelanotide, a MC4R agonist) which are available for some genetic disorders.

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Table 3: Genetic forms of obesity.

Condition	Gene(s) involved	Clinical features	Age of onset	Prevalence in general population
With developmental delay[1]				
Albright hereditary osteodystrophy (phenotype PHPIa)	*GNAS* (chromosomal region 20q13.32)	Obesity, short stature, skeletal defects (brachydactyly type E, subcutaneous ossifications), resistance to several hormones	Variable; weight gain begins in infancy	1–8/1,000,000
Bardet-Biedl syndrome	19 genes: *BBS1* to *BBS19* (located in different chromosomes)	Obesity, pigmentary retinopathy, postaxial polydactyly and hypogonadism; often accompanied by renal impairment, cardiac anomalies and intellectual disability	Variable; weight gain from first year of life	1–9/1,000,000
Cohen syndrome	*COH1* (*VPS13*B; chromosomal region 8q22)	Abdominal obesity (arms and legs are thin), intellectual disability, progressive retinopathy, cyclic neutropenia, head/face defects (small jaw, high raised palate, buck teeth), sometimes seizures and deafness	Neonatal or during infancy	Unknown; <1,000 patients identified worldwide
SIM1 deficiency	*SIM1* (chromosomal region 6q16.3)	Severe early-onset obesity, hyperphagia, autonomic dysfunction (e.g. low blood pressure), variable presence of cognitive and behavioral impairments such as autistic spectrum behavior and memory deficits; some patients present with Prader-Willi-like features such as anxiety	Neonatal or during infancy	Unknown; <50 patients identified worldwide
BDNF deficiency (sub-phenotype of WAGR syndrome)	*BDNF* (chromosomal region 11p14.1)	Hyperphagia and obesity, together with other features of WAGR syndrome[2] such as higher risk of Wilms' tumor, aniridia, genitourinary anomalies and intellectual disability	Childhood	Unknown (but WAGR syndrome affects 1–2/1,000,000)
TrkB deficiency	*NTRK2* (chromosomal region 9q21)	Hyperphagia, obesity, developmental delay, hyperactivity, impaired concentration and short-term memory, altered pain sensation	Variable; weight gain from infancy or childhood	Unknown; <10 patients identified worldwide
TUB deficiency	*TUB* (chromosomal region 11p15.4)	Obesity, night blindness, decreased visual acuity, electrophysiological features of a rod-cone dystrophy (from the description of 1 case)	Variable; may start during childhood or adolescence	Unknown; 3 patients identified worldwide
16p11.2 deletion syndrome (SH2B1 deficiency)	Deletion of chromosomal region 16p11.2 containing *SH2B1* and 8 other genes	Obesity, hyperphagia, insulin resistance, developmental delay, intellectual disability, delayed speech and language development, tendency for social isolation and aggressive behavior	Childhood	200–300/ 1,000,000
Without developmental delay				
Alström syndrome	*ALMS1* (chromosomal region 2p13)	Abdominal obesity, vision and hearing loss, dilated or restrictive cardiomyopathy with congestive heart failure, hypothyroidism and hypogonadism, hyperinsulinemia, type 2 diabetes, acanthosis nigricans, and short adult stature.	Variable; many symptoms appear during infancy	Unknown; 950 patients identified worldwide
MC4R deficiency	*MC4R* (chromosomal region 18q21.32)	Hyperphagia, early-onset obesity, severe hyperinsulinemia, accelerated linear growth in early childhood, ACTH insufficiency, hypopigmentation	Variable; hyperphagia from first months of life	500–1,500/ 1,000,000; present in 2–5% of obese hyperphagic patients
Leptin deficiency or dysfunction	*LEP* (chromosomal region 7q32.1)	Severe hyperphagia and early-onset obesity, hypogonadotropic hypogonadism, mild hypothyroidism, frequent infections due to immunologic dysfunction, absence of growth spurt	Neonatal period; hyperphagia from first weeks of age	Unknown; <100 patients identified worldwide
Leptin receptor deficiency	*LEPR* (chromosomal region 1p31.3)	Severe hyperphagia and early-onset obesity, hypogonadotropic hypogonadism, thyrotropic and somatotropic insufficiencies, immunologic dysfunction	Neonatal period; hyperphagia from first weeks of age	Unknown; present in 2–3% of obese, hyperphagic patients
POMC deficiency	*POMC* (chromosomal region 2p23.3)	Severe hyperphagia and early-onset obesity, adrenal crisis due to ACTH insufficiency, mild hypothyroidism, hypopigmentation	Neonatal period; hyperphagia from first weeks of age	Unknown; <10 patients identified worldwide
PC1 deficiency	*PCSK1* (chromosomal region 5q15)	Severe obesity, postprandial hypoglycemia, sometimes severe diarrhea, inefficient conversion of proinsulin to insulin, diabetes insipidus, hypogonadotropic hypogonadism, central hypothyroidism, adrenal insufficiency	Neonatal period; hyperphagia from first weeks of age	Unknown; <20 patients identified worldwide
KSR2 deficiency	*KSR2* (chromosomal region 12q24.22)	Severe obesity, mild hyperphagia, insulin resistance and type 2 diabetes, low basal metabolic rate, bradycardia, irregular menses	Childhood	Unknown; <70 patients identified worldwide

[1] Prader-Willi syndrome, also associated with developmental delay, is not included in this table since it is exhaustively presented in the second part of this paper.
[2] WAGR syndrome is a rare genetic condition (deletion of genes on chromosomal region 11p13) that predisposes patients to a higher risk of Wilms' tumor (i.e. a type of kidney cancer), aniridia, genitourinary anomalies and a range of developmental delays including intellectual disability. WAGR syndrome affects 1–2/1,000,000 population.
ACTH, adrenocorticotropic hormone; ALMS1, ALMS1 centrosome and basal body associated protein; BBS1(-19), Bardet-Biedl syndrome 1(-19); BDNF, brain-derived neurotrophic factor; COH1, Cohen syndrome 1; GNAS, GNAS complex locus; KSR2, kinase suppressor of Ras 2; LEP, leptin; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; NTRK2, neurotrophic tyrosine kinase receptor type 2; PC1, proconvertase 1; PCSK1, proprotein convertase subtilisin/kexin type 1; PHP, pseudohypoparathyroidism; POMC, pro-opiomelanocortin; SH2B1, SH2B adaptor protein 1; SIM1, single-minded 1; TrkB, tropomyosin-related kinase B (BDNF receptor); TUB, tubby bipartite transcription factor; VPS13B, vacuolar protein sorting 13 homolog B; WAGR, Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation.

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Developmental exposure to Bisphenol A : a contributing factor to the increased incidence of obesity ?

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Keywords

Endocrine disruptors, perinatal exposure, Bisphenol A, adipose tissue, hypothalamus

Abstract

Recent data suggest a possible involvement of endocrine disruptors in the current trend of increased incidence of metabolic syndrome and/or obesity. Indeed, by altering hormonal environment, endocrine disruptors can affect homeostatic mechanisms involved in the regulation of metabolism and the control of adipocyte function.

According to Barker's hypothesis, prenatal and early postnatal life are critical periods for future health. Exposure to endocrine disruptors perinatally could be associated with disorders of energy balance throughout subsequent life.

Bisphenol A is a widespread endocrine disruptor, commonly found in food and beverages stored in polycarbonate plastic and epoxy resin containers. Humans are exposed to Bisphenol A through dietary intake but also through non food sources (transdermal exposure from skin contact with thermal paper; dental materials, medical devices). More than 90% of the Belgian population has detectable levels of Bisphenol A in their urine, illustrating the widespread exposure.

In this article, we will first describe animal studies suggesting the potential role of early exposure to Bisphenol A in the alteration of energy balance, through peripheral as well as central effects on circuits involved in the regulation of energy homeostasis. The second part of the article will be dedicated to human data currently available.

Introduction

The rise in obesity, diabetes and metabolic disease incidence during the last 50 years is attributed to genetic factors associated with increased caloric intake, decreased physical activity, sleep deficit and aging (1). However, other environmental factors, among which endocrine disrupting chemicals (EDCs), seem to play a significant role in the global deterioration of metabolic health.

The concept of developmental origin of health and disease has been first developed by Barker. He showed that lower birth weight was associated with a higher risk of cardiovascular disease and premature death in young adult (2). The potential impact of early exposure to endocrine disruptors has been dramatically illustrated by the story of diethylstilbestrol (DES), a pharmaceutical oestrogen prescribed to pregnant women to avoid pregnancy complications. Daughters of mothers treated with DES presented an increased incidence of vaginal adenocarcinoma and benign reproductive lesions but also diabetes and cardiovascular disease and hypercholesterolemia (3,4). Those examples highlight the critical role of intra-uterine and early postnatal life for future health and suggest that the increased incidence of obesity and metabolic syndrome could be explained in part by early alteration of early hormonal environment through EDCs exposure. Many rodent studies have addressed this hypothesis, examining the effects of early (foetal and neonatal) exposure to endocrine disruptors on adiposity and metabolic control. Data in human are scarce but a few longitudinal studies is currently available. Bisphenol A (BPA) was initially synthetized as an estrogenic compound but is now used in polycarbonate plastic and epoxy resin. In Belgium, its use is forbidden in food containers for children under 3 years of age. However, the vast majority of the population is constantly exposed (5).

Several endocrine disrupters are now considered to be obesogens (table 1). In this article, we will use BPA to illustrate some important concepts regarding obesogenic EDCs as it is one of the most widespread and studied chemicals.

Animal studies

Animal studies have shown that early exposure to BPA predisposes individuals to weight gain and accelerated growth rate. A study by Howdeshell *et al* revealed that pups prenatally exposed to low dose of BPA (2,4 µg/kg/day) were heavier than control pups before puberty (6). This finding was confirmed in 2001, by Rubin, who showed that male and female offspring exposed to BPA *in utero* and through lactation (0.1 mg BPA/kg body weight (bw)/day or 1.2 mg BPA/kg bw/day) had increased body weight. The increase started soon after birth and was more persistent in females than males (7). Additional studies confirmed the link between perinatal exposure to BPA and increased body weight (8-11). However, heterogeneity of the results is high and explained by periods of exposures, doses and animal strains. Many studies have reported nonmonotonic effects on weight gain and insulin resistance. Thus, BPA is an obesogenic EDC whose effects needs to be further characterized.

Table 1: list of potential obesogens

Name	Use
Dibutyltin	Polyvinyl chloride (PVC) plastics
Bisphenol A	Plasticizer
Bisphenol F, bisphenol S	Plasticizers
Acrylamide	Manufacture of paper and dye, byproduct of carbohydrate-containing food (frying, baking, roasting)
Dioctyl sodium sulfosuccinate	Dietary emulsifier
Carboxymethylcelluclose, P-80	Dietary emulsifier
Dichloro-diphenyl-trichloroethane (DDT)	Pesticide
Methoxyclor	Pesticide
Imidacloprid	Insecticide
Glyphosate	Herbicide
Quizalofop-p-ethyl	Herbicide

Following initial evidence of alterations of energy balance caused by BPA, many studies have focused on the effects of perinatal and lactational exposure to BPA on specific tissues involved in the regulation of energy homeostasis. We will first summarize the central effects of early BPA exposure on the hypothalamus. We will then focus on data illustrating the impact of BPA on adipose tissue and pancreas.

Effect of BPA on hypothalamus

The hypothalamus is connected to the hindbrain and plays a central role in the control of energy homeostasis and feeding behaviour (12). Regulation of energy intake in the hypothalamus takes place in the arcuate nucleus (ARC) where two neuronal populations with antagonistic effects coexist: neuropeptide Y (NPY) and agouti- related protein (AgRP) expressing neurons have an orexigenic action and proopiomelanocortin (POMC), cocaine expressing neurons and amphetamine-regulated transcript protein (CART) expressing neurons have an anorexigenic action. The establishment of such central control of feeding behaviours takes place both in utero and neonatally. Thus, it seems that the metabolic impact of EDC exposure during this critical period may be significantly greater (13).

Males perinatally exposed to BPA exhibit reduced POMC fibre density into the paraventricular nucleus of the hypothalamus during adulthood, when fed a high-fat diet, suggesting that BPA exposure could make them more susceptible to diet-induced obesity or metabolic disease (14). The pattern of oestrogen receptor alpha expression in POMC neurons in females exposed to BPA was similar to that seen in males, suggesting a masculinizing effect of BPA. Interestingly, female exposed to BPA gained more weight, and ate more calories daily compared to control without any effect on energy expenditure whereas male exposed to BPA and high fat diet exhibited decreased energy expenditure compared to control, illustrating a sexually dimorphic effect of early BPA exposure on energy homeostasis.

Perinatal exposure of mice to BPA also disrupts the action of leptin on the hypothalamus. Leptin is an adipokine hormone that interacts with POMC and neuropeptide Y / agouti- related protein neurons in the ARC to control food intake and plays a crucial role in the establishment of those hypothalamic circuits postnatally. Male and female mice exposed to BPA are less sensitive to leptin effects on POMC expression and weight loss compared to controls. The postnatal leptin surge is delayed in mice exposed to BPA, suggesting permanent alterations of the neurocircuitry involved in the metabolic homeostasis (15).

Effects of BPA on adipose tissue

BPA enhances differentiation of pre-adipocytes into adipocytes *in vitro* and causes higher accumulation of triglycerides and lipoprotein lipase in target cells (16,17). Additionally, BPA has been shown to increase mRNA expression and enzymatic activity of 11β-HSD1, an enzyme which converts inactive cortisone into cortisol in adipose tissues and promotes adipogenesis (17). A concentration of 100nM also activates glucocorticoid receptors and thereby increases lipid accumulation and expression of adipocytic proteins in mature adipocytes (18). Basal glucose uptake in mature mouse 3T3-F443A adipocytes is enhanced after BPA exposure, in relation with an increased expression of the GLUT 4 protein (19). Some studies *in vivo* showed evidence of similar actions of BPA on adipocytes differentiation and function: gestational and lactational exposure to BPA leads to adipocyte hypertrophy in female pups and increased expression of adipogenic markers such PPAR-γ, SREBP-1C, SCD-1 and C/EBP-ALPHA I (20). Notably, BPA at low doses (1 and 10 nM) also inhibits adiponectin secretion from human adipose tissue (21). Adiponectin is an adipocyte-specific hormone that increases insulin sensitivity and reduces tissue inflammation while the release of IL-6 and TNF alpha, two inflammatory cytokines involved to obesity, is stimulated by BPA exposure (22,23).

Effects of BPA on the pancreas

Exposure to BPA has been shown to affect different aspects of β-cell function. *In vivo*, a single dose exposure to BPA in adulthood has been shown to increase insulin release and glucose stimulated insulin secretion in an estrogen-receptor–dependent manner (24). When exposure occurs *in utero*, BPA reduces glucose tolerance and increases insulin resistance in male offspring at 6 months of age (25). These opposite effects illustrate the disruption of foetal programming caused by BPA which could predispose mice to metabolic disorders. Interestingly, some studies suggest that these changes in glucose regulation are persistent in adult offspring and are worsened if the offspring is fed with a high fat diet (26). The pregnant mice exposed to BPA during gestation also develop profound glucose intolerance and impaired insulin sensitivity. Those mice remain heavier several months after delivery and show impaired beta-cell function and mass (27).

Transgenerational effects of BPA exposure on obesity

Developmental exposure to EDCs is associated with epigenetic alterations that can be passed from one generation to another and persist in adulthood (28). Animals born from female exposed to a mixture containing BPA and phthalates have a higher incidence of obesity throughout the third generation (29). Mechanisms involved in such transmission remain to be elucidated. It was proposed that obesogen exposure can permanently reprogram mesenchymal stem cells to favor the adipose lineage (30). Thus EDCs could promote epigenomic changes favoring the development of obesity (30).

Human studies:

The potential effects of BPA exposure on energy balance in children and adolescents have been investigated in recent epidemiological studies. Trasande *et al* have shown that higher urinary BPA concentrations in children and adolescents were associated with increased incidence of obesity (31). Another cross sectional study in school-age children in Shangai, reported that incidence of overweight was increased amongst girls aged 9-12 who had higher urinary BPA concentrations (32). Interestingly, this association was not found in boys, suggesting a sexually dimorphic effect of BPA exposure. In contrast, the association between higher urinary BPA levels and incidence of obesity was predominantly observed in American boys (33). Increased BPA concentrations have been also linked to abnormal waist circumference-to-height ratio in the US population (34). More recently, a study performed on a small number of Iran children has shown that, in addition to the increased body mass index and waist circumference, it appears that systolic and diastolic blood pressure as well as fasting blood glucose were increased in children with higher urinary BPA levels (35).

In all those studies, BPA exposure is assessed by the measure of BPA concentrations in one urinary sample. Given the short half-life of BPA, the use of a single urine sample to categorize exposure is an important limitation for data interpretation (36). Moreover, drawing conclusions from those cross sectional studies remains difficult because obese children ingest more BPA contaminated food such as canned sodas or have greater adipose stores of BPA which would explain the higher urinary concentrations.

Only a few longitudinal human studies focused on the effects of early exposure to BPA on metabolic health later in life. One prospective study in a Spanish birth cohort showed a positive association between prenatal exposure to BPA (assessed by urine BPA concentration during the first and the third trimester of pregnancy) and the risk of obesity at 4 years of age. This association was not present at earlier ages (37). In contrast, other prospective studies have demonstrated an inverse correlation between early exposure to BPA and BMI in childhood (38, 39). Once again, a sexually dimorphic effect of early BPA exposure has been suggested since the inverse correlation was only present in girls (38). Currently, it remains difficult to draw any conclusions from prospective studies aiming at evaluating the effects of early BPA exposure on metabolic health in children and large prospective birth cohorts with multiple measurements of urinary BPA concentrations during pregnancy are needed.

Conclusion:

In conclusion, the perinatal period is a crucial window for the organization of the control of energy balance. While many animal studies indicate that developmental exposure to BPA disrupts the central and peripheral control of energy balance, large longitudinal studies are needed to explore the metabolic consequences of BPA in children.

Factors such as the gut microbiome composition, stress and disrupted circadian rhythms have been recently identified as playing a role in metabolic disease. As these factors are targeted by EDCs, further studies will need to focus on such interactions.

BPA is slowly being phased out and replace by other chemicals such as BPS (Bisphenol S) which appear to have endocrine disrupting properties. Thus effects of replacement chemicals as well as mixture on obesity will need to be further explored.

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The interactions between obesity and sleep

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Keywords

sleep, obesity, weight gain, sleep-disordered breathing

Abstract

The interplay between sleep and obesity is complex. Sleep duration is linked both to weight gain as to metabolic consequences of obesity through several neurohormonal processes. Furthermore, children with obesity are more prone to developing sleep-disordered breathing and consequential metabolic dysregulation. Treating sleep disorders in children with obesity remains challenging and must be an individualized and multidisciplinary approach.
This review provides an overview of normal sleep and development, the neurohormonal processes influenced by sleep and the effects and treatment of sleep-disordered breathing in children and adolescents with obesity.

Introduction

Sleep is defined as a behavioural state that includes reduced sensorimotor activity, responsiveness and interactions with the environment and is easily reversible. It is an essential process both in children and in adults as it has beneficial effects both on physical and mental health (1). The regulation of sleep and wakefulness and the associated physiological effects are complex and still subject of many ongoing research projects.

In this review, an overview of normal sleep throughout childhood and adolescence is given with a focus on the interactions between sleep and paediatric obesity, both regarding causes and consequences.

Normal sleep

Normal sleep exists of two stages, more specifically rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep represents “dream” sleep. NREM sleep is further divided into three distinct stages of which stage 1 sleep is the lightest sleep phase and stage 3 represents deep sleep. The different stages of normal sleep all have distinct characteristics and functions and they alternate in different sleep cycles throughout the night (2). Sleep architecture is one of the many items that is evaluated during a sleep study or polysomnography (PSG). Polysomnographies are scored according to international criteria as proposed by the American Academy of Sleep Medicine, with the latest version published in January 2020 (3). The scoring of PSG’s however is beyond the scope of this review.

Sleep development

Sleep evolves with age and is the result of different behavioural, developmental and neuro-chronobiological changes. There is a decline of the total sleep duration from infancy to adulthood with the most marked decline in sleep amount the first years of life. Infants show a predominance of REM sleep (about 50% of the total sleep time), whereas the proportion of deep sleep is the highest in preschool children. As we grow older, sleep is getting more efficient and sleep needs decrease. Normal sleep development also leads to age specific sleep problems, such as parasomnias that present during deep sleep (e.g. sleep terrors) more frequent in young age and delayed sleep phase disorder in puberty (2).

Sleep and the metabolism

To understand the link between sleep and weight gain and obesity it is important to acknowledge the many underlying mechanisms.

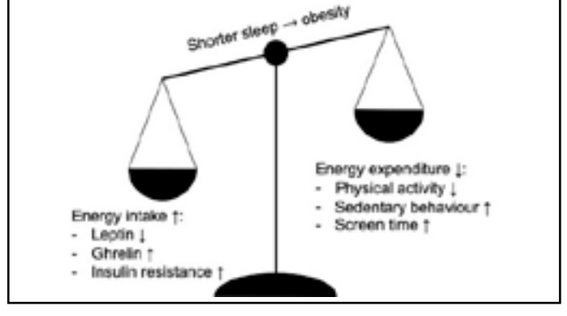
The most evident one is that sleep deprivation and fatigue leads to more sedentary behaviour and a decreased physical activity. In addition, a relationship has also been shown in which a shorter sleep duration leads to increased screen time. Many studies also investigated the association between sleep duration and dietary choices and all showed the same link between shorter sleep duration and an increased intake of high energy density foods. Of course, it is clear that these factors cause a decreased energy expenditure and an increased energy intake and therefore contribute to weight gain (4).

Next to the factors causing lower physical activity and higher caloric intake, there are also some complex hormonal factors linking sleep quality and duration to weight gain and obesity. Leptin and ghrelin are both hormones that regulate satiation and appetite. In short, ghrelin stimulates the feeling of being hungry whereas leptin gives satiety. Sleep duration regulates the secretion of both leptin and ghrelin where a shorter sleep duration increases the level of ghrelin and decreases the level of leptin, leading to an altered dietary behaviour that may be summarized as increased hunger and appetite for more specifically carbohydrate containing foods and drinks and thus once again increased energy intake (4-6).

Additionally, sleep has also beneficial effects on the glucose homeostasis with sleep deprivation leading to insulin resistance. The causes for this are multifactorial with an increase of circulating cortisol during the evening and the upregulation of proinflammatory markers (e.g. C-reactive protein) (5).

The link between shorter sleep and obesity is summarized in figure 1.

Figure 1: The mechanisms that promote obesity with shorter sleep.



Sleep-disordered breathing

Obstructive sleep disordered breathing (SDB) comprises a spectrum from primary snoring to obstructive sleep apnea syndrome (OSA). It is defined as recurrent partial and/or complete collapse of the upper airway during sleep. The result is abnormal nocturnal ventilation and a disrupted sleep architecture. The gold standard to diagnose SDB in children is by performing a polysomnography. This polysomnography is able to detect both apneas and hypopneas. An apnea is defined as the complete cessation of airflow for at least 2 breaths with or without a drop in oxygen saturation or a consecutive arousal. A hypopnea is characterized by a decrease of at least 30% in airflow for the duration of 2 breaths at minimum and in combination with either a drop in oxygen saturation of at least 3% or a consecutive arousal. Apneas may be central (no respiratory effort recorded) or obstructive (continued or increased respiratory effort). Based on the detection of obstructive apneas and hypopneas it is possible to calculate the obstructive apnea-hypopnea index (oAHI), which is the average number of obstructive apneas and hypopneas per hour of sleep (3). OSA is diagnosed with an oAHI of at least 2 events per hour of sleep.

Presenting symptoms of OSA may be broad and ranging from snoring and witnessed apneas, over increased blood pressure and bedwetting, up to behavioural problems and poor school performance. It is clear that OSA has many adverse effects in children that are not necessarily linked to the presence of SDB by the parents, but where the clinician should very well be aware of (7).

The prevalence in the general paediatric population is believed to be between 1 and 4% (8). The major cause in these children is adenotonsillar hypertrophy leading to obstruction because of disproportionate growth of the upper airway. Therefore, the most common treatment option in children still is adenotonsillectomy (9).

Although adenotonsillar hypertrophy is the main etiology in children, there are several predisposing factors increasing the risk of developing OSA, such as craniofacial anomalies, several genetic syndromes (e.g. Down syndrome, Prader Willi syndrome), but also obesity (7). Obesity is thought to be an independent risk factor for developing SDB in childhood with reported prevalences between 13 and 59% of children (10). Obesity leads to fatty infiltration of the soft tissue surrounding the upper airway, the neck, chest wall and abdomen. This creates an increased collapsibility of the upper airway, especially during REM sleep (with low muscle tone) and in a supine position (11).

OSA in children is linked to several metabolic and cardiovascular complications, such as insulin resistance, dyslipidemia, systemic hypertension and the metabolic syndrome comprising the aforementioned complications (12,13). The mechanisms by which OSA may contribute in children with obesity to higher rates of metabolic disruption are not completely clear and still subject of ongoing research. It is hypothesized that the process of intermittent hypoxia and reoxygenation leads to oxidative stress and systemic inflammation (14). Previous research has shown that OSA in children with obesity has a negative effect on several biomarkers of systemic inflammation, mostly tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6), and adipokines such as adiponectin and leptin, but many studies show different methodology and power (15). However, a recent review for example that focused on pooled data on TNF-alpha and IL-6 has shown that the increase in these biomarkers does most likely reflect the risk of the presence of end organ disease (16).

As mentioned, the first line treatment for OSA in the general paediatric population is adenotonsillectomy, but this is associated with high treatment failure rates in children with obesity. Up to 33 to 76% of children with obesity have persistent OSA after adenotonsillectomy, depending on the definition of OSA, the degree of obesity and the age of the patient (17). Moreover, weight gain after adenotonsillectomy is a complication that is often seen after surgery and increases the risk of persistent or recurrent OSA in this specific population (18). It is quite clear that treatment for OSA in children with obesity must be performed by a multidisciplinary team and must consist of an individualized approach that may be a combination of different treatment options. However, the corner stone of treating OSA in children with obesity seems to be weight loss. A meta-analysis published by Roche et al, beginning of 2020, showed that most of the studies regarding multidisciplinary weight loss programs showed a significant decrease in OSA rates after the intervention with a normalization of polysomnography in 46.2 to 79.7% of the subjects. And in 75% of the children and adolescents there was an improved sleep duration (19). Other treatment options may include continuous positive airway pressure (CPAP) treatment and pharmacological treatment such as intranasal corticosteroids and leukotriene receptor antagonists.

Conclusion

Sleep is an important part of life that has many beneficial effects both on physical and on mental health. Adequate sleep in children and adolescents is important, as sleep deprivation is linked to biological factors, such as increased ghrelin secretion and insulin resistance and decreased leptin production, and behavioural factors, such as decreased physical activity and more sedentary behaviour and screen time, that promote weight gain. Moreover, children and adolescents with obesity are more prone to developing sleep disordered breathing and OSA. OSA in this population is linked to increased metabolic disruption and the development of the metabolic syndrome and cardiovascular disease. Treating children with obesity and sleep disorders is challenging and must comprise a multidisciplinary approach aimed at lifestyle changes and weight loss as it has been shown that this improves both the degree of OSA and the sleep duration and therefore targets the entire spectrum of sleep difficulties.

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What about our vulnerable children in the multidisciplinary approach of childhood obesity or overweight?

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childhood obesity, prevention, environmental influences

Abstract

In the global problem of childhood obesity/overweight multidisciplinary treatment programs can be considered as a golden plan B, whereas prevention is or should be the golden plan A. Multiple factors are important in the pathogenesis and each of them needs attention in the family-centered treatment program as well as in global policy decisions.

Introduction

It is no longer necessary to argue that obesity is a global problem. In Belgium, 19% of children between the ages of 2 and 17 years are diagnosed with overweight and 5.8% with obesity. More and more attention is being paid to existing comorbidities in (young) children. Tracking studies also indicate a significant risk that childhood obese status will be continued in adulthood if treatment is not initiated. The younger the age at which we can intervene, the smaller the risk of health hazards in adulthood.

In that sense, treatment of childhood obesity is the main form of prevention of obesity in adulthood. In addition to impact on health, this has also economic implications.

Children's weight status is influenced by several factors.

Genetic abnormalities, hormonal disorders, motor disturbances, sleep deprivation, medication, psychological factors,… can all contribute to weight gain.

Aiming at early intervention, it is important to gain insight into these determinants that make a child vulnerable to the development of overweight. In other words, which influenceable factors play a role in the development of overweight in children?

To tackle as many as possible of these factors we propose a multidisciplinary approach. Our team 'Gezond Opgroeien' consists of 2 child psychologists, a child dietician, a pediatric nurse, a social worker, a physiotherapist and a pediatrician. It is a particular challenge to raise awareness of children / families from as young as possible to start guidance and support for healthy growing up. We will briefly describe our working method in this article.

Today guidelines support a child friendly multidisciplinary approach in counseling children with overweight and obesity. In Belgium, these guidelines are summarized in the BASO (Belgian Association for the Study of Obesity) consensus text, version 2020. These guidelines describe a step-by-step approach from screening to treatment. Core elements are: multidisciplinarity, stepped care approach and a treatment tailored to the specific child.

In contrast to the treatment of obesity in adults, two other aspects are special for the target group of children. First, children are not mini-adults and the factor growth plays in their favor. This has implications for the view on and objective of the treatment.

Secondly, children grow up in a family and by extension an environment and society, each of which exerts its influence. This implies that the parents, siblings and the wider living environment of the child must also be involved in the treatment.

The goal is to implement a healthy lifestyle for everyone.

Starting from our activities within the team "Gezond Opgroeien" we experience more and more the need for networking around the child and his family.

At registration, the child and his parents are seen by the pediatrician, the dietician and psychologist in a combination consultation as well as by the physiotherapist or a physical therapist. Different influencing factors are pointed out and evaluated.

Medical evaluation with full clinical assessment, biometrics and biochemistry will mainly determine the treatment objective for a child, namely weight stagnation or weight loss, ambulatory or preferentially residential care. The ultimate goal is health gain. A tool for this evaluation is the Edmonton Obesity staging system for pediatrics (EOSS-p) (figure).

On the other hand, and this is what we want to draw attention to in this article, an evaluation of the child and his functioning within the family, the school, etc. is very important to achieve a successful program.

The family is certainly a very important role model for the younger age groups. They depend most on what groceries are being done, how food is cooked, where food is eaten, how people move, ...

Options offered, particularly at young age play an important role and are influenceable. Some families may have several acute personal, financial, or other concerns that push long-term lifestyle goals into the background.

In our vulnerable families we often see that the neighborhoods where they live have fewer green areas or are perceived as less safe, which means that parents are less disposed to play outside with the kids, or let kids romp with each other. For these families, the search for an accessible form of physical exercise is not an easy one and should be supported.

The attention of future urban architecture for more green areas, less high-rise apartment blocks is certainly a welcome initiative that has been increasingly seen in recent years.

In addition, the impact of the lower socio-economic status (SES) is also felt in other areas.

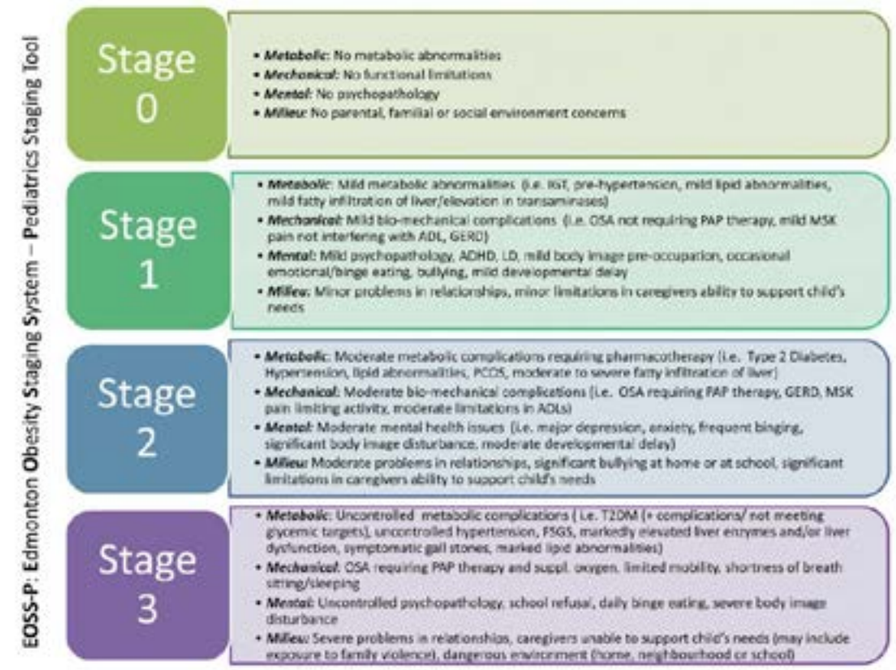
First, families may have financial concerns. The financial picture is often a reason to drop out. The extra reimbursement that was recently obtained for diet consultations is certainly a big step in the right direction.

Secondly, to practice a healthy lifestyle (including fresh, healthy food, sufficient physical activity and a peaceful mind) is an expensive affair for many families . A wider range of fresh, affordable food in supermarkets in neighborhoods, known for their lower SES population, has previously been suggested in studies as having a positive impact on what would come on the families' daily menus.

Finally, being confronted with multiple stressors means there is also less time and (mental) space to engage in a healthy lifestyle for the whole family.

Therefore, SES, family stress and well-being have already before been linked to the development of obesity, as a risk factor.

Figure: The Edmonton Obesity Staging System for Pediatrics (EOSS-P).



The usefulness of psychological counseling, either for the family or for the child itself, should not be ignored in the support of children and young people who are overweight. Coaching families to choose the healthy lifestyle for everyone is very important to achieve a success story.

In our older children, especially teenagers, the family context may not be as important as role model anymore, their group of friends and the freedom they enjoy are. Friends from the same residential area will often have similar lifestyles and the young person will sometimes experience a barrier to do things "differently". Young people want to 'belong to the group'. A sensitization within the group of young people can certainly have an impact on this. For example, no longer offering sugar snacks and soft drinks in secondary schools is an initiative in this direction.

But there is often more involved. Teenagers who register for the multidisciplinary consultation have often sought help for years without the desired (permanent) result. Strict diets for the child only put extra pressure on the child as well as the parents, who in turn experience stress. Our advices to our children, our teenagers must be achievable for them and for their entire family. By betting on lifestyle advice instead of dieting.

In other teenagers we see underlying emotional factors that were never recognized, but which are the gate to start with the weight problem.

With these young people, we have to work on motivation and emotion before discussing healthy lifestyle in terms of nutrition and exercise. The psychologist is a key member of the multidisciplinary team. Psychological counseling, however, is expensive and only partially refundable. .

Every registered child is discussed at a multidisciplinary meeting. Vulnerable families are also discussed with the social worker to develop a personalized and achievable plan.

A close collaboration is established with the general practitioner and, by extension, the district health centers which can also provide support with regard to dietary advice and / or physiotherapy and / or psychological support. At that time, the multidisciplinary team assists them as a coach.

For our youngest children, the child family, CLB (centrum voor leerlingenbegeleiding - centres psycho-médicaux-sociaux) and attainable home counseling services are partners to provide tailored family support.

In these partnerships it is important for our team to continue to monitor the evolution of the child and family in the weight care program. It is the task of our pediatric nurse and social worker to organize meetings for that purpose.

Pooling expertise and building a network within the small area around families is very important. As part of the expertise of "Eetexpert" , supervision groups have been established that meet regularly to share both practical and scientific insights. Different disciplines from the 1st and 2nd line are represented in these groups. This network contributes to short-term and tailored assistance for children and families

As previously described, the existence of multidisciplinary teams to detect and treat overweight / obesity early is crucial, but this should not diminish the need for broader prevention initiatives at the social level! More attention must be paid to daily life factors that can be influenced in our society.

Learning how to be a role model, how to run errands and prepare meals, how to combine work and a healthy lifestyle, how to have a healthy day and night rhythm, how to reduce the stress levels in our vulnerable families, these are the challenges we are facing and on which our health policy should focus..

And preferably for the child and his family in a safe and green environment that lends itself to physical activities.

Mens sana in corpore sane… it is just as topical today.

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Prenatal, natal and postnatal determinants of childhood obesity

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Keywords

Childhood obesity, determinants, prenatal, postnatal

Abstract

Although there is an important genetic contribution to the development of obesity in childhood environmental factors can affect the influence of the genetic risk of obesity and adiposity, and the relationship between obesity-related genes and body mass index is strengthened in an obesogenic environment. Early-life experiences in utero and postnatal influences can induce changes in the physiological functions that program the regulation of energy balance. These changes can then adversely affect the risk of obesity later in life. The risk factors can be categorised into two groups: prenatal factors, and natal and postnatal factors. Important prenatal factors are parental body mass index, maternal gestational weight gain, gestational diabetes and maternal smoking. To the natal and postnatal factors belong the type of delivery and birth weight, breastfeeding, formula feeding, rapid infant growth, complementary feeding and macronutrient intake during infancy. Since obesity can be programmed in utero and during early childhood, health-care professionals should promote normal weight status at childbearing age and during pregnancy. Careful monitoring of infant growth is mandatory to detect early excessive weight gain. Obesity preventive measures should be initiated before conception, during pregnancy and during early childhood.

Introduction

In the past decade much research has focused on the identification of early risk factors for the development of childhood and adult obesity (1,2). While there is an important genetic contribution to the development of excessive adiposity in childhood, environmental factors can affect the influence of the genetic risk and the association of obesity-related genes with body mass index (BMI) is strengthened in an obesogenic environment (3,4). Early-life experiences *in utero* and postnatal influences can induce changes in the physiological mechanisms that program the regulation of energy balance. These changes can then adversely affect the risk of obesity later in life. Since obesity can be programmed *in utero* and during early childhood, preventive measures should be initiated before conception, during pregnancy and during early childhood. This review summarises current knowledge of the most important early determinants for the development of childhood obesity. The risk factors are categorised into two groups: prenatal factors, and natal and postnatal factors (Table 1).

Table 1. Prenatal, natal and postnatal factors associated with child obesity

Prenatal factors during pregnancy
· Parental obesity
· Gestational weight gain
· Gestational diabetes mellitus
· Maternal smoking
· Antibiotica during pregnancy
· Environmental obesogens
· Maternal psychosocial stress
Natal and postnatal factors up until 2 years of age
· Type of delivery
· Birth weight
· Breastfeeding
· Formula feeding
· Rapid infant growth
· Complementary feeding and macronutrient intake
· Sleep duration

Prenatal determinants

Parental Obesity

There is considerable evidence of a strong relationship between maternal preconceptional adiposity and overweight and obesity in childhood. A meta-analysis of 45 studies found that, compared with subjects with normal BMI, prepregnancy maternal overweight or obesity increased the risk of overweight (Odds Ratio (OR) 1.95; 95% confidence interval (CI) 1.77, 2.13) and obesity (OR 3.06; 95% CI 2.68, 3.49) in offspring from infancy to adolescence (5). In two studies that described a relationship between maternal preconceptional overweight or obesity and the relative odds of having overweight or obesity in childhood, the estimated OR was 1.37 (95% CI 1.18, 1.58) at 3 years and 4.25 (95% CI 2.86, 6.32) at 7 years (6,7). The association also persists at later ages, with one study identifying maternal obesity as the strongest predictor of obesity at all ages in childhood (8). These findings suggest that the effect of maternal obesity on childhood overweight may be due to an early tendency to gain weight which is perpetuated as the child becomes older.

A major problem in understanding the relationship between maternal and offspring obesity is distinguishing the influence of the intrauterine environment from that of the shared postnatal environment, making it difficult to find out whether the identified association is due to factors acting in the prenatal period or in infancy. A study that provides some insight into the effects of maternal obesity examined the prevalence of obesity in children who were conceived and born to 113 obese mothers before and after bariatric surgery (9). The prevalence of overweight and obesity among 45 children born prior to surgery was 60%, whereas the prevalence among 172 children born after surgery was 35% (9). This finding indicates that bariatric surgery, followed by a reduction in maternal adiposity, contributed to the prevention of transmission of obesity to the offspring. This study supports the hypothesis of a direct influence of maternal obesity on the intrauterine environment with long-term effects on the regulation of body weight of the offspring. However, the offspring of surgically treated mothers still had a higher obesity prevalence than expected (35%), stressing the role of common genetic modifiers and a shared obesogenic postnatal environment.

Paternal obesity also contributes to the risk of childhood obesity. In a systematic review comparing the associations of maternal and paternal prepregnancy BMI with offspring obesity/adiposity three studies showed a direct association of parent–offspring BMI (10). In only one cohort a statistically stronger maternal influence was found.

Several potential mechanisms to explain the association between parental and offspring obesity have been put forward, amongst which (1) genetic mechanisms; (2) foetal dysregulation of glucose, insulin, lipid and amino acid metabolism; or (3) a shared familial environment (e.g. similar food preferences, physical activity levels or sedentary time) (3,11,12). Investigation of offspring epigenome-wide DNA methylation in the Avon Longitudinal Study of Parent and Children (ALSPAC) suggests that epigenetic modifications are a possible mechanism to explain the association between maternal and offspring obesity (13). The results showed evidence of a relationship between maternal obesity with greater offspring adiposity through varied DNA methylation of the neonatal epigenome. Offspring methylation was more strongly associated with maternal than with paternal obesity, stressing the importance of the prenatal environment (13). Further research is needed to understand the effects of maternal obesity and to find out whether a predisposition to gain excess weight in childhood is, at least partially, a consequence of influences acting during foetal life.

Gestational Weight Gain

The Institute of Medicine, USA, has defined recommendations for gestational weight gain (GWG) (14). Excessive GWG is associated with an increased risk of overweight and obesity in childhood. A systematic review and bias-adjusted meta-analysis showed that pregnant women with excessive GWG had an increased risk of obesity in the offspring (OR 1.40; 95% CI 1.23, 1.59), while women with an inadequate GWG had a 14% reduction in the risk of offspring obesity (OR 0.86; 95% CI 0.78, 0.94) (15). Moreover, the association between GWG and offspring BMI is stronger during early- and mid-pregnancy than during late pregnancy, as suggested by another systematic review (16).

It has also been shown that excessive GWG can be associated with increased adipose tissue deposition in newborns and childhood. A systematic review and meta-analysis of 7 studies observed positive relationships between maternal GWG and offspring body fat percent (17).

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is another risk factor for the development of overweight and obesity in childhood. In a recent meta-analysis including 160,757 mother–offspring pairs from 34 cohorts GDM was associated with a higher odds of overweight throughout childhood (OR 1.59 (95% CI 1.36, 1.86); OR 1.41 (95% CI 1.26, 1.57); OR 1.32 (95% CI 0.99, 1.78) for early-, mid- and late-childhood, respectively) when compared to uncomplicated pregnancies (18). Body composition is also altered by GDM. A meta-analysis including data from more than 24,000 infants reported that GDM is associated with significantly higher fat mass, body fat percentage and skinfold thickness in infancy (19). Is it hypothesised that in concert with a genetic susceptibility to obesity altered maternal fuels, especially hyperglycaemia, act as mediators of foetal growth and risk of obesity in offspring exposed to maternal diabetes in utero (20).

Maternal Smoking

Maternal smoking during pregnancy increases the likelihood of the offspring developing overweight and obesity in childhood. In a systematic review and meta-analysis an elevated odds of maternal smoking in pregnancy for childhood overweight (OR 1.37, 95% CI 1.28, 1.46) and childhood obesity (OR 1.55, 95% CI 1.40, 1.73) was found (21). Although smoking often is associated with certain sociodemographic and lifestyle factors, such as less healthy diet and lifestyle, the association persisted after adjustment, suggesting that the effects of confounding influences cannot completely explain the association (21). In another meta-analysis Albers et al. reported a linear dose-response association of maternal smoking in the range of 1 – 15 cigarettes per day with no further risk increase for doses above 15 cigarettes (22). The dose-response association supports to the evidence that the relationship between prenatal smoking and offspring obesity is causal. There is also evidence of a time-dependent relationship, such that smoking in the first trimester of pregnancy appears to be more relevant to an offspring's risk of obesity, while smoking in the last trimester is rather associated with low birth weight (23).

The mechanisms to explain the effect of prenatal smoking on the development of obesity in the offspring are not fully understood, although a number of plausible mechanisms have been proposed. Prenatal smoking has been associated with low birth weight, possibly through the vasoconstrictive action of nicotine leading to foetal hypoxia (21). It has been hypothesised that this may affect postnatal growth patterns (cfr. infra) leading to a higher risk of obesity. There also is some evidence that increased adiposity in childhood may result from foetal exposure to nicotine, which has been shown to have long-term effects on programming the regulation of appetite and the control of food consumption (24).

Antibiotics during pregnancy

There is some evidence that maternal antibiotic use can be associated with changes in infant birth weight and an increased risk of childhood obesity. Jepsen et al. reported that the adjusted mean birth weight of neonates born to amoxicillin-exposed mothers was 57 g [95% CI 9, 105] higher than that of those born to controls (25). Mor et al. showed that, after adjusting for confounding factors, prenatal exposure to systemic antibacterials was associated with an increased risk of overweight and obesity at school age (26). Exposure to antimicrobials during gestation may affect the postnatal metabolism by altering the composition of the 'pioneer' microbiota, ultimately leading, in susceptible persons, to overweight or obesity (27).

Environmental obesogens

Epidemiological studies suggest that prenatal exposure to certain environmental pollutants (e.g. dichlorodiphenyldichloroethylene, perfluoroalkyl substances) are associated with childhood obesity (28). However, reports from longitudinal studies involved with prenatal maternal exposure are limited. In a pooled analysis of seven European birth cohorts is was found that dichlorodiphenyldichloroethylene exposure was associated with a significant higher weight-for-age SDS (standard deviation score) at the age of 24 months (29). A prospective cohort study reported that higher prenatal perfluoroalkyl substance exposure was associated with greater adiposity at 8 years and a more rapid increase in BMI between 2 and 8 years (30).

Maternal psychosocial stress

It has been reported that severe maternal psychosocial stress can be associated with offspring alterations in the glucose–insulin metabolism and in the regulation of the hypothalamic–pituitary-adrenal axis (31). Depending on the severity and timing of stress, and sex of the offspring, exposure to maternal psychosocial stress could contribute to the development of childhood overweight and obesity (31). In a meta-analysis of 17 studies Tate et al. found that higher levels of prenatal maternal psychological stress were associated with higher risk of childhood obesity (32).

Natal and postnatal determinants

Caesarean section

There is some evidence that caesarean section is associated with an increased risk of overweight and obesity in offspring. A systematic review and meta-analysis revealed that the overall pooled OR of overweight/obesity for offspring born by caesarean section compared with those born vaginally was 1.33 (1.19, 1.48); the OR was 1.32 (1.15, 1.51) for children, 1.24 (1.00, 1.54) for adolescents and 1.50 (1.02, 2.20) for adults, respectively (33). The association between caesarean birth and obesity might be attributable to the fact that neonates born by caesarean section bypass the bacterial inoculum of the vaginal canal at birth. Dominguez-Bello et al. showed that vaginally delivered infants harboured bacterial communities resembling their mother's vaginal microbiota, whereas infants born by caesarean section acquired bacterial communities similar to those found on the mother's skin (34). It has been shown that the gut microbiome plays a role in the pathogenesis of obesity (35) .

Birth weight

High birth weight (BW) is also identified as a risk factor for the development of obesity. In the ALSPAC study increasing BW was independently and linearly associated with increasing prevalence of obesity at age 7 years (per 100 g : OR 1.05; 95% CI 1.03, 1.07) (7). In a systematic review and meta-analysis the association between BW and childhood obesity was studied (36). The

results revealed that high BW (>4000 g) was associated with increased risk of obesity (OR 2.07; 95% CI 1.91, 2.24) compared with subjects with BW ≤ 4000 g. Interestingly, Yuan et al. observed a J-shaped relationship between BW and BMI SDS in 16.580 subjects aged 7 to 17 years (37). After adjusting for confounders the risk of overweight and obesity was higher in children with higher BW than in children with BW of 3000-3499 g (3500-3999 g: OR 1.14, 95% CI 1.02, 1.28; 4000-4499 g: OR 1.39, 95% CI 1.19, 1.63; and 4500-4999 g: OR 1.36, 95% CI 1.06, 1.76). Children with a very low BW (< 1500 g) had the highest obesity risk with an adjusted OR of 2.30 (95% CI 1.03, 5.14) relative to children with BW of 3000-3499 g (37). In a recent study with more than 70.000 children aged 3 – 12 years the authors also found that low BW (< 2500 g) was associated with an increased risk for severe obesity (OR 1.27, 95% CI 1.03,1.55) (38). Taken together, there is evidence that both babies born with low (<2,500 g) or high BW (>4,000 g) have an increased risk of developing overweight or obesity.

Body mass index is, however, an inaccurate marker of adiposity. Studies that use more accurate measures of body composition showed that larger babies are more likely to have greater lean body mass but not greater fat mass as children, adolescents, and adults (39). Rather, it appears that low BW babies, born following intrauterine growth restriction, often have an accelerated weight gain and are more likely to become more adipose with higher risks for obesity-related diseases in later life (40).

Breastfeeding

The superiority of breast milk over formula preparations in the prevention of obesity is well accepted (41,42). In a meta-analysis of thirty prospective studies conducted to determine the relative influence of potential risk factors for child obesity development the authors found that compared to non-breastfed infants breastfed newborns had a 15% decrease in the odds of childhood overweight incidence (43). In contrast, in a large randomised controlled trial (The Promotion of Breastfeeding Intervention Trial) involving more than 17,000 healthy newborns no statistically significant effect of breastfeeding on children's BMI was found (44). It must, however, be taken into account that most of the literature in favour of the protective effect of breastfeeding towards the development of childhood obesity might not be replicable if applied to different and improved artificial milk formulations developed more recently. Pathophysiologically the most widely accepted hypothesis for the protective effect of breast milk is the difference in child growth rates between breastfed and formula-fed infants: in the first year of life, body mass gain is usually slower in breastfed than in formula-fed infants (45). In summary, although breastfeeding has many benefits the protective effect of breastfeeding on obesity prevention is still a matter of debate and further studies are needed.

Formula feeding

Formula-fed infants are usually larger than breastfed infants by the end of the first year of life (45). It has been proposed that the composition of infant formula may be a critical factor to the rate of weight gain in infancy. The main proposed mechanism for this effect is the protein composition of infant formula. In one study, infants consuming protein hydrolysate formula, as compared to those fed cows' milk formula, were satiated sooner and had more normative (less excessive) rates of weight gain (46). In a randomised controlled trial among more than 1000 infants randomised to low- versus high-protein infant formula, those consuming the lower-protein formula, which is most similar in protein content to breast milk, had lower rates of weight gain up to age 6 years (47). It is hypothesised that high levels of ingested protein may promote production or secretion of hormones that increase infant weight gain and growth: circulating levels of insulin and insulin-like growth factor 1 (IGF-1) are lower in infants fed breast milk or low-protein formula than in those fed higher-protein formula (48).

Rapid infant growth

There is a lot of evidence that rapid growth and excessive body mass gain in the first 2 years of life is associated with an increased risk for the development of obesity. In a systematic review with 22 cohort and two case-control studies the relation between infant size and growth, and subsequent obesity was assessed (49). The results showed that infants who were defined as "obese" or who were at the highest end of the distribution for weight or BMI were at increased risk of obesity. Compared with infants without obesity, ORs for subsequent obesity ranged from 1.35 to 9.38 in those who have obesity (49). Compared with other infants, the infants with rapid growth had an ORs of later obesity ranging from 1.17 to 5.70 (49). In a study with 1031 children who were evaluated at birth and during a 6-year follow-up rapid infant weight gain (increase in body weight SDS > 0.67) from birth to 6 months of age was identified as an independent predictor of overweight and obesity at the age of 6 years (50).

The impact of early infant growth on later body composition has also been studied. Several studies have focused on the first 6 months of life, wherein body mass gain is primarily a gain in fat mass, while fat-free mass increases preferentially after this age (1). In a prospective cohort study of 233 children the investigators observed that rapid weight gain from birth to 5 months (SDS > 0.67) was associated with increased fat mass index (FMI) at the age of 3 years (51). In another study evaluating body composition in 234 healthy children and adolescents aged 4–20 years, it was found that rapid weight gain in the first 6 months of life, but not in the second 6 months, was related to increased total and central adiposity (52).

In preterm infants and infants born small for gestational age rapid weight gain during early postnatal life has been associated with increased long-term risks for central obesity and chronic diseases later in life (53). A recent meta-analysis and systematic review confirmed that preterm infants had a greater likelihood of childhood obesity than term infants (OR = 1.19, 95% CI 1.13, 1.26) (54). Accelerated weight gain significantly increased the probability of subsequent obesity among preterms (aOR = 1.87, 95% CI 1.57, 2.23) (54).

Complementary feeding and macronutrient intake

The term "complementary feeding" embraces all liquid and solid foods other than breast milk or infant formula and follow-on formula (55). In a systematic review Pearce et al. investigated the relationship between the timing of the introduction of complementary feeding and overweight or obesity during childhood (56). The authors concluded that there is no clear association between the timing of the introduction of complementary foods and childhood overweight or obesity. However, there was some evidence suggesting that very early introduction (at or before 4 months), rather than at 4–6 months, may increase the risk of overweight. A meta-analysis of prospective cohort studies confirmed that introducing complementary foods before 4 months of age compared to at 4 to 6 months was associated with an increased risk of being overweight (RR, 1.18; 95% CI 1.06, 1.31) or obese (RR, 1.33; 95% CI 1.07, 1.64) during childhood (57). A recent study showed that early (< 4 months) introduction to solid foods in infancy is associated with altered gut microbiota composition and higher BMI in early childhood (58). Based on the available data the introduction of complementary foods to infants before 4 months of age should be avoided to reduce the risk for the development of obesity.

There is observational evidence that high-protein intake in infancy is a risk factor for the development of obesity. Günther et al. observed that a consistently high-protein intake at 12 months (14.8% of energy, range: 13.8–15.6) and between 18–24 months (13.8% of energy, range: 12.9–15.2) was independently related to a higher mean BMI SDS and percentage body fat at the age of 7 years (59). In a study in 2154 twins followed up until the age of 5 years, Pimpin et al. found that total energy from protein at the mean age of 21 months was associated with higher BMI (β = 0.043; 95% CI 0.011, 0.075) and weight (β = 0.052; 95% CI 0.031, 0.074) but not with height (β = 0.088; 95% CI -0.038, 0.213) between 21 months and 5 years (60). In the Generation R cohort, it was observed that, after adjustment for confounders, a 10 g per day higher total protein intake at 1 year of age was associated with a 0.05 SD (95% CI 0.00, 0.09) higher BMI at the age of 6 years (61). This association was solely due to a higher FMI (0.06 SD (95% CI 0.01, 0.11)) and not to a change in fat-free mass index (-0.01 SD (95% CI -0.06, 0.05)). The associations of protein intake with FMI at 6 years remained significant after adjustment for BMI at the age of 1 year (59). Based on the available evidence high-protein intake in infancy should be avoided to protect against childhood obesity.

Concerning dietary fat intake and the risk for childhood obesity, limited information is available in children up to 2 years of age. Agostoni et al. measured dietary fat intake at 1 and 5 years of age and BMI at 5 years in 147 children (62). The authors could not find any association between intake of total fat, saturated fatty acids, monounsaturated fatty acids or polyunsaturated fatty acids at 1 or 5 years of age and BMI at 5 years (62). In another study 1062 children aged 7 months were assigned to an intervention group or to a control group (63). The intervention children received individualised counselling focused on physical activity and healthy diet aimed at the reduction of the child's intake of saturated fat. The development of overweight and obesity was assessed up to the age of 10 years. At the age of 10 years, 10.2% of the intervention girls and 18.8% of the control girls were overweight, whereas 11.6% of the intervention boys and 12.1% of the control boys were overweight (63). As the intervention consisted of the promotion of healthy eating and physical activity patterns, it is not certain whether the effects were caused by a low-saturated-fat diet or other effects of the lifestyle advice. In a 2016 systematic review of systematic reviews the authors concluded that there is no evidence of a relationship between fat intake in the first years of life and childhood BMI or early adulthood adiposity, neither was there any evidence that polyunsaturated fatty acid intake in early childhood influences long-term risk of overweight, obesity, or body fat content (42). Based on the available evidence there seems to be no consistent association between fat intake in infancy and the development of obesity.

Total sugars include all mono- and disaccharides; namely, glucose, fructose, lactose, sucrose and maltose (64). The updated WHO definition of "free sugars" is "monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook, or consumer (i.e. added sugars), plus sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates (i.e. non-milk extrinsic sugars) (65). The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommends that the intake of free sugars should be minimised with a desirable goal of <5% of total energy intake for children aged ≥2 years, and even lower for infants and toddlers <2 years old (66). In a review of worldwide studies on sugar intake, the authors observed that the intakes of added sugars expressed as a percentage of total energy (%TE) ranged from 1.9% for 9-month-olds in Iceland to 11.9% for 1.5–3-year-olds in the UK (67). Herbst et al. evaluated associations between added sugar intake during early childhood at different ages and BMI (68). They observed that a higher total added sugar intake at 1 year was related to a lower BMI SDS at age 7 years (adjusted β ± SE: -0.116 ± 0.057 BMI-SDS/percent energy (%TE) added sugar; P = 0.04), whereas an increase in total added sugar during the second year of life (Δ%TE between age 1 and 2 y) tended to be associated with a higher BMI SDS (adjusted β ± SE: 0.074 ± 0.043 BMI-SDS/Δ%TE added sugar; P = 0.09). No associations were found with body fat percentage (68). Sugar-sweetened beverages (SSBs) are important contributors to added sugars in a human diet (66,67). In the Infant Feeding Practices Longitudinal Study, the obesity prevalence at 6 years among children who consumed SSBs during infancy was twice as high as that among non–SSB consumers (17.0% vs 8.6%) (69). Cantoral et al. estimated the relationship between the age of introduction and cumulative SSB consumption with the risk of obesity in a cohort of 227 children to whom SSBs were introduced before 24 months of age, and in the majority (73%) before 12 months (70). The authors observed that SSB intake before 12 months was not associated with increased odds of obesity (OR 2.00; 95% CI 0.87, 4.59) (70). However, subjects in the highest tertile of cumulative SSB consumption had almost three times the odds of general (OR 2.99; 95% CI 1.27, 7.00) and abdominal (OR 2.70; 95% CI 1.03, 7.03) obesity at age 8-14 years compared to the lowest tertile (70). Based on the available data free sugars should be limited to a maximum of 10% of energy intake and the consumption of SSBs should be avoided during the first 2 years of life to prevent the development of obesity.

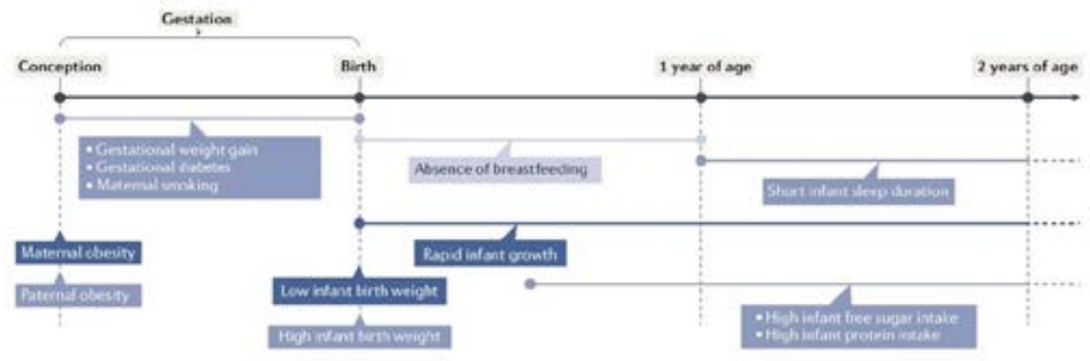
Sleep duration

There is evidence that short sleep duration in infancy is associated with an increased obesity risk. In the ALSPAC study children in the lowest two quarters of sleep duration (< 10.5 hours and 10.5-10.9 hours) were more likely to have obesity at age of 7 years than children in the highest quarter (> 12 hours; $\chi 2$ test for linear trend 17.8) (7). Halal et al. investigated in 4231 children the association between short sleep duration at any time between 1 and 4 years of age and the prevalence of overweight/obesity at the age of 4 years. They observed that among short sleepers, the prevalence ratio for overweight/obesity after adjusting for maternal and children's characteristics was 1.32 (1.03; 1.70) (71). Taveras et al. studied prospectively the effect chronic sleep curtailment from infancy to school age in 1046 children (72). They not only observed that children with the lowest sleep score had higher odds of obesity (OR 2.62; 95% CI 0.99, 6.97) at the age of 7 years but they also had a higher overall and central adiposity in mid-childhood (72). In a recent study in a sample of 1- to 3-year old children sleep duration was positively associated with moderate to vigorous intensity physical activity (β = 0.038±0.015, p = .019) and inversely associated with body fat percentage (β = -0.119±0.033, p = .003) (73). Taken together, these data suggest that sleep may be an important variable in efforts to promote healthy weight and body composition.

Conclusions

Compelling evidence from numerous studies, systematic reviews and meta-analyses show that prenatal, natal and postnatal factors influence the development of childhood obesity (Fig. 1). Important prenatal parameters are parental weight at conception and maternal weight gain during pregnancy. Gestational diabetes mellitus, maternal smoking, use of antibiotics, environmental obesogens and even maternal psychosocial stress contribute to the risk of offspring obesity. Natal parameters are the type of delivery and birth weight. Postnatally nutritional factors, rapid infant growth and sleep duration play an important role. Healthcare professionals should promote normal weight at childbearing age and normal weight gain during pregnancy. Postnatally, infant growth should be carefully monitored to detect early excessive weight gain. Obesity preventive measures should be initiated before conception, during pregnancy and during early childhood.

Figure 1. Relevant prenatal and postnatal factors contributing to child obesity. The risk of obesity in childhood is modulated by early nutrition and environmental factors. Environmental factors include parental obesity at conception, as well as gestational weight gain and gestational diabetes, whereas nutritional factors include the absence of breastfeeding during the first year of life and high infant protein intake. Dark blue boxes correspond to the factors having the strongest scientific evidence. Adapted by permission from Springer Nature; Nat Rev Endocrinol. From conception to infancy – early risk factors for childhood obesity, Larqué E, Labayen I, Flodmark C-E, Lissau I, Czernin S, Moreno LA, 2019.



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A heavy question: how do we approach children with overweight or obesity in 2020?

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Abstract

Childhood overweight and childhood obesity are major public health problems as they increase the risk of developing metabolic problems like diabetes but also cancer, heart diseases, not only in adulthood, but some also in childhood. Next to these somatic problems, they also cause psychosocial effects, such as anxiety, depression, sleep disorders and decrease the social relationships and academic achievements of these children.

As such any health care worker who encounters a child with either overweight or obesity, should also include this observation into the clinical approach in order to prevent the possible morbidity and mortality associated with these conditions. We provide 'best practice guidelines' for paediatricians who encounter these situations in their daily practice.

Although prevalence of childhood overweight and obesity in Belgium does not show the alarming trends as in the US, preventive efforts that start in early childhood and continue during the lifespan are important. But despite the fact that Belgium performs better than average concerning prevalence of overweight and obesity, our youth has high rates of body dissatisfaction. This is an important caveat for health care workers who deal with children and adolescents. A balanced communication about a topic as sensitive as weight and eating behaviour, is a key aspect of prevention and treatment, as body dissatisfaction and dieting issues play a central role in the development and maintenance of obesity.

INTRODUCTION AND QUESTIONS

A paediatrician will often encounter children with weight problems in daily practice. Sometimes weight gain, overweight or obesity will be the main reason for consultation, but often the weight problem is a 'secondary' finding as the child consults for other medical issues. And when a physician surveys the literature about this topic, the majority of studies, reviews and editorials concern the increase of obesity in the paediatric population, cardiovascular risk factors in relation to metabolic syndrome and the very short-lived effects of most major weight reduction trials. Many of these aspects can instil a less than optimistic attitude towards overweight and obesity in anyone who is confronted with the problem in a medical context.

Personally, I questioned some of my own practices after a recent clinical encounter with an overweight child and the questions of an inquisitive junior doctor about my handling of this 'co-morbidity' (or secondary finding). As part of my literature search, I consulted the guidelines of the CLB (the Flemish Pupil Guidance Centre) and frowned when looking at the suggested approach to this problem in their flow chart (Figure 1, Panel A). It states that when a CLB physician or nurse encounters a child with overweight during a medical check-up, she/he first has to consult previous weight measurements and if there is no recent increase in the weight of the child, she/he should 'confirm the normality'. This oddly phrased advice suggested to me that the frontline physicians in the preventative medical care of our youth would allow a child to continue life with overweight, and possibly progress towards obesity with minimal 'alarm'.

This led me to phrase three questions about this topic.

Question 1: what are the medical consequences of childhood overweight? Do these children progress towards obesity without a structured intervention? Do they have an increased cardiovascular risk later in life?

Question 2: What is the best (evidence based) approach to a child with overweight? Should you have a firm talk with the child? Explain the medical consequences to the parents? Send them immediately to a dietician?

Question 3: What are the data about childhood overweight and obesity in Belgium? Do we anticipate a 'tsunami' of children with obesity in 10 years' time? Are we turning into another USA in this context? How worried do we have to be?

In this paper we aim to provide an answer to these questions based on the available current literature and the expertise of the professional organizations that take care of these children in Flanders.

ANSWER 1: the medical and psychosocial consequences of overweight and obesity in childhood

The international Obesity Taskforce (IOTF) classifies overweight and obesity in childhood using centiles corresponding to a BMI (body mass index) of 25 and 30 kg/m2 at age 18 years (1). When you look at the literature about childhood overweight and obesity, it is very difficult to separate both entities. It is almost impossible to find prospective data or studies that focus on overweight apart from obesity. In most publications they are grouped together.

It is however clear that the probability that children with obesity will have obesity in adulthood is 5 times greater than their non-obese peers (2). This would suggest that obesity persists during life and that the BMI curve either follows the same trajectory or rises, but rarely decreases (3). Besides the health risks tied to overweight or obesity in adulthood, overweight and obesity have immediate detrimental effects on numerous organ systems already during childhood (4). As a consequence of this, childhood obesity is associated with increased healthcare utilization (5).

Endocrine system

The overall prevalence of metabolic problems in the paediatric population is climbing (6). More specifically, there is a positive correlation between BMI and the prevalence of metabolic problems in children (3,6). Having overweight or obesity in early childhood also predicts an increased risk of suffering from metabolic syndrome in adulthood (7). Diabetes, impaired insulin sensitivity and glucose intolerance are common among children with obesity (8,9). Obesity puts girls at risk for early puberty, a higher BMI is associated with earlier onset of menarche (10,11).

Cardiovascular system

Established cardiovascular disease risk factors such as dyslipidaemia, insulin resistance, or diabetes and hypertension are more common in children with overweight or obesity (9). Moreover, obesity correlates positively with serum triglycerides, low density lipoprotein cholesterol and insulin levels, but it correlates negatively with serum high density lipoprotein cholesterol levels (12). Interestingly, the elevated risk disappears when the child grows into a non-obese adult, highlighting the importance of intervention at an early age (13). In contrast, children who had obesity since early childhood have higher cardiovascular and metabolic risks than children whose BMI increased later in life (3). Other factors that contribute to cardiovascular disease, like arterial stiffness and carotid intima-media thickness, are also increased in children with obesity (3).

Respiratory

BMI z-score has an inverse linear relationship with respiratory function (14). Overweight and obesity are strong risk factors for childhood asthma, while it complicates management as well (15). Additionally, obesity puts children at risk for obstructive sleep apnoea. Compared to normal-weight peers, the probability to develop this condition is 4 to 5 times greater (16). Cardiorespiratory fitness decreases with increased adiposity (9).

Other systems

Obesity is strongly associated with non-alcoholic fatty liver disease (NAFLD) in children (4).

Children with overweight suffer more from fractures and are more likely to encounter complications during the healing phase. Additionally, they are more prone to malalignment of the lower limbs and experience more musculoskeletal discomfort and reduced mobility (17).

Psychosocial

Both children and adolescents with obesity reported lower quality of life and lower self-esteem, including body dissatisfaction, compared to healthy weight peers (18). On top of this, obesity puts children and adolescents at risk for major depressive disorder. Clinical depression seems more prevalent in children and adolescents with overweight and obesity (19).

Experiences of stigmatization play an important role in this: they are more often ostracized or bullied by their peers, teachers have lower academic expectations, and family members are more likely to make comments about their weight or food choices (20). Eating pathology can be a part of the weight problem, e.g. when negative emotions are regulated through eating behaviour, or when weight loss attempts get out of hand (21).

Therefore, medical and psychological health risks are taken into account in the Edmonton Obesity Staging System for Pediatrics (EOSS-P), which introduces several aspects of health in the assessment of childhood overweight. It also defines barriers for a positive prognosis, such as difficult socioeconomic circumstances or mental health problems in the family. More intensive or specialized treatment is indicated at a higher stage of the EOSS-P (22).

ANSWER 2: how to approach childhood overweight and obesity in an evidence-based manner.

Paediatricians and other health care practitioners encounter a dilemma: on the one hand, they feel urged to promote weight loss, to decrease the negative health effects of excess weight during childhood and prevent the weight problem to continue in adulthood. On the other hand, they are aware of the harmful effects of body dissatisfaction and low self-esteem, and do not want to incite these feelings in children.

Indeed, an unbalanced focus on weight loss can be counterproductive. First, dietary restraint can disrupt the metabolism and homeostatic regulation of appetite, promoting weight gain in the long run. Second, it takes resources to restrain oneself from eating, and these resources tend to be depleted in a context of emotional stress or fatigue. This can be followed by loss of control and binge eating. Third, the causes of overweight and weight gain are multifaceted and complex. We want to address the determinants of the problem, not the biomarker. Fourth, a focus on weight loss communicates that weight is malleable and controllable, with enough will power, and overweight is a 'bad' thing. It ignores the fact that changes in lifestyle do not necessarily translate in weight loss, even when overall health is improved by this lifestyle. Thus, overweight can reflect a past state of malnutrition, and families with overweight can have a healthy lifestyle. This is in stark contrast with the common view in society that associates overweight with poor lifestyle choices (23).

When health care practitioners advise how to decrease caloric intake and increase exercise, without enquiring about the current lifestyle or the psychosocial factors that impact lifestyle choices, they unintentionally fall into the trap of stigmatisation. What is the alternative? Basically, a shift from focussing on weight (loss) to focussing on health (improvement) in every communication and using techniques that stem from motivational interviewing and related theories (24–26). Furthermore, a focus on caloric restriction is replaced by diet quality, embedded in healthy lifestyle in a broad sense: eating behaviour, exercise, sleep, stress regulation/relaxation and investing in more several domains of self-worth (academic, relational, recreational…). A decrease in overweight is not a goal in itself, but a possible consequence of healthy lifestyle (change). The benefit of this approach is that it is:

a. more effective in the long run, as lifestyle changes can more easily be maintained than dieting behaviours and do not cause weight cycling
b. more motivating, as health and fitness improve even in the absence of weight change, and there is a broader range of parameters that can mark improvement
c. destigmatising and inclusive for all patients, as normal weight does not guarantee healthy lifestyle or the absence of health risks,
d. protective against a broad range of health problems, including eating and weight problems, this way reinforcing the preventive role of child health care

How does this translate to the paediatrician's daily practice? First, it is important to start with a broader inquiry about the child's well-being. Next, you can ask whether the child is curious about their growth, before you communicate weight and height as part of your routine clinical conversation. It is important to show the evolution of weight and height, not just the child's BMI at one point in time. This way, the conversation about weight is framed within a normal concept of growth and development. This is called a "normalizing approach", which was referred to in the introduction. Further, it is possible to identify sudden increases or declines, which are always a topic for further inquiry, either for medical reasons or because they mark a change in eating and /or exercise behaviour. And these changes warrant screening for eating disorders. Thus, a normalizing approach by no means implies ignoring the possible impact of childhood overweight and allowing the child to progress towards childhood obesity. This is also the approach adopted by health care practitioners at the pupil guidance centres (CLB/CPMS). We have to take into account that the relationship between health care practitioners and pupils at a pupil guidance centre does not originate from a child or parent's request for clinical care as in the physician office, it is part of the regulatory health care follow-up within the Belgian educational system. This approach strengthens the relationship between the young patient (and their caregivers) and the health care provider, which lays the foundation to discuss future health concerns. It also responds to a basic need in human being to feel accepted by and connected with others, which supports motivation. In Figure 1 Panel B one can find the adjusted flow chart, where the confusing 'normality' approach has been replaced with one that focuses on a healthy lifestyle.

To create a non-judgmental and weight-friendly environment, it is helpful to pay attention to language (person-first language, e.g. a child with overweight; avoid terms with a negative connotation such as 'fat') and to possible triggers for guilt or shame in the environment. Those triggers include fashion

magazines that promote the thin ideal and fad diets. Chairs without armrests are more comfortable for people with overweight or obesity, and examination equipment and scales should be appropriate for a range in body sizes (20,26).

Last but not least, the reasons to consult a health care practitioner in children with overweight or obesity can be equally varied as in children without overweight. A possible pitfall in a consultation with a patient with overweight, is to automatically attribute health complaints to weight or lifestyle. Keeping an open mind in every patient is maybe the core advice against stigmatisation and to protect child physical and mental health (20).

ANSWER 3: the epidemiology of childhood overweight and obesity in Belgium

Alarming messages of an obesity epidemic in the United States, where obesity rates in children and adolescents are as high as 18.5%, are not transferrable to Belgium (27). The Belgium Health Interview Survey, conducted every four years, monitors weight status among other parameters of public health (28). The most recent data gathered in 2018, based on self- or parent-reported weight and height, show that on a national level, 19.0% of children between 2 and 17 years old have a weight status above the normal range for their age and gender. One in three of them (5.8%) classify as obesity (see Table 1). Although since 1997, the prevalence in Flanders and Wallonia have been fairly stable, there is a rise in the Brussels capital region. Furthermore, lower parental education, as an indicator of lower socioeconomic background, is a clear risk factor for childhood obesity.

Recently, the Flemish government published detailed information on the BMI of children between 2 and 14 years old, based on weight and height measurement gathered by preventative health care services (Kind & Gezin, CLB), between 2011 and 2016 during routine health consultations (29). At any age, at least 78% of children in the Flemish Community have a normal weight status. Overweight and obesity increase with age, and at age 14, one in five children have a BMI above the normal range for their gender and age: 17% categorizes as 'overweight', and 4% as 'obesity'. These data necessitate the health care services to support the normal development of eating and healthy weight at an early age. Overall, these data show no general increase in childhood overweight over time, in this 5-year timeframe. More data will be added in the subsequent years, to adequately monitor the evolution of childhood overweight in Flanders.

How do these rates of childhood obesity compare with other countries? The Health Behaviour in School-aged Children Study (HBSC), a collaborative cross-national study from the WHO in Europe and Canada (30) shows that

a. Belgium performs better than average compared with other participating countries concerning several dietary health parameters, such as daily consumption of fruits and vegetables;

b. Belgium performs better than average concerning prevalence of overweight and obesity;

c. Despite these moderate levels of overweight and obesity, Belgium has high rates of body dissatisfaction.

This supports the importance of a 'do not harm' approach in obesity prevention, with careful communication about weight and dieting practices, and a focus on healthy lifestyle.

Table 1. Prevalence of childhood overweight and obesity in Belgium.

	Belgium	Flanders	Wallonia	Brussels capital region
Weight status above normal range	19.0%	16.2%	20.6%	27.3%
Overweight	13.2%	11.6%	14.6%	16.8%
Obesity	5.8%	4.6%	6.0%	10.5%

Source: Health Interview Survey, Belgium, 2018 (28).

CONCLUSION

It is clear that childhood overweight holds significant risk for children's health and socioemotional wellbeing and deserves attention from policy makers and early intervention from child healthcare practitioners. Although prevalence of childhood overweight and obesity in Belgium does not show the alarming trends as in the US, preventive efforts that start in early childhood and continue during the lifespan are important, with specific attention towards groups at risk. Communication about a topic as sensitive as weight and eating behaviour, is a key aspect of prevention and treatment, as body dissatisfaction and dieting issues play a central role in the development and maintenance of obesity. Furthermore, body dissatisfaction in Belgian youth is high. Strategies that moved away from a focus on weight loss and towards a focus on health improvement are fundamental in a childhood obesity approach that avoids causing harm on other aspects of children's wellbeing. In Belgium, efforts have been made to include health improvement in every aspect of children's life, including the school environment and child health care services. This allows building a supportive relationship with health care practitioners from an early age on, where questions and concerns about eating behaviour and weight are framed within a normal concept of growth and development.

Insert 1. The 5 A's of obesity management (Adapted from the Canadian Obesity Network: https://obesitycanada.ca/5as-pediatriques/)

The 5 A's of obesity management (25), which were adapted for a paediatric population by the Canadian Obesity Network, can help in building our weight-related conversation and assessment:

1. **Ask** for permission to discuss weight. This is as straightforward as "would it be OK if we discussed your (child's) weight?" Enquire in a non-judgemental way about experiences and efforts already made. Don't assume the child or their family have an unhealthy lifestyle.
2. **Assess:** do not only asses weight (the evolution of the child's BMI for age), but also causes, health risks and barriers on the several domains of health: physical health (including metabolic and musculoskeletal aspects), mental health, and socioeconomic factors. The EOSS-P can be a useful tool in this.
3. **Advise** on the benefits of healthy lifestyle with a focus on improvement of health risks in the short and long term, instead of aggressive weight loss practices promoted by the diet industry. This means a step-by-step approach, in which every step must be feasible at this time point and sustainable in the long run, preferably at a family-level. Treatment options in the area, to support these changes and to treat underlying causes or risks, can be discussed.
4. **Agree** on a realistic treatment goal (improvement in certain health risks or symptoms; stabilizing or slowing down weight gain) and on a plan to achieve health improvement. Depending on the risk profile and the cause, the child health care practitioner and the family can already agree on one or two small feasible steps that the family can implement in their current lifestyle. To optimize motivation, this step is based on the efforts already made by the family and the family can choose between multiple possibilities.
5. **Assist** in identifying and tackling barriers (e.g. accessibility of recreational activities) and in getting support from other health care services, such as dietary and/or psychological counselling, or referral to a paediatric multidisciplinary team.

Insert 2. Useful resources (in Dutch)

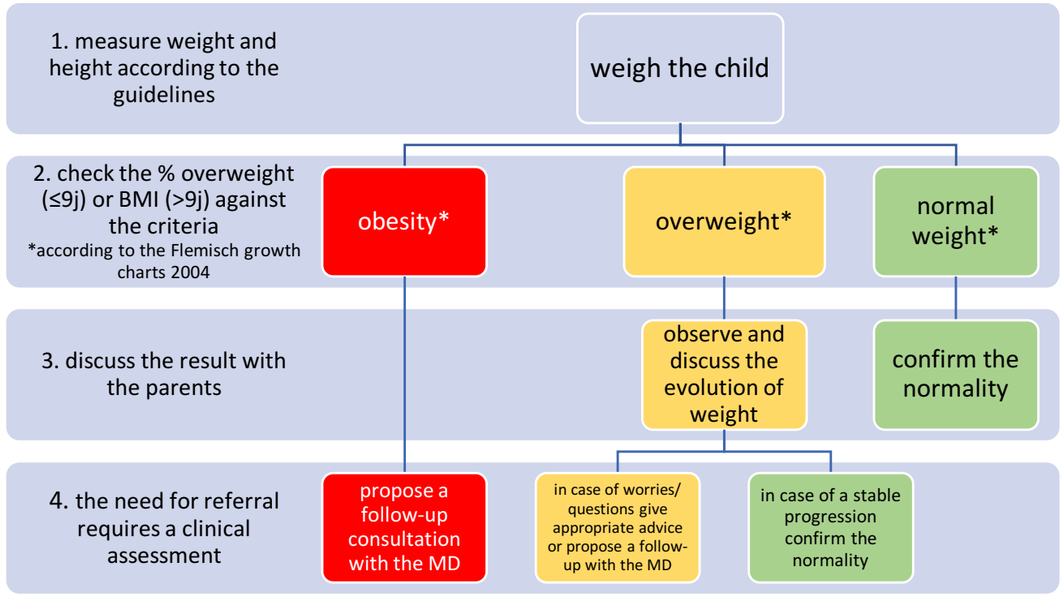
TVWVJ – Standaard gewicht: monitoring weight at school. See https://www.vwvj.be/gewicht

Eetexpert – draaiboek CLB: includes useful handouts to support the conversation about weight during routine check-ups. See http://www.draaiboeken.eetexpert.be/clb-draaiboek-2018 ("overzicht fiches")

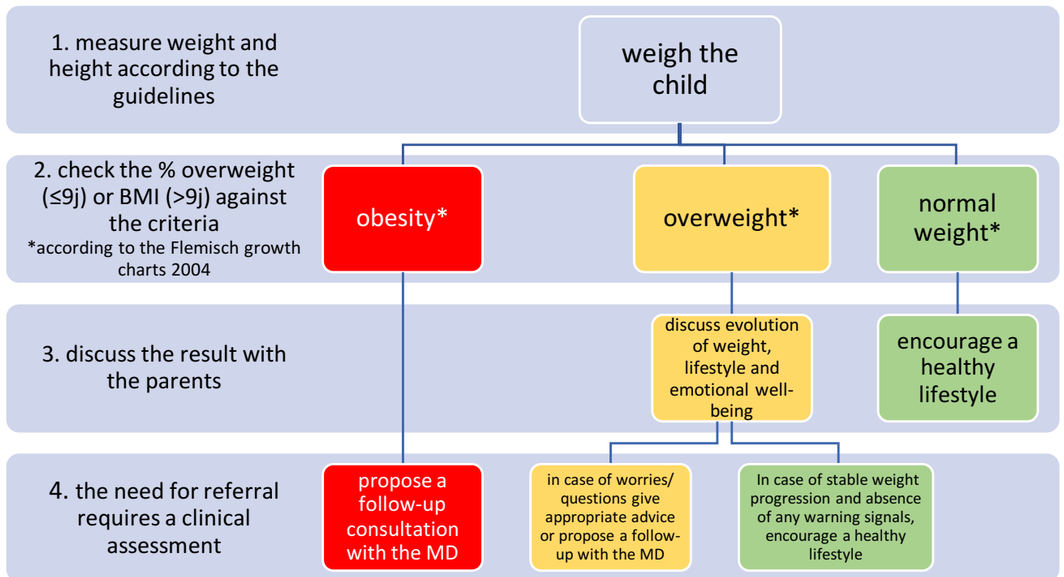
Eetexpert – INNOVATE: waiver with a brief practice guide on how to approach childhood overweight in primary care. See https://eetexpert.be/wp-content/uploads/2020/05/Fiche_innovate_eerstelijn.pdf

Figure 1. flow chart of the CLB for toddlers with normal weight, overweight and obesity, original version (Panel A) and revised version (Panel B)

A. ORIGINAL CLB FLOWCHART



B. REVISED CLB FLOWCHART



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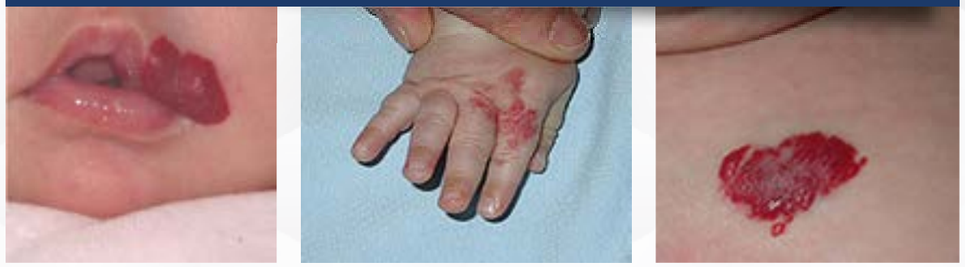

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Interdisciplinary overweight outpatient management in pediatrics

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Keywords

pediatric, obesity, interdisciplinarity

Abstract

Childhood obesity is a major health concern around the world and requires a multidisciplinary approach with medical evaluation, diet evaluation, physical activity and sedentarity evaluation and psychologist evaluation. However, this management is challenging and shows limited success.

It is therefore essential to include parents or the larger family structure in the interventions programs, to consider the impact on the quality of life, to manage the manner in which overweight children perceive their own weight and to fight against weight stigma.

In this article, we present the interdisciplinary overweight outpatient management set up in our overweight patient's clinic, based on an approach from a health-centered rather than a weight-centered perspective.

Introduction

Childhood obesity represents a major concern worldwide (1). Its management is a challenge for all teams in charge of this population including children and their family. Such interventions have shown only limited success (2). The management involves a medical and genetic evaluation in order to identify causes and complications of this disease (3). However, this affection results from multifactorial obesogenic factors (4). Clinicians must consider the short term risk of physical and psychological complications and the long term risk for the patient to remain adults with obesity with lifestyle-related morbidity and mortality (5). Most studies and guidelines recommend to focus treatment on physical activity (PA), diet and behavioral change to promote a decrease in body mass index (BMI) (3,6-10). It also seems important that the first step is to understand the pathway leading to obesity and the family involvement in physical activity and dietary behaviors (11).This management needs to adapt strategies and take the patient age into account since advice will be different from toddlers to teenagers. The team will need to know the key reasons for parents and children/teenagers to come to the overweight clinic and participate to an intervention program avoiding the risk of attrition (12-14). So the management of overweight patients requires a multidisciplinary approach with diet evaluation, physical activity and sedentary behavior evaluation and psychological evaluation. In children and at the beginning of puberty, BMI may decrease with maintaining weight as linear growth proceeds and lifestyle modification may reduce fat mass, increase lean mass and improve cardiovascular fitness. However, most intervention programs have been found ineffective (3,15). This may be due to targeting children only without involving parents or the larger family structure, or to focusing only on weight reduction. Such programs do not take into account the improvement in quality of life (3,15). Programs also often fail to address overweight children perception of their own weight (3). Weight stigma is an additional phenomenon that can affect youth with overweight and lead to harmful behavioral and psychological effects with a decrease in their overall quality of life. Sources of stigma may come from peers, family, educators and media as well as healthcare professionals (16). The term "obesity" is an emotionally charged word for most children and adolescents and it would be preferable to use the term "overweight" in clinical practice (7).

Overweight, physical activity and sedentary behavior

Children who are overweight often lack motivation in sports in general. They often suffer rejection by their peers due to the lack of skills or pain (17). However, exercise is a safe activity in children/teenagers and recommendations include at least 60 minutes per day of moderate to vigorous intensity physical activity (MVPA) with an emphasis on aerobic types of exercises (walking, bicycling, swimming, etc) as well as strengthening exercises at least 3 days a week (18). For children less than 5 years old, at least 180 minutes of any physical activity at any intensity throughout the day is recommended (19). Physical activity is any bodily movement produced by contraction of skeletal muscles that results in energy expenditure above resting levels. Moderate exercise allows talking but not singing and vigorous exercise makes it impossible to sing and difficult to talk. In exercise physiology terms, expended energy (EE) should correspond to at least 3 metabolic equivalents tasks (MET) with a MET representing EE for a subject at rest, sitting. Physical fitness is the ability to carry out daily tasks with vigor and alertness without inducing fatigue and with ample energy to enjoy leisure-time and unforeseen circumstances. Sedentary behavior is defined as any waking behaviors characterized by an energy expenditure (EE) equal or lower than 1.5 MET.

Meta-analysis of randomized trials, suggest that exercise intervention for adolescents with overweight or obesity improves body composition, particularly by lowering body fat with moderate improvements in HOMA-IR (homeostatic model assessment for insulin resistance) and systolic blood pressure but these late findings should be interpreted with caution since methodological heterogeneity is high (20). It has also been suggested that aerobic exercise and combined aerobic exercise and strength training are associated with reduction in BMI z-score in overweight children and adolescents with improvement of adiposity outcomes such as fat mass and percent body fat. However, the overlapping 95% prediction intervals across treatments suggests that some participants would benefit while others would not (21). Exercise is also important for overall physiological health. In addition to improving metabolic profile in children, exercise has been linked to improvement in cognitive function, concentration and self-confidence as well as better socialization (3 22).

Intervention strategies also need to target sedentary behaviors. TV watching for more than 1 hour per day in young children has been associated with a high consumption of fast foods, sweets, chips and pizza and lower consumption of fruits and vegetables (23).

In our overweight outpatient clinic, we aim at helping children and their families to gradually and safely increase physical activity (favoring activities such as swiss ball, swimming, bicycle and walking) and limit sedentary behavior. Physical activity is not limited to sport, it is important to adapt it to everyone's abilities, needs and desire so that children acquire a taste for it and feel comfortable in practicing. Daily physical activity should be as varied as possible and reach 60 minutes every day. That can be obtained by accumulating short durations over the day: walking or biking to school or getting off the bus one stop earlier, gardening, walking up the stairs, going shopping on foot, walking the dog, playing outside. The pleasure of practicing is the condition for sustainability of the commitment to an active life style.

In summary, physical activity and reduction of sedentary behavior can achieve and maintain weight loss, but with better result in combination with nutritional advice (3,6,8).

Overweight and nutritional advice

Eating behavior is under the control of the homeostatic or metabolic system (hormonal signals) and hedonic system (external sensory information processing, reward processing, cognition and executive function). The integration of those central and peripheral signals depends on individual genetic/epigenetic predispositions (24). Food marketing targets children/adolescent via a variety of media and food products most commonly advertised are candy, snacks, cereal and soft drinks which are obesogenic (11,25). In our society, hedonic food intake has taken an important position explained by the rewarding properties of food (4). Likewise, many children are exposed to food as a reward for "good" behavior, strengthening the hedonic system. In European adolescents, emotion-driven impulsiveness is related to the type of snacking (sweet and fatty) and not to the energy intake of the food itself (26).

So assessment begins with an understanding of the child and family's dietary pattern before any modifications are proposed. The family needs to learn to define snack periods rather than something used to combat 'boredom" and identify emotional hunger. Parents and children will learn the mechanisms of food preference and dislike. Repeated exposure to a variety of food and flavor facilitates a varied diet (27).

Diet needs to be adapted to meet specific needs at each period of growth. Counseling and recommendations must be made within the context of the family 's culture, living environment and socioeconomic status (13).

So the main goal is to encourage healthy eating behavior using food pyramid, food plate, food energy density, the importance of macro and micronutrients, nutritional composition of food and drink, control of portion size, strategies for eating out, preparation of healthy food and feeding frequency. Advice will need to be personalized. Family meals appear to play an important role in promoting positive dietary intake among children. Nutritional education will focus on fruit and vegetable intake, healthy snacks, reducing intake of sugar-sweetened beverages and/or fat and portions sizes.

In our overweight outpatient clinic, the dietician, based on what the family has explained, will try to target dietary errors and guide the patient and his family toward more appropriate choices. This is always discussed with the young and his family to hope that the proposals will be better accepted and maintained over time. Each case is unique, but all children and adolescents will be informed of the goals to be achieved on the basis of the food pyramid during these consultations. Nothing is forbidden, but some food is often consumed in excess by young people (sugary drinks, sweets, meat ...) and others in insufficient quantities (water, vegetables, fruits ...). It is useful to evaluate their current knowledge and what can be improved. Regular follow-up is offered to them to discuss what has been put in place at home, but also about the possible difficulties encountered in order to help them maintain their efforts in changing eating habit.

Overweight, psychological past and support

Self-esteem and body image are lower in children and adolescents with obesity compared with healthy weight peers (28). A recent meta-analysis shows that pediatric obesity treatment with both dietary and physical activity components improves self-esteem and body image in the short and medium term (28). Improvement in weight-related outcome appears important to achieve improvement in weight-loss but not self-esteem. However, a very interesting paper has recently proposed a self-regulation failure hypothesis based on a dual process model perspective. According to this model, underlying mechanisms of impulsivity in childhood obesity explain that the weight lost during treatment is often regained subsequently. Thus in order to obtain better long term results, it is important to support the child with a regular psychological follow-up.

Overweight should be considered as a consequence, a symptom of a complex history of life events, familial interaction or socio-cultural backgrounds. More than a simple nutritional or behavioral rehabilitation, the psychologist in our overweight outpatient clinic works on management of some risk factors such as relation with peers, the question of the body and self-image, emotional experience,… Thus, psychological consultation is a space for development and introspection, to explore and use resources, to consider the food problem as a symptom.

Overweight and parental support

Parents play a critical role in helping children to become well-adjusted adults (23). Parents can influence their children's dietary practices, physical activity, sedentary habits and body satisfaction by controlling availability and accessibility to foods, meal structure, food socialization practices and food-related parenting style.

However, some studies show that 48% of the parents incorrectly classify their child's weight and underestimate their child's weight status (29). Thus, it is essential for prevention and treatment that health care professionals help parents at high risk of misperception to correctly evaluate their child's weight status.

For example, the availability of soft drinks during meals and negative parental role modeling are important predictors for intake of sweet and fat foods in children from European country (30). Our obesogenic environment idealizes thinness and stigmatizes fatness, but paradoxically encourages excessive food intake, sedentary time and reduced physical activity (23). Therefore, parents should understand the interplay between genetic, environmental, and familial influences in disease expression.

Family-based interventions emphasizing reasonable and coordinated goals for both parents and children and incorporating positive reinforcement and tools to facilitate behavior change and increase problem solving capabilities appear most likely to succeed.

Conclusion

Interdisciplinary outpatient overweight management has been described in the literature for several years even though the results in terms of weight loss are not always satisfactory. Although there is still no clear treatment strategy, it is important that the team develops interpersonal skills needed to work with children and parents and influence their behavior.

Effective interventions for prevention and treatment of weight-related problems should be approached using a health-centered rather than a weight-centered perspective. The management of overweight patients requires a regular multidisciplinary approach with diet evaluation, physical activity and sedentary behavior evaluation and psychologist evaluation. It is also essential to take the socio-family environment into account to improve long-term results.

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Inpatient treatment of children and adolescents with severe obesity

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Keywords

obesity, children, comorbidities, treatment, rehabilitation

Abstract

The Zeepreventorium is a residential rehabilitation center where children and adolescents with severe obesity are being treated. All patients have several medical comorbidities, the most frequent ones being exercise induced dyspnea (95%), insulin resistance (87%), debilitating musculoskeletal pains (74%), hypertension (65%), obstructive sleep apnea (62%), dyslipidemia (55%), non-alcoholic fatty liver disease (42%). In addition, the majority also have emotional psychopathology, behavioral problems and school problems. The 3 main pillars of the treatment program are working towards healthy nutritional habits, a normal level of physical activity and psychological well-being. The treatment is offered in a warm, patient and family friendly, supportive environment. Motivational therapy and working towards positive self-determination are key to obtain short term and also long term results. In these young people, the program not only leads to weight loss but also to resolution of nearly all medical comorbidities as well as to a more positive self-image. A closer link with the home environment and a seamless transition between the tertiary residential care and the ambulatory secondary care level would be beneficial to consolidate the benefits of a residential stay.

Introduction

Although numerous actions and interventions have been developed to support children and families in adopting a healthier lifestyle, and as such prevent severe obesity, the number of youngsters with overweight is increasing. In Belgium 19 % of children and adolescents (2-17 year) are overweight and 5,8 % of them suffer from obesity (1).

Most children and adolescents with obesity continue to be overweight into adulthood and are at risk of life shortening complications like type 2 diabetes, vascular and coronary diseases, or present comorbidities like e.g. urinary incontinence and mental health problems (2-4) .

The Edmonton Obesity Staging System for Pediatrics proposes a clinical staging system for children with obesity (5). The tertiary care level is described as a multidisciplinary paediatric clinic for comprehensive assessments which may include subspecialty care to manage comorbidities, provision of intensive family-centred counselling and lifestyle/behavioural intervention. In Belgium two such residential clinics exist: Zeepreventorium in De Haan and Clairs Vallons in Ottignies.

Patient population

Since 1995, Zeepreventorium De Haan has a rehabilitation program for children and adolescents with severe obesity and their family and larger context. In July 2019 The Belgian Health System revised the admission criteria in a new convention. Since the new convention, children and adolescents with severe obesity can be referred to the tertiary level rehabilitation centre Zeepreventorium De Haan under the following conditions :

- Severe obesity: Body Mass Index (BMI) above cut off value as defined by the International Obesity Task Force IOTF (6)
- Presence of at least 2 comorbidities such as insulin resistance (according to Homeostatic Model Assessment HOMA), disabling musculoskeletal pain, obstructive sleep apnea (OSA); hypertension (blood pressure above P95 for age, sex and height); exertional dyspnoea; non-alcoholic fatty liver disease (NAFLD); dyslipidaemia; urinary incontinence, polycystic ovary syndrome (PCOS); gastroesophageal reflux disease (GERD)
- Treatment in the outpatient setting has failed

Rehabilitation needs of children with obesity

The Word Health Organization (WHO) describes rehabilitation as a fundamental health service for people with a wide range of health conditions, throughout all stages of life, and in a continuum of care from acute over sub-acute to long-term care. Rehabilitation addresses the impact of a health condition on the person's life by focusing primarily on improving his/her level of functioning and by reducing his/her experience of disability. Rehabilitation focuses on the functioning of an individual and not on his disease. It does so through a strong emphasis on educating and empowering people to manage their health condition, to help them adapt to their situation and remain as independent and active as possible. By doing this, rehabilitation enables better participation in education, employment and community life, with far-reaching health, social and economic benefits (7). For the population with obesity admitted to Zeepreventorium De Haan, this definition is translated into working towards the following goals :

- Improved adherence to therapy
- Improved physical condition
- Restoration of the psychosocial imbalance
- Support to the context in raising the chronical ill child or youngster
- Reduction of school problems

To qualify for admission to the obesity program, needs in at least 3 of these domains have to be present. The Belgian health care insurance recognises that the lower socio economic context (SES), in which children and adolescents with obesity often live, can also be considered an important parameter (8). SES influences both the food choices and the activity level of families (9). Integrating children and adolescents with obesity from a poor SES background in an inpatient facility offers them a better start upon returning to their family environment.

Treatment ingredients

Already in 1998 the WHO concluded that interventions for children and adolescents with severe obesity should include a physical activity program, dietary measures and psychological treatment (10). The medical paediatric rehabilitation centre Zeepreventorium offers an inpatient treatment program with these 3 components. On admission and during the stay, the exact treatment plan is individualised to meet the specifics needs of each patient. In addition, the necessary attention goes to improving the patients' medical condition, more particularly addressing all his/her comorbidities.

The evidence-based programme consists of 3 treatment phases: admission and observation, intermediate phase and consolidation phase (11). To achieve the individualised treatment goals and given the young age of the population in Zeepreventorium, considerable time is devoted to include the family and the larger context in the treatment process.

Over the years and in collaboration with different Belgian universities the program has evolved based on new insights following research, on as well as off site. One of the most recent changes is the introduction of a brain game to train the working memory of children and adolescents to help them to resist the 'immediate gratification' of unhealthy food but rather achieve long-term life style changes.

Motivational theory as an overarching framework

The decision to apply for an admission to an in-patient rehabilitation programme doesn't happen overnight. Children, adolescents and their family often have considered and re-considered it, weighing the benefits and the drawbacks. Although upon referral they are asked why an admission is important to them, what motivates them and what they'd like to achieve, during admission motivation can fluctuate. To help patients and families achieve the results they desire, it is important that each team member has a framework from which they can understand that motivation is variable, multi-faceted and open to change within a relational context. The self-determination theory of Deci and Ryan and motivational interviewing offer such a framework (12,13). Although both theories define motivation as a psychological drive, they accentuate how it is influenced by the relational context. As such they offer the multidisciplinary team, regardless of their discipline, tools to motivate their young patients to persevere. The theories are evidence based and widely applied within the context of health care and health promotion (14).

The inpatient context at the Zeepreventorium

Children and youngsters, aged 5 to 18 years, live together in groups of 10, according to their age and developmental possibilities. The group context is a warm and safe basis, offering learning possibilities, routine and support guided by trained group leaders. Taking children and adolescents out of their original context helps them break with old routines and integrate new and healthy habits. The group offers a safe environment to try out, practice, adjust if necessary and consolidate the skills learned during individual and group therapeutic sessions. Thanks to the interdisciplinary collaboration, adjustments can continuously be made following the observations in the group.

The group also offers social support. As many children and adolescents with obesity have low self-esteem due to being bullied before admission, the group is the ideal context to (re-)discover their competences, strengths and weaknesses in relation to peers.

Medical comorbidities in children and adolescents with obesity

In table 1 we present an overview of medical comorbidities linked to obesity and how since 2019 these are screened for during the residential stay. In table 2 we list the comorbidities in order of frequency in year 2020 as encountered in patients treated at the Zeepreventorium. Over the years, the proportion of children with comorbidities as well as their mean BMI have risen, in part due to the strict admission criteria and in part because we no longer only rely on what is stated on referral but rather actively assess the presence of comorbidities. In 2017, insulin resistance was reported in almost half of the cohort; musculoskeletal pain, OSA, hypertension and exertional dyspnea in around a third; NAFLD, dyslipidemia and urinary incontinence in a quarter to a fifth of the cohort. In 2020 when actively searching for these comorbidities, the prevalence of specific comorbidities has doubled or even tripled.

Throughout the residential stay, routine physical examination is done 3 monthly or more often depending on the patient's comorbidities and complaints. In addition, the nurses are in daily contact with the patients and monitor specific comorbidities like hypertension and musculoskeletal pains.

When laboratory tests reveal abnormal on initial screening, these tests are repeated 3 months later, or earlier if deemed necessary. Before discharge,

Table 1 Common comorbidities of obesity and how these are diagnosed/screened for at the Zeepreventorium, always in addition to history and physical exam. See also Styne DM et al. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;1021:709-57 (25)

Comorbidity	Values to diagnose or cut-off values to suspect a specific comorbidity	Source
(Pre) hypertension	- 1- 18 years: standardized according to sex, age and height percentile BP > 90th percentile to < 95th percentile: prehypertension BP ≥ 95th percentile to < 99th percentile + 5 mm Hg: stage 1 HTN BP ≥ 99th percentile + 5 mm Hg: stage 2 HTN - ≥ 18 years: BP ≥ 120/80 to 139/89 mm Hg = prehypertension BP ≥ 140/90 to 159/99 mm Hg = stage 1 HTN BP ≥ 160/100 to 179/109 mm Hg = stage 2 HTN BP > 180/110 mm Hg = stage 3 HTN	Expert Panel Summary Report; Mancia et al., 2013 (26)
Metabolic Inflammation	Hs-CRP (mg/l): > 5.0 Uric Acid (mg/dl): - Boys: > 7 - Girls: > 5.7	
Non Alcoholic Fatty Liver Disease	ALT (U/l): - Boys: ≥ 41 - Girls: ≥ 33 AST (U/L): - Boys: ≥ 40 - Girls: ≥ 32	
Dyslipidemia	Triglycerides (mg/dl): ≥ 150 Total Cholesterol (mg/dl): ≥ 230 HDL-Cholesterol (mg/dl): - Boys: < 40 - Girls: < 45 LDL- Cholesterol (mg/dl): ≥ 135	European Atherosclerosis Society 2/ Lipid Club FH consensus
(Pre)Diabetes	Fasting plasma glucose: - ≥ 100 mg/dl but < 126 mg/dl: impaired fasting glucose - ≥ 126 mg/dl: diabetes	American Diabetes Association (27)
	Homeostatic Model Assessment of Insulin Resistance Fasting HOMA-IR= fasting serum glucose*fasting serum insulin/22.5 - 7-8.9 y: boys > 1.76, girls > 1.39 - 9-10.9 y: boys > 1.97, girls > 2.62 - 11-12.9 y: boys > 2.65, girls > 3.02 - 13-14.9 y: boys > 3.21, girls > 3.46 - 15-17.9 y: boys > 2.39, girls > 2.89	Carlos Alberto Nogueira-de-Almeda, 2017 (28)
	Oral Glucose Tolerance Test is performed when - fasting glucose > 100 mg/dl, at any time after admission - HOMA IR ≥ cut-off towards end of admission Two-hour glucose: - ≥ 140 but < 200 mg/dl: impaired glucose tolerance - ≥ 200 mg/dl: diabetes	American Diabetes Association (27)
Polycystic Ovary Syndrome	Physical exam: acnea, hirsutism Total testosterone (ng/dl): < 7y: > 10 7-9y: > 15 > 10y: > 9-55 Sex Hormone Binding Globulin to calculate free testosterone level	Legro et al., 2013 (29)
Exercise intolerance/ Exercise induced dyspnea	Spirometry > 14y: ECG and Ergo-spirometry Parameters abnormal for age and sex	
Obstructive Sleep Apnea	> 10y: using Apnealink® - Obstructive Apnea Hypopnea Index > 2 - Oxygen Desaturation Index > 2	
Nocturna or diurnal enuresis	Uroflowmetry	

the tests as listed in table 1 are repeated, as is the measurement of percent body fat. Spirometry and sleep study are only repeated if abnormal initially.

The success of an intensive inpatient treatment for children and adolescents with obesity has been clearly documented (15). Also at the Zeepreventorium we observe that the standardised life style intervention program as described in detail below not only results in a decrease in BMI but also in normalisation of many of the comorbidities. We educate patients that by losing weight and gaining health now, they lower the risk of life shortening complications during adulthood.

Almost all patients suffer from exercise induced dyspnoea. Before admission many patients are not physically active and on starting to exercise they experience dyspnoea, mainly due to deconditioning. At times spirometry tests show obstructive lung disease and undiagnosed asthma is uncovered. When treated appropriately, this leads to a marked increase in physical activity. On admission quite a few children are being treated with metformin because of insulin resistance, but many of them can be withdrawn from medication towards discharge. Musculoskeletal complaints are the consequence of having to carry excess weight and improve after weight loss. Common complaints are lower back pain (either vertebral facet joint or muscular pain), painful knees (with increased risk of patellar luxation and/or injury to the meniscus), ankle instability and increased risk of ankle distortion. Musculoskeletal complaints usually improve during weight loss and improved physical fitness. Occasionally an individualised treatment for specific orthopaedic problems is started e.g. quadriceps exercises to prevent patellar luxation. Pedes plani and genua valga are frequently noticed and arch supports may be needed. Hypertension is a comorbidity that commonly normalizes during weight loss and antihypertensive treatment is rarely needed. OSA is also frequently diagnosed but only in a minority further treatment will eventually be indicated. Apart from liver function disorder and dyslipidaemia, slight elevations of TSH (thyroid stimulating hormone) and DHEAS (dehydroepiandrosterone sulphate), or a decreased level of testosterone in boys are measured in obese patients. Most of the time all these values normalise when weight loss has been accomplished. In refractory cases, further testing may be required and/or patients may need referral to a paediatric endocrinologist. Gastroesophageal reflux disease is more common in people with obesity and there is increased risk of erosive esophagitis, Barrett's disease and in the long run oesophageal adenocarcinoma. Children or adolescents with obesity and a history of urinary incontinence undergo uroflowmetry and are treated by a dedicated physiotherapist. Therefore, also this comorbidity is often resolved at discharge.

Table 2 : Occurrence of comorbidities in children and adolescents residing at the Zeepreventorium De Haan

	2006 (n=139)	2016 (n=147)	2017 (n= 289)	2020 (n=95)
BMI mean	34,5	38,0	37,2	37,4
Exertional dyspnoea	23,0 %	24,7 %	31,1 %	94,7%
Insulin resistance	6,0 %	57,3 %	48,2 %	87,4%
Musculoskeletal pain	2,0 %	20,0%	38,2 %	74,5%
Hypertension	7,0 %	26,0 %	31,4 %	65,3%
Obstructive Sleep Apnea		28,7 %	36,6 %	61,6%
Dyslipidemia	No data	37,3 %	23,9 %	54,7%
Non Alcoholic Fatty Liver Disease	No data	24 %	20,0 %	41,9%
Gastroesophageal Reflux Disease	1,4 %	2,7 %	No data	31,5%
Polycystic Ovary Syndrome	No data	8,7 %	7,1 %	27,1%
Urinary incontinence	4,3 %	16,0 %	18,0 %	12,6%

Teaching to become physically active

During their stay children progressively increase their level of physical activity, following the guidelines of the 'Vlaams Instituut Gezond Leven'. The patients are offered an individualized and monitored exercise program of 3 hours a week, in small groups and guided by the physiotherapist. The aim is to improve the physical fitness so that the children's or adolescents' ability to participate in daily activities, sports and occupation is increased. The program consist of aerobic exercise, resistance training and improving motor skills. All exercises are adapted depending on the patient's age and his physical activity level. Throughout the program, the focus is on education. We teach the children and adolescents a correct and healthy way to build up their physical fitness and activity level towards long term success. Furthermore, each patient has a monthly individual counselling session with the physiotherapist to evaluate the weekends at home, the activities in the group and any orthopaedic discomfort they may experience. We offer them advice on how to change their behaviour at home and during leisure time to meet the physical activity guidelines. Alongside the monitored and guided exercise program, the children and adolescents are offered many group activities, group games and supervised team sports. We aim for participation during at least 1 hour a day. This gives the children and adolescents the chance to practice and implement the things they have learned.

In children with obesity, stretching exercises by the physiotherapist can also be part of the inpatient therapy. Sometimes, the physiotherapists uncover a Developmental Coordination Disorder (DCD) in children with inadequate movement and if needed these are referred to a paediatric neurologist (16).

The dietary program

The basic dietary objective is to acquire healthy as well as regular eating habits. The diet is not based on strict caloric calculations and restrictions because the basal metabolic rate and the physical activity level differ considerably between individuals. Instead of prescribing a specific number of calories, the dietician defines minimum and maximum portions for every meal. These portions are based on the Flemish Nutrition Pyramid and are adjusted for age and gender (table 3). The daily energy and nutrient intake must contain all necessary components as prescribed by the Superior Health Council of Belgium and the Flanders Institute for Healthy Living (17,18). Ten % of total energy-intake (En%) consists of proteins, 50-55 En% of carbohydrates (with <10 En% of mono and disaccharides) and 30-35 En% of fat (with <10 En% of saturated fatty acids and attention to adequate intake of mono and poly unsaturated fatty acids).

At each meal, the children and adolescents decide for themselves whether they take the minimum or the maximum portion. If requested, caloric calculations can be done. During the treatment programme, the individual diet is adjusted according to the evolution of weight, height and the level of activity. The children and adolescents take 6 meals a day: 3 main meals (breakfast, lunch and dinner of which 2 cold meals and 1 hot meal) and 3 snacks consisting of one piece of fruit (10 am, 16 pm, 20 pm). Once a week they have the option to choose a biscuit instead of fruit. After every lunch one dairy product is given as dessert (yoghurt or pudding). On top of this and if they wish so, children and adolescents are allowed a high calorie snack twice a week and/or a can of low sugar soda three times a week. Children and adolescents are encouraged to drink water throughout the day.

Twice a week children and adolescents are weighed; these results are discussed during individual sessions. During each stay at home, children and adolescents are asked to document their caloric intake (by photographing a meal or noting its content) so that these can be discussed with the dietician at least every two weeks,. Any evolution is encouraged. If difficulties were encountered, the dietician challenges the children and adolescents to find creative solutions.

Cooking lessons and educational sessions help to prepare children and adolescents to reintegrate into their home environment. To maintain the motivation of children and adolescents to continue healthy eating habits despite the obesogenic environment in which they live, the dieticians have to be very creative and build in the motivational techniques based on Deci and Ryan as explained above (12).

Table 3 Minimum and maximum portions for healthy nutritional intake according to age and sex

BREAKFAST	- Basic: 2 slices of bread + minarine + savoury topping of the day - Supplement with: 1-2 slices of bread + minarine + savoury topping of SWEET spread (1x/2days also Fat spread is possible) - Milk: 1-2 glasses (age 8-13: girls and boys 2 glasses/ age 14-18: girls 1 glass/boys 2 glasses) - If desired: 1 cup of coffee or tea without sweetener - 1x/week possibility of cereals instead of/or in combination with bread. - 1x/week possibility of milk + cacao - Total quantity of bread: min. 2 slices and max. 4 slices of bread (boys age 14-18 max. 6 slices)
MID MORNING SNACK	- Fruit - Water
LUNCH	Healthy plate: - Soup - 1 piece of meat/fish (guideline: 120g) - 1/4 plate of potatoes (guideline age 13-18: 150g girls and 200g boys) or rice/pasta (guideline age 13-18: 150g girls and 200g boys)/(guideline age 8-12: 150g boys and girls) - 1/2 plate of vegetables (guideline: 200-250g) - 1 spoon of sauce - Dairy product - Water
AFTERNOON SNACK	- Fruit and/or yoghurt - Water
DINNER	- Basic: 2 slices of bread + minarine + savoury topping of the day - Supplement with: 1-2 slices of bread + minarine + savoury topping - Vegetables + 1 tablespoon of dressing - Milk: 1-2 glasses (age 8-13: girls and boys 2 glasses/ age 14-18: girls 1 glass/boys 2 glasses) - If desired: 1 cup of coffee of tea without sweetener - Total quantity of bread: min. 2 slices and max. 4 slices of bread (boys age 14-18 max. 6 slices)
EVENING SNACK	- Fruit and/or yoghurt - Water
EXTRA	- 1x/week moment of choice (afternoon or evening snack) - 2x/week can of light soda (33cl) (light-soda > 5 kcal/100ml).

Psychological evaluation and interventions

Understandably, children and adolescents with obesity admitted to the tertiary care level have problems other than just controlling their eating behaviour. Being overweight has a strong correlation with psychological and psychiatric comorbidities such as depression, emotional and behavioural disorders etc. (19).

On admission children and adolescents are evaluated thoroughly by history and by the following screening instruments for eating disorder, quality of life and general psychopathology; social relations and their influence on eating pathology are also plotted.

- Youth Self Report (YSR) Verhulst F., van der Ende J., Koot H., Sophia Kinderziekenhuis, Rotterdam, 2001; a child-report measure that assesses problem behaviours along two broadband scales: internalizing and externalizing
- Eating Disorder Questionnaire (EDE-Q) originally Fairburn & Cooper (1993) ; assesses eating disorders
- Pediatric Quality of Life Inventory Version 4.0 Generic Core Scales (Peds QL 4.0); measures health related quality of life

An analysis of 309 files of children and adolescents suffering from severe obesity and residing at the Zeepreventorium in 2017, uncovered that 86 % of them had at least one emotional psychopathology (depression, anxiety, …), 68 % had a behavioural problem and 69 % had a problem at school (table 4). Given these numbers and often the combination of problems, the psychological interventions are tailored-made. Interventions are conducted individually as well in group sessions following a dual pathway model. On the one hand therapists help children and adolescents to find the necessary tools to develop the competences to control their eating behaviour. On the other hand, based on the observed psychological comorbidities, therapists create an environment where counselling can help to untangle and address these comorbidities.

In addressing the eating behaviour, the treatment is mainly cognitive behavioural based, as put forward in the work of Braet et al (20). The main components of the behavioural life style program are: self-monitoring, stimulating control techniques, coping and problem solving techniques. Children and adolescents are being challenged and encouraged to practise the new competences in the security of their own group and to extend this gradually to more difficult contexts. Given the obesogenic environment in which we live, the influence of friends, school and media also needs to be assessed. We aim to enhance awareness of their eating behaviour and to reinforce their capacity to change their life style. All interventions aim to support the self-regulation of the patient and his/her capacity to resist temptation resulting in long-term healthy life style changes. Deficits in executive functioning are being trained by teaching children and adolescents how to delay gratification in favour of long term lifestyle goals (21,22). Emotional eating is being countered by practising coping skills (23).

To address the emotional psychopathology, therapists include additional individual sessions according to the needs of the patient. These vary in content and intensity depending on the screening test results or the observations in the group and family environment.

Table 4. Occurrence of psychopathology in children and adolescents residing at the Zeepreventorium De Haan in 2017

N= 309	Assessed by	
Bonding problems	Experiences in Close Relationships Scale (ECR- R (Brennan et al., 1998)	60 %
Autism spectrum disorder	History	7 %
Attention Deficit and/or Hyperactivity Disorder	History	11 %
Emotional psychopathology	-Gedragsvragenlijst voor kinderen van 6 tot 18 jaar (CBCL/6-18; Achenbach & Edelbrock, 1983; vertaald door Verhulst, Koot, Akkerhuis & Veerman, 1990) -Zelf in te Vullen Vragenlijst voor 11 tot 18 jarigen (YSR; Achenbach & Edelbrock, 1983; vertaald door Verhulst, Koot, Akkerhuis & Veerman, 1990) - Children Depression Inventory (CDI; Kovacs 1992 vertaald door Timbremont, Braet & Roelofs, 2008) -De Competentie Belevingsschaal voor adolescenten (CBSA; Harter, 1985; vertaald door Veerman, Straathof, Treffers, Van den Bergh & Brink, 1997)	86 %
Behavioural problems	-Gedragsvragenlijst voor kinderen van 6 tot 18 jaar (CBCL/6-18; Achenbach & Edelbrock, 1983; vertaald door Verhulst, Koot, Akkerhuis & Veerman, 1990) -Zelf in te Vullen Vragenlijst voor 11 tot 18 jarigen (YSR; Achenbach & Edelbrock, 1983; vertaald door Verhulst, Koot, Akkerhuis & Veerman, 1990) -Vragenlijst voor emotieregulatie bij kinderen en jongeren (FEEL-KJ; Braet, Cracco, Theuwis, Grob & Smolenski, 2013) -Executieve Functies gedragsvragenlijst (BRIEF ; Nederlandse bewerking van de Amerikaanse Behavior Rating Inventory of Executive Function (BRIEF) van Gioia, Isquith, Guy en Kenworthy)	68 %
School problems	History of - School drop out - Special education - Learning disabilities	69 %
Parental stress	Nijmeegse Ouderlijke Stress Index (PSI; Parenting Stress Index (1983) Abidin vertaald door de Brock et al., 1992)	63 %

School

School plays a central role in the life of children and adolescents. Sadly, more than half of the children with obesity report unpleasant experiences related to their school trajectory: being bullied or excluded, difficulty participating in physical education or sports, learning difficulties, behavioural problems or insufficient social skills to properly network with peers. The consequences are: shame, anger, skipping classes, poor grades or eventually total school refusal. Consequently, during the stay at the Zeepreventorium the needed attention goes towards the school curriculum. We stimulate children with school related problems to take a fresh start, to catch up or to orient themselves towards a more suitable trajectory. The safe context of being amongst children with similar experiences helps them to regain trust in their peers, to grow in self-confidence and to start building their future. For the latter, successfully finishing the school curriculum and obtaining a diploma or certification is an important milestone.

Parental involvement

Children and adolescents admitted to an inpatient obesity treatment program must re-integrate in the home environment as quickly as possible. To make sure the learned competences are transferred to the home environment, patients return home each weekend. These weekends are prepared by the multidisciplinary team and evaluated afterwards with the patient and his or her care givers. Care givers are also invited to participate in psychoeducation in small groups to enhance a healthy life style at home and to practice new parenting skills. Care givers generally enjoy these group moments that allow them to share their difficulties and progress with other care givers. The goal is to install a supportive environment in which the healthy life style is adopted by as many family members as possible.

Addressing parenting skills is important because research shows that parents of children with obesity are more likely to lack confidence in their parenting skills and to use more permissive and coercive discipline techniques in comparison with parents of a healthy weight children (24).

The same internal study, mentioned above, confirmed these findings: for 69 % of the children and adolescents with obesity (N= 289) parents mentioned difficulties in the education of their child. It is important to take into account that some parents don't have the (immediate) strength to create a supportive and positive environment. If during the rehabilitation process of a child or adolescent it becomes clear that care givers or the family need additional or a different kind of support than what the centre can offer, they are supported in contacting other services that can address their needs.

Follow up

Although referral to outpatient treatment in the neighbourhood of the residence is the first option, the Belgian health care insurance allows a maximum 3 year follow up after discharge. Seventy % of the patients use this option in the first year after discharge. These moments are organised in individual and group sessions and resume the basic principles of the inpatient rehabilitation period: physical activity, dietary support and psychological treatment. The main goals of these sessions are to support the children or adolescents and their environment to continue the healthy life style. If during these sessions the need for referral to outpatient treatment is detected an adapted trajectory is set up. After one year, we observe a drop out from this follow up program; the long distance to the inpatient facility is the most frequent reason. The use of modern multimedia for follow up are not yet supported by the Belgian health care system, but the Covid-19 pandemic revealed this is an interesting and time efficient option. A denser network of secondary ambulatory care could help to build a seamless transition between the tertiary residential care and the ambulatory secondary care level. This would be beneficial to optimally consolidate the benefits of a residential stay.

Conclusion

A residential stay can support children and adolescents with severe obesity to lose weight, to acquire healthier eating habits, to experience the importance and joy of physical activity and to overcome psychological problems like shame, fear, anger, low self-esteem. The contact with youngsters with a similar problem helps them to accept their disease and to find the motivation to adopt a new lifestyle. Involving the parents in the treatment is a must because obesity is usually a problem of the whole family with a strong genetic as well as social behavioural basis.

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Physical determinants of weight loss during a residential rehabilitation program for adolescents with obesity

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Keywords

Obesity, adolescent, cardiorespiratory fitness, weight loss

Abstract

Background and Objectives:
Comprehensive obesity management programs emphasizing appropriate nutrition, exercise and behavioral modification generally yield positive results, but with a large variability in outcome. This retrospective cohort study evaluates a possible correlation between physical determinants at baseline and weight loss at completion of our residential rehabilitation program.

Methods:
Patient records for 27 boys and 37 girls aged 14-18 years who finished the 1-year program were selected from available data. Body mass index, body composition and cardiorespiratory fitness (as VO2peak in ml/min per kg lean body mass) at baseline were used to investigate a possible correlation with age-, sex- and height-corrected weight loss (change in body mass index standard deviation score (BMIz).

Results:
Both baseline BMIz (boys R=0,459; girls R= 0,432) and baseline VO2peak (boys R=-0,418; girls R=-0,579) are significantly correlated with the change in BMIz. When patients are divided into two groups according to baseline BMIz above or below 3 standard deviations (SD), the change in BMIz is smaller for those with BMIz > 3SD (boys: 0,29SD with p=0,116 ; girls: 0,39SD with p=0,001). Comparing groups according to physical fitness at baseline, the change in BMIz is significantly smaller for those with below average fitness (boys: 0,42SD with p=0,021 ; girls: 0,36SD with p<0,001).

Conclusions:
Less obese and fitter adolescents lose more weight than their heavier and more deconditioned peers during a one-year residential obesity treatment program, advocating early intervention in treating adolescent obesity.

Introduction

Prevalence of obesity keeps increasing globally and in all age groups, with 23,8% (95%CI 22,9-24,7) of boys and 22,6% (95%CI 21,7-23,6) of girls with overweight or obesity in 2013 (1). These children/adolescents carry a significantly increased risk for adult obesity, multiple obesity-related comorbidities (including hypertension, dyslipidemia, insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease and psychosocial complications), increased healthcare costs as well as cardiovascular death (1-7). Therefore, establishing a comprehensive management program that emphasizes on appropriate nutrition, exercise and behavioral modification is crucial (1, 8, 9). These interventions are often managed on an outpatient basis, but can effectively be implemented in an inpatient multidisciplinary program (10-12). At our pediatric rehabilitation center Zeepreventorium (De Haan, Belgium) we already published positive results regarding weight loss measured by Body Mass Index (BMI) or BMI standard deviation scores (BMIz) using this approach, but find that there are large differences in effectiveness of the intervention within this obese population (10, 13, 14). Therefore this retrospective cohort study aims to evaluate a possible correlation between physical determinants at baseline and weight loss at completion of the 1-year multidisciplinary diet- and exercise-based residential rehabilitation program. This would allow to identify subgroups at baseline that might benefit from a more tailored approach.

Material and Methods

1. **Study subjects**
Subjects were selected from available data of adolescents aged 14-18 years that participated in and finished the 1-year weight loss program offered at Zeepreventorium (De Haan, Belgium) in the years 2015-2017. Only children up to 18 years and with a BMI above the 97th percentile (z-score > 1,88) are admitted to the program.

2. **Measurements**
2.1 Anthropometrics
Stature was measured to the nearest 0,1cm using a stadiometer (Holtain Ltd, Crymmych, Pembs, UK). Body mass was measured to the nearest 0,1kg using a digital scale (Seca GmbH & Co KG, Hamburg, Germany). BMI was then calculated.
Standard deviation scores according to Flemish growth charts (Vrije Universiteit Brussel, 2004) were used to correct for differences in sex, age and height. Body composition, more specifically fat and lean body mass, were measured with dual-energy X-ray absorptiometry (DXA) using a Lunar Prodigy Advance full size (GE Healthcare, Diegem, Belgium).

2.2 Physical fitness
Symptom limited cardio-pulmonary exercise was performed on a cyclometer with an Ergocard (Medisoft Belgium, Sorinnes, Belgium). Peak oxygen uptake (VO2peak) was determined as the mean value of VO2-measurements during the final 50 seconds of exercise and expressed in ml/min per kilogram lean body mass (kgLBM). Starting workload (30 or 50 Watt) was increased with 20 or 25 Watt respectively every 2 minutes until exhaustion (13). Standardized 12-minute running/walking test (or Coopertest) was performed in all subjects as measure for running capacity. Swim test was comprised of a similar exercise measuring the maximal swimming distance within a 12-minute timeframe.

3. **Treatment**
In-patient treatment included dietary restriction, physical activity and psychological support under medical supervision as described in a previous publication (14). Dietary restrictions consist of scheduled meals, in group, adding up to 1500-1800kcal daily, depending on sex and age group. The increased physical activity consists of physical education at school, supervised training sessions and daily playful activities promoting an active lifestyle. Weekly sessions with a psychologist focus on lifestyle change, coping mechanisms and self-confidence.

4. **Statistics**
All statistical analysis was performed with SPSS 22 software (IBM, Armonk, USA). Most data are presented as 'mean (SD)' unless stated otherwise. Normality testing was performed with Shapiro-Wilk test of normality. Comparison of groups was performed with Student's t or Mann-Whitney U tests, according to (non-)parametric nature of the variable. Correlations given are the result of Spearman correlation testing.

5. **Ethical approval**
All patients and their parents/legal guardians agreed to the anonymous scientific use of collected data before entering the program. No specific formal approval for this analysis from an ethical committee was obtained, because the readily available data was used anonymously as stated in the informed consent.

Results

1. **Population characteristics**
We evaluated baseline and post-intervention measures of body mass and body composition for 27 boys and 37 girls, aged 14 – 18 years. At baseline boys and girls differed significantly in height, total mass and body composition. When corrected for age, height and sex by using BMI standard deviation scores or z-scores (BMIz), both groups had comparable BMIz at baseline (table 1).

Table 1: Physical characteristics of the patient population presented as 'average (standard deviation)' and p-value for unpaired t-test.

TABLE 1 – Physical data	Boys (n=27)		Girls (n=37)		
	Mean	(SD)	Mean	(SD)	p-value
Age	15,48	(1,0)	15,95	(1,2)	0,123
Height	175,60	(8,2)	167,23	(6,5)	<0,001*
Baseline BMIz	2,90	(0,6)	2,87	(0,5)	0,644
Baseline TM(kg)	120,14	(25,5)	108,90	(23,0)	0,033*
Baseline Fat%	46,98	(4,7)	51,30	(3,4)	0,001*
Baseline LBM%	51,21	(4,4)	46,25	(3,1)	<0,001*
Baseline VO2peak (ml/min/kg LBM)	39,71	(7,8)	38,82	(7,9)	0,656
Baseline Coopertest (m)	1419	(295)	1243	(244)	<0,001*
Baseline Swimtest (m)	358	(74)	278	(73)	<0,001*
End BMIz	1,70	(0,9)	1,99	(0,7)	0,219
End TM(kg)	91,68	(18,8)	88,92	(21,6)	0,384
End Fat%	29,39	(8,8)	43,91	(6,5)	<0,001*
End LBM%	67,74	(8,2)	53,72	(6,2)	<0,001*
Difference in height (cm)	2,53	(1,58)	1,16	(1,01)	<0,001*
Difference in TM(kg)	- 28,45	(11,4)	-19,98	(6,3)	<0,001*
Difference in BMIz	-1,20	(0,5)	-0,87	(0,4)	<0,001*
Difference in fat mass(%)	-52,80	(12,7)	-31,50	(11,3)	<0,001*
Difference in LBM(%)	1,30	(9,1)	-5,80	(6,7)	0,001*
Days to -10% TM	57	(20)	75	(22)	0,001*
TM=total mass, LBM=lean body mass					* Significant at p<0,05

Regarding physical fitness assessed at baseline, boys performed better on 12-minute walk/run and swim tests, but when peak oxygen consumption was assessed relative to lean body mass to evaluate intrinsic cardiorespiratory capacity, girls at the start of the intervention seem to have comparable physical fitness (table 1).
After the intervention, average weight loss was around 28kg and 20kg for boys and girls respectively, resulting in a significant decrease in BMIz of 1,20±0,5 SD for boys and 0,87±0,4 SD for girls (table 1). The weight-loss program has a smaller effect on change in BMIz for girls than boys (p<0,001) and when we evaluate the time to loss of first 10% of total mass, boys lose weight significantly faster than girls as well (18 days; p=0,001)(table 1). Standard deviation increases for BMIz post-intervention compared to baseline BMIz in both boys and girls, indicating a greater spread in BMIz following variable weight loss (table. 1).

Effect of the intervention on body composition is difficult to measure, as a lot of changes such as total mass change, growth and body maturation occur. Change in fat mass (as % of baseline absolute fat mass) and difference in lean body mass (as % of baseline absolute lean mass) show that while both sexes lose significant amounts of fat mass, boys relatively lose more fat mass (boys -52,8%; girls -31,5%; p<0,001) and girls unfortunately also lose lean mass (boys +1,3%; girls -5,8%; p=0,001) (table 1).

2. **Correlations**
Since several body mass and body composition indices are significantly different for both sexes, we evaluated correlations in both groups separately.
Both BMIz and VO2peak at baseline are significantly correlated with the age-, sex- and height-corrected weight loss calculated as change in z-score (Table 2), correlation coefficients resp. 0,459 and -0,477 for boys; 0,432 and -0,572 for girls. Positive correlation between BMIz at baseline and change in BMIz points out that a heavier patient seems to lose less weight during the program. Fatness in itself did not correlate with outcome as difference in BMIz (table 2).
A negative correlation between VO2peak at baseline and the change in BMIz post-intervention identifies a lesser weight loss for patients starting with lower physical fitness. Similar correlations are found between physical fitness as VO2peak and changes in body composition (table 2). Only in boys, the result of a 12-min run/walk test correlates with the BMIz-outcome. A swim-test does not seem to provide information relevant to future weight loss (table 2).
Physical fitness as measured by VO2peak at baseline also correlates well with BMIz at that time, understating an interdependency of obesity and deconditioning (table 2)

3. **Subgroup analysis**

When patients are grouped according to physical fitness at baseline [above or below the average within this population measured by VO2peak (ml/min/kg LBM)], we notice a significant difference in BMIz-change of 0,42SD for boys and 0,36SD for girls (table 3). A similar analysis for subgroups according to BMIz at baseline (grouping below or above +3 SD) shows that in both sexes the heavier group has a smaller average reduction in z-score, but only for girls this difference reaches statistical significance (table 3).

Lowering the patients BMIz to ≤1,646 SD (= 95th percentile) proves to be more difficult starting from a BMIz >3 SD compared to those starting the program with a BMIz <3 SD (table 4). Odds ratios are 33 (95% CI ; 3,96 – 275,99) and 31,7 (95%CI ; 1,69 – 593,73) for boys and girls respectively. For girls, a similar effect is observed for the group with lower than average physical fitness (table 4).

Table 2: Correlations of physical characteristics with changes in BMIz or body composition

Variable	Correlations			
	Boys (n=27)		Girls (n=37)	
	Correlation coefficient	p-value	Correlation coefficient	p-value
Correlation with the difference in BMIz				
Age	-0,062	(0,758	0,170	0,314
Height	0,076	0,705	0,044	0,798
Baseline BMIz	0,459	0,016*	0,432	0,008*
Baseline Fat%	0,112	0,597	0,075	0,660
Baseline LBM%	-0,153	0,445	-0,030	0,861
Baseline VO2peak (ml/min/kg LBM)	-0,447	0,019*	-0,572	<0,001*
Baseline Coopertest (m)	-0,497	0,011*	-0,142	0,408
Baseline Swimtest (m)	-0,025	0,900	-0,281	0,093
Correlation with baseline VO2peak				
Baseline BMIz	-0,418	0,030*	-0,579	<0,001*
Difference in fat mass (%)	-0,341	0,081	-0,585	<0,001*
Difference in lean mass (%)	0,379	0,052	0,523	<0,001*

Baseline VO2peak (ml/min/kg LBM)

Table 3: Subgroup analysis of change in BMIz.

Subgroups according to above/below average VO2peak at baseline				
		≤ av. VO2peak	> av. VO2peak	M-W U test
Difference in BMIz	Boys	1,02 (0,46)	1,44 (0,46)	0,021*
	Girls	0,70 (0,34)	1,06 (0,31)	<0,001*
Subgroups according to BMIz above/below 3SD				
		≤ 3 SD	>3 SD	M-W U test
Difference in BMIz	Boys	1,35 (0,44)	1,06 (0,53)	0,116
	Girls	1,01 (0,37)	0,62(0,23)	0,001*

(M-W U test = Mann-Whitney U test)

Table 4: Odds table for reaching BMIz ≤1,646 for different subgroups..

			BMIz post-intervention			Fisher's exact
			≤1,646	>1,646		
Boys	BMIz at baseline	≤3	11	2	13	<0,001*
		>3	2	12	14	
			13	14	27	
	VO2peak (ml/min/kg LBM)	≤mean	5	10	15	0,128
		>mean	8	4	12	
			13	14	27	
Girls	BMIz at baseline	≤3	13	11	24	0,001*
		>3	0	13	13	
			13	24	37	
	VO2peak (ml/min/kg LBM)	≤mean	2	17	19	0,001*
		>mean	11	6	17	
			13	23	36	

Discussion

Our data understate that weight loss programs, even as standardized as in a year-long residential program, yield positive but quite variable results. Boys lose more weight than girls during this 1-year timeframe, but also within each sex category there is considerable variation in weight loss and change in BMI z-score. We aimed to assess the role of baseline physical characteristics, both by simple and more technical measures, in explaining this variation as a way of identifying those at risk of not reaching their target at the end of the program.

In the current literature we find similar attempts to predict treatment response. Braet identified a higher adjusted BMI and older age to be predictors of greater weight loss while Danielsson et al reported from their large cohort study that both female sex and higher BMIz (in this study ³3,5) were both predictive of smaller or even no decrease in BMIz after 1-3 years (15, 16) .

In our analysis, both BMIz and VO2peak at baseline correlate well with weight loss presented as a decrease in BMI standard deviation scores and body fat percentage, suggesting that less obese and fitter adolescents lose more weight than their heavier and more deconditioned peers.

This should alert treating physicians that patients fitting this profile have a high chance of needing a more intensive treatment. Of course this is an incomplete linear correlation due to several influential factors that were not addressed in this analysis (among which psychological well-being, socio-economic status and motivation). Odds ratios for not reaching the 95th percentile target are therefore wide but still strongly indicative of a high chance of still having obesity even after a one-year program once both boys and girls surpass a BMIz of 3 SD.

We used the 95th percentile for BMI (1,646SD) as definition for childhood obesity and thus as target for treatment. However, no final consensus has yet been reached in literature on defining pediatric obesity: the CDC uses the 95th (1,646SD), the WHO uses 2SD (or 97,7th percentile) while the IOTF recommends the 99th percentile (2,3SD) for defining childhood obesity (17-19). A similar issue arises for classifying obesity severity: where Kelly and Freedman use this 99th percentile as the threshold for 'severe obesity', Cole defines 99,8th percentile (2,93SD) as threshold (19-21). Since 57 of 64 patients in our cohort (or almost 90%) had a BMIz > 2,3SD, using this treshold would not allow for a reasonable comparison. For practical reasons we used 3SD (or 99,9th percentile), which roughly corresponds to the threshold for severe obesity in childhood defined by Cole et al (19).

Surely it is harder to reach the 95th BMI-percentile when starting with a much longer road ahead, but these findings also understate that an earlier intervention, before deconditioning and reaching +3SD, will yield better results in terms of decrease in BMIz as well as more success in reducing obesity numbers. Which of both, body mass or physical fitness, has more influence on outcome is difficult to address since linear regression could not be performed. As is also addressed in the Edmonton Obesity Staging System for Pediatrics (EOSS-P), a classification for pediatric obesity to determine health risks and determine weight management success, it should alert clinicians if their patients with overweight or obesity shows decreasing physical fitness and exercise capacity (identified as increasing dyspnea with physical activity or measured as lower VO2peak) to the same extent as increasing BMI or BMIz (22). The use of VO2peak (ml/min/kg LBM) is one of several new approaches to quantifying cardiorespiratory fitness in (overweight) adolescents (23, 24) but no reference values are yet available. In this study low VO2peak was defined as < 39 ml/min/kg LBM being the average in this cohort, but hopefully in the future we will have references for comparison.

As mentioned above, the groups that are constructed and the tresholds used in this analysis are somewhat arbitrary, but still suggestive of 'risk groups' that need to be identified and allow treating physicians to predict which patients will not lose weight as easily as others and thus need longer or different treatment and have a higher chance of remaining obese. Larger studies could possibly clarify which thresholds should warrant intensification of treatment to avoid progression to an obese state from which it is even more difficult to return. The need for characterizing such subgroups that may respond differently to treatment was recently stressed in the report of an NIH workshop (25), since at present no clear subgroups or thresholds have yet been identified.

As surrogate but easier to obtain markers of physical fitness, 12min walk/run- and swim-test did not correlate as well as VO2peak with the outcome of reduction in BMIz. This might be explained by the difficulty in running with excess (fat) mass or influence of swimming technique on the results. Therefor we advise to use VO2peak (ml/min/kg LBM) in assessing physical fitness in patients with (severe) obesity, especially in assessing the risk of a more difficult weight treatment.

Strengths and Limitations

This is a retrospective cohort study in a specific preselected patient population referred to an in-patient treatment program by their caretakers or physicians. Applicability is thus somewhat limited to this population, but still has important implications for referring physicians and for residential treatment programs. For this cohort, we did not have data on Tanner staging and evolution therein during the program, therefore we cannot adjust for body maturation and it's influences on physical parameters used. Since not all variables where parametric, the use of non-parametric testing was mandatory, instead of more robust parametric tests. Unfortunately we could not perform multiple linear regression due to the characteristics of the data available.

Conclusion

Adolescents of female gender and/or with low physical fitness and/or with a high BMIz are at higher risk of struggling to lose weight and still suffer from obesity even when participating in an intensive residential weight loss program. These findings highlight the importance of secondary prevention in overweight and less active adolescents, where early intervention is essential to achieve good results and to avoid more difficult treatment of their obesity in the future. If these heavier and deconditioned patients do start a residential program, their treatment should probably be intensified from the start to avoid a lag in weight loss and disappointing end results.

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Bariatric surgery in adolescents: information for the general pediatrician

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Keywords

Bariatric surgery, Adolescents, Morbid Obesity

Abstract

The prevalence of obesity in children and adolescents is increasing, and current prevention strategies are gravely failing, especially in adolescents with severe obesity. Conservative multidisciplinary approaches unfortunately do not have the desired long term results. Where bariatric surgery in adults is considered the 'golden standard' for obesity, in adolescents it is only proposed exceptionally. The differences between results in adults and adolescents after bariatric surgery are only recently being examined. The perioperative risks are very low, but not completely absent. And the postoperative comorbidities also need to be taken into consideration when the decision for surgery is taken. The long-term outcomes after bariatric surgery in adolescents are only just beginning to be known, but they seem promising.
Primary care physicians and general pediatricians play an important role in the complex management of morbid obesity, and in the preparation towards and the long term follow-up after bariatric surgery. With this article we want to give the pediatric profession a background on the challenges confronted in the management of obese adolescents and the indications for bariatric surgery in this patient group. The International and Belgian guidelines, the known published results after bariatric surgery in adolescents, and common barriers and challenges in the preparation and follow-up of will be discussed.

Introduction

The prevalence of obesity in children and adolescents has increased worldwide and in Belgium in the last decades (1). Current prevention strategies are failing, and conservative multidisciplinary approaches such as behavioral or pharmacological treatment do not have the desired long term results. In severe obesity, bariatric surgery has superior therapeutic outcomes with respect to weight loss and resolution of comorbid diseases over other existing treatments, and some professional societies support the use of bariatric surgery in obese adolescent patients (2-3). But surgical risks are still an issue and long-term outcomes after bariatric surgery in adolescents are only just beginning to be known. There is more heterogeneity of results in the adolescent population compared with adult patients, and it remains a challenge to identify the ideal young patient who will have the greatest benefit from surgical treatment for obesity (4).

Primary care physicians and general pediatricians play an important role in education patients and their parents regarding the benefits and risks of bariatric surgery, potential side effects, expected changes in nutritional needs and the lifelong requirement for regular medical follow-up.

In this article, we aim to provide information on bariatric surgery in adolescents for general pediatricians and family physicians, so they can be able to identify adolescents that need referral to a tertiary center and to aid in the multidisciplinary management of these patients. We offer some background information on bariatric surgery and the current international guidelines on bariatric surgery in adolescents. We describe the clinical pathway and preoperative evaluation protocol; the outcomes with respect to weight loss, comorbidity resolution, and complications on short and medium term; some of the challenges in the surgical management of adolescent obesity; and lastly the importance of the primary care physician in the education, preparation and long term postoperative follow-up of these patients.

A bit of history

Since the first publication of a jejuno-ileal bypass in adolescents in 1974 (5), metabolic and bariatric surgery has undergone a complete (r)evolution. Bariatric surgery has always been a part of the group of 'metabolic surgery'. In the 1990's the surgical treatment of morbid obesity had gained popularity, mostly because it was performed laparoscopically with few complications and very good results. The metabolic aspect was lost since bariatric surgery was considered a popular, fast and lazy solution for obesity.

In the meantime over 50 different surgical procedure for morbid obesity have been described (6). Surgeons experimented with different types of bowel constructions, lengths of bypassed bowel and different types of restrictive pouches or implanted devices. Since the early 2000's, there has been a shift again, and bariatric surgery is nowadays considered as one of the most effective metabolic surgical procedure in the treatment of type 2 diabetes mellitus (T2DM), hyperlipidemia and hypertension.

Bariatric surgery has systematically gained popularity in Belgium over the last decade with an increase from 7.500 bariatric patients in 2009 to up to more than 13.000 patients in 2016. The most performed type of surgery is the Roux-en-Y Gastric Bypass (RYGB: 8.402 in 2016), followed by the Sleeve Gastrectomy (SG: 4.648 in 2016) which is gaining popularity (figure 1) (1).

There are no known absolute numbers of adolescents undergoing bariatric surgery in Belgium, but in 2009-2011 there were 659 (146 males, 513 females) operations performed in the age category 18-19 years (1). These patients were in all probability candidates for surgery at an earlier age, but waited until they were 18 years old to have a reimbursement of the procedure. These patients were most likely treated as adults, and didn't get the more extensive work-up and guidance that they would've had as adolescents.

International and Belgian guidelines

Bariatric surgery is considered safe and effective in the treatment of obesity in adolescents, but despite the favorable results in the existing literature, there is a large variation of its utility worldwide. While numbers of adolescents with obesity undergoing bariatric surgery in the United States are increasing, surgeons in Europe seem more reluctant to perform this type of procedures

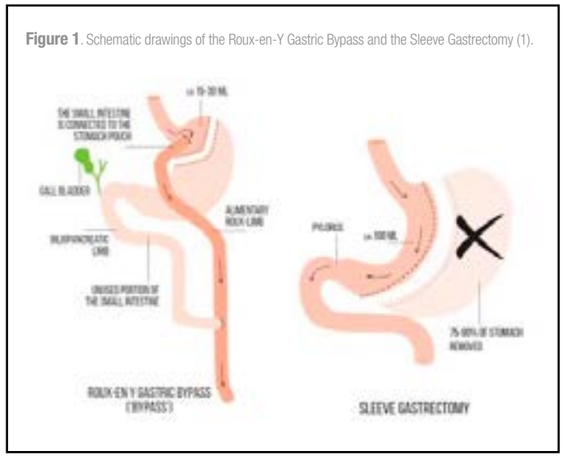

Figure 1. Schematic drawings of the Roux-en-Y Gastric Bypass and the Sleeve Gastrectomy (1).

in adolescents (2,7). Bariatric surgery is clearly not considered a first-line therapy for adolescent obesity and is supported only when non-surgical treatments have been unsuccessful in patients whose obesity is classified as severe, and whose health is already detrimentally affected by their obesity (2). The criteria should restrict the use of bariatric surgery to a limited group of adolescents, in whom the benefits appear to significantly outweigh the drawbacks.

Official guidelines for bariatric surgery exist already in many countries. For adults, the guidelines are generally agreed upon internationally if the patient has a body mass index (BMI) ≥40 kg/m², or ≥35 kg/m² in combination with a significant comorbidity that could be improved with weight loss (1). In the adolescent population, there are still many differences between countries, especially considering physiological maturity, BMI thresholds, and the clinical setting of the treatment. A synopsis of the published guidelines for bariatric surgery in adolescents can be found in table 1 (3, 8-15). The significant increase in data supporting the use of bariatric surgery in adolescents strengthens these guidelines from prior reports, but continuous adaptation is still necessary if new scientific evidence is published.

What with the Belgian rules and guidelines?

First and foremost we must get rid of the idea that bariatric surgery in adolescents is forbidden in Belgium, which is not the case. However, these operations are not reimbursed by the government up until the age of 18 years, which seems unfair in these changing times of obesity pandemic and increasing knowledge of the safety and effectiveness of these procedures in adolescents. In 2019 an official report by the Belgian Health Care Knowledge Centre was published and they concluded that weight loss and safety are comparable to the adult population in the short term. They did underline the fact that the evidence is primarily based on procedures conducted in specialized centers and in patients with a high BMI (ca. 39-59 kg/m²). They concluded that the decision to carry out the procedure should primarily be guided by the severity of the medical situation, rather than solely age, and should therefore remain exceptional (1). The BASO (Belgian Association for the Study of Obesity) also emphasizes this in their 2020 guidelines. The criteria for bariatric surgery in adolescents currently used at our institution can be found in table 2.

At the moment, there are no clear benefits for bariatric surgery in adolescents with eating disorders based on deteriorations in the satiety regulation such as melanocortin 4 receptor (MC4R) mutation or leptin resistance. There is no proof that their eating behavior is normalized after bariatric surgery, and these patients may experience a deterioration of their quality of life because of food restriction post-surgery (2).

In genetic causes of obesity, Prader-Willi syndrome (PWS) is considered the most common cause, with 40% overweight or obesity in children, and up to 82-98% in adults (16). Bardet-Biedl syndrome (BBS) is also known to be associated with central obesity and is characterized, as is PWS, by cognitive impairments and/

Table 1: INTERNATIONAL GUIDELINES of bariatric surgery in adolescents.

Country / association	Definition 'age limit'	BMI without comorbidities	BMI with comorbidities	Strength of recommendation, 'wording'
USA: ASMBS - 2018 (3)	10-19 years	≥40kg/m²	≥35 kg/m²	'Should be considered standard of care'
USA: ADA - 2020 (8)	'adolescent'	/	>35 kg/m² + T2DM (uncontrolled glycemia and/or serious comorbidities)	'considered' if uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention
USA: US Endocrine Society - 2017 (9)	≥ Tanner Stage 4 (final or near-final adult height)	≥40kg/m²	≥35kg/m²	Expert consensus
UK: NHS England - 2017 (10)	≥ Tanner Stage 4	≥40kg/m² (SD ≥3.0)	≥35kg/m² (SD ≥3.5)	'not generally recommended, may be considered in eligible individuals after MDT discussion'
FRANCE: HAS - 2016	≥ Tanner Stage 4 (bone age ≥ 13y in girls, ≥ 15y in boys)	≥40kg/m² (with major deterioration in quality of life)	≥35kg/m²	Pluridisciplinary treatment, in specialised obesity centers.
GERMANY - 2019	≥ Tanner Stage 4	≥50 kg/m²	≥35 kg/m²	Expert consensus
NL: NHG	<18 year	morbid obesity	morbid obesity	'only in research setting'
EASO - 2013 (11])	skeletal and developmental maturity	/	> 40 kg/m²	Expert consensus; 'in centres with extensive experience'; 'multidisciplinary approach'
ESPGHAN - 2015 (12, 13)	<18 year	≥50kg/m² + mild (AHT, dyslipidemia, mild OSAS, mild NASH, GERD, panniculitis...)	≥40kg/m² + severe (T2DM, OSAS, PC, advanced NASH)	'exceptional indications'
AAP - 2007 (14) BASO - 2020 (15)	physical (generally girls 13 y & boys 15y), emotional and cognitive maturity	≥50kg/m²	≥40kg/m²	Expert consensus; 'suggest'; in specialized pediatric weight management centers with comprehensive services, multidisciplinary

AAP: American Association of Pediatrics (14); ADA: American Diabetes Association (8); AHT: Arterial Hypertension; ASMBS: American Society for Metabolic and Bariatric Surgery (3); BASO: Belgian Association for the Study of Obesity (15); EASO: European Association for the Study of Obesity (11); ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition (12, 13); GERD: Gastro-Esophageal Reflux Disease; GERMANY: https://www.awmf.org/uploads/tx_szleitlinien/050-002l_S3_Therapie-Praevention-Adipositas-Kinder-Jugendliche_2019-11.pdf; HAS: Haute Authorité de Santé (https://www.has-sante.fr/portail/); MDT: Multidisciplinary; NASH: Non-Alcoholic Steatohepatitis; NICE: National Institute for Health and Care Excellence (10), NHG: Nederlands Huisartsen Genootschap (https://www.nhg.org/standaarden); NHS: https://www.england.nhs.uk/wp-content/uploads/2017/04/16053p-obesity-surgery-children-severe-complex-obesity.pdf; NL: the Netherlands; OSAS: Obstructive Sleep Apnoea Syndrome; PC: Pseudotumor Cerebri; SD: standard deviation; T2DM: Type 2 Diabetes Mellitus; UK: United Kingdom (https://www.nice.org.uk/guidance/qs127); US Endocrine Society (9)
The Tanner score (ranging from 1 to 5) refers to the physical development of children and adolescents.

Table 2: Adolescent bariatric surgery eligibility criteria [Queen Fabiola Children's University Hospital].

Candidates for adolescent bariatric surgery	1. BMI >35 kg/m2 with T2DM, OSA, BIH, hypertension resistant to triple therapy 2. BMI >40 kg/m2 with OSA (>5), insulin resistance, impaired fasting blood glucose, dyslipidemia, impaired quality of life, NASH
Eligibility criteria	1. Unsuccessful at healthy weight reduction using a structured program for a 12 month period, from which 6 month at a tertiary center 2. Tanner stage ≥IV 3. Understanding and willingness of lifestyle changes and dietary requirements after surgery, no pregnancy in the first 2 years after surgery, and agreeing to life-long follow-up 4. Good psychological well-being with strong social support (family)
Contraindications	1. Correctable medical cause of obesity 2. Psychological disability (unstable eating disorder, unstable psychiatric condition) 3. Substance abuse 4. Pregnancy 5. Medical contraindications for surgery (e.g. previous major abdominal surgery, metastatic malignant disease, …)

BMI: Body Mass Index ; T2DM: Type 2 Diabetes Mellitus ; OSA: Obstructive Sleep Apnea ; BIH: benign intracranial hypertension ; NASH: Non-alcoholic Steatohepatitis

or developmental delay. To date, bariatric surgery experience in patients with cognitive impairment is limited (mostly from case reports or small cohort studies), but different bariatric procedures have been used with similar short-term success rates compared to normal obese adolescents (17). Since the results are promising, experts do consider bariatric surgery as an optional treatment, especially in patients with life-threatening comorbidities (16, 17). We should however take into account the possibility that these patients will have more risk of later weight regain and long term complications, especially if follow-up protocols are not respected which can be a challenge in this group of patients.

Preoperative pathway

We will not elaborate on the general diagnostic work-up of obesity in children and adolescents, since this isn't the scope of this article. All obese children should get a basic medical work-up (endocrine, glucose metabolism, metabolic syndrome, growth/height evaluation) to exclude any medical reason for their weight gain, and to exclude and treat existing comorbidities. Specific genetic testing should only be considered when there is early onset obesity (before 5 years old), extreme hyperphagia, other clinical findings of genetic obesity syndromes or a family history of extreme obesity (9).

Before considering referral to a tertiary weight loss center for surgical treatment and embarking upon a surgical treatment pathway, all possible conservative measures should be taken and exhausted. It may also be beneficial to ensure compliance to treatment and follow-up is demonstrated, in order to minimize the risk of nutritional deficiencies and associated potential complications.

At the University Children's Hospital in Brussels, we have a conservative follow-up of minimum 6 months before starting the process for evaluation for surgery. The patients follow a clinical pathway which includes not only dietary, psychological and medical follow-up, but also workshops, group sessions, family sessions and physical therapy (in group or private). After 6 months an evaluation of the patient's' progress will be discussed during a multidisciplinary meeting after which the preparatory process starts. If the patient fulfills all necessary criteria, his/her case will be presented to an obesity committee consisting of members from all departments in the hospital. After thorough evaluation of the patient files, and an unanimous positive decision of the committee, the planning of the procedure can go ahead.

If not yet performed during the general work-up, some extra pre-surgical assessments will be organized, such as a consultation with the anesthesiologist, a cardiac assessment and a gastroduodenoscopy with Helicobacter Pylori testing. Minimum two extra consultations with the dietitian will be organized to prepare the patient for the changes in diet in the weeks before and after surgery, and to explain the supplements that need to be taken lifelong. The surgeon will see the patient one last time to explain the procedure again, to go over the possible complications, the course of the hospitalization and the follow-up schedule. The patient and parents have the opportunity to ask questions and always sign a consent form before surgery.

Rarely, the surgeon will ask for more investigations on the body composition of the patient such as a dual X-ray absorptiometry (DXA) scan or magnetic resonance imaging (MRI) to assess skeletal muscle and fat distribution, and to evaluate the changes after weight loss surgery. These investigations are mostly performed in investigational settings.

The importance of psychological preparation:

The psychological workup in obese adolescents is an intense procedure, but a very important part in the preparation for bariatric surgery. Children and adolescents with obesity are known to have a low quality of life (QoL), significant psychosocial comorbidities, including poor self-esteem, increased risk of depression, anxiety, eating disorders and substance abuse (9). Psychosocial results after bariatric surgery are very controversial in literature. The Swedish AMOS study reported no uniform improvement of anxiety and depression scores after surgery. They also reported 2 cases of attempted suicide and 5 cases of drug abusers after surgery (18). This highlights the importance of screening all patients and to try to identify those patients that will benefit the most from the intervention, and to exclude those that will likely deteriorate after surgery. Unfortunately, accurate instruments to guide this decision are not yet available.

It is indispensable that all candidates for surgery undergo a thorough psychological and psychiatric evaluation before considering a surgical intervention. Next to a thorough analysis of the demand of the patient, we take multiple psychosocial assessments: psycho-affective (Rorschach and Thematic Apperception Test), anxiety (Multidimensional Anxiety Scale for Children), depression (Children's Depression Inventory), eating behavior (Dutch Eating Behavior Questionnaire), self-esteem (Coopersmith scale), family structure (Family Adaptability and Cohesion Scale-IV), and an intellectual assessment (only if relevant, Wechsler Intelligence Scale for Children). We ask the patient and their parents to fill in an auto-questionnaire, the Child Behavior Checklist, and multiple evaluations are performed by the psychologist and psychiatrist of the team.

There are no fixed results or ranges of results of these tests that prohibit or support a surgical treatment, but when a test shows a psychosocial issue, the treatment plan should be adapted, and surgery might be postponed or even refused. The patient has to be prepared to the best of his/her capacities and should understand the challenges of the surgical treatment and life-long follow-up.

Results after bariatric surgery

A significant and growing body of well-constructed research demonstrates the safety and effectiveness of metabolic surgery in adolescents, with the largest series coming from Sweden (Adolescent Morbid Obesity Surgery (AMOS)), Germany (German Obesity Registry, and the United States of America (Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS)) (8, 19-27). The results published in literature are very promising, but we need to remain skeptic, since very long term results are not yet known.

It has been proven that weight loss results are greater within adolescent bariatric surgical programs compared to dietary and lifestyle programs that generally fail to achieve positive long-term results. Typical BMI loss is about 1,49 kg/m² after 18 to 24 months of lifestyle intervention, which is significantly different compared with surgical results after RYGB (mean loss of 16.6 kg/m²) or SG (mean loss of 14.1 kg/m²) (21, 28).

Existing studies in adolescents have shown T2DM resolution in 79–100% cases after RYGB, and 50–94% after SG (21, 26). Compared to adults, adolescents are significantly more likely to have remission of T2DM (86% vs. 53%) (27). Evidence suggests that T2DM behaves more aggressively when the onset is in adolescence, with earlier failure of first-line drug pharmacotherapy and more rapid progression to insulin requirement (2, 27). In adults, >90% remission is achieved when T2DM diagnosis is new (<1 year), compared to <40% in established T2DM (>4 years) (2). This means that the diagnosis of T2DM should not mean a delay in surgical treatment, but on the contrary, maybe it should be offered at lower BMI values when there is a diagnosis of T2DM.

In the adult population the risk of hypertension almost halves, the risk of dyslipidemia reduces by two-thirds and inflammation is reduced, leading to a reduction in the risk of myocardial infarction, stroke and death, each by around 50% (2). Adolescents experience similar degrees of improvement of cardio-metabolic risk factors for at least 3 years after surgery (8, 26, 30).

Joint pain, impaired physical function, and impaired health-related quality of life significantly improve after bariatric surgery. These benefits in patient-reported outcomes support the use of bariatric surgery in adolescents with severe obesity and musculoskeletal pain, and suggest that bariatric surgery in adolescence may reverse and reduce multiple risk factors for future joint disease (30).

Many of the concerns against bariatric surgery in adolescent relate to the known and unknown side effects. The same literature presenting the good results also show that side effects are limited and mostly well tolerated (22, 24, 25, 30). All surgical procedures have comorbidities, complications and even mortalities. But non-surgical treatment also has side effects, and severe childhood obesity can present with lethal complications (31). Significant advances in surgical techniques, anesthetics, patient selection and multidisciplinary management has reduced mortality of bariatric surgery to 0.08-0.31% in adults (2). There has been 1 report of perioperative death of an adolescent in literature (32).

Perioperative complications are seen in 2.6-3% for gastric bypass and 0% for sleeve gastrectomy (24, 33). Short-term postoperative complications are not frequent, and include general complications such as urinary tract infections, postoperative fever or pulmonary complications (5.2% for RYGB and 9.1% for SG), or surgical complications such as bleeding requiring surgery, intra-abdominal abscesses, peritonitis or wound problems (1.7% for RYGB and 7.8% for SG) (24).

One series from Belgium on long-term follow-up, reports 21% minor complications and 15.7% major complications (gastric ulcer, internal hernia) in 19 adolescent patients with a mean follow-up of 7.2 years (34). Additional surgery is performed in 13-21% of patients up to 5 years after RYGB, almost half are cholecystectomies and one third of these operations are performed in the first year post-RYGB. Other reasons for reoperations are mostly bowel obstruction or internal herniation after RYGB (23, 27). After SG we see about 10% additional procedures, again mostly cholecystectomies, but also hernia repair, wound drainage and even conversion of SG to RYGB (25).

There are concerns about growth retardation and reduced bone health after metabolic surgery but these have not been confirmed with any scientific evidence. Research showed normal growth velocity after SG, and even an increased height in adolescents operated under the age of 14 years compared with non-operated peers, and evidence shows normal levels for bone mineral content and density after surgery (2). Also, most criteria include a minimal Tanner stage of IV, so by definition, there is little outstanding growth to be affected in the majority of patients eligible for bariatric surgery in adolescence. Post-operative vitamin D deficiency (43% in adolescents versus 52% in adults) should also be evaluated knowing that 42% of healthy adolescents has a vitamin D deficiency (2).

Vitamin and nutrient deficiencies are well recognized in the short and long term after adult bariatric surgery and should not be used as a reason to postpone surgical treatment for obesity since rates of significant nutritional abnormalities appear comparable between adolescent and adult groups after bariatric surgery (2). Post-operative low ferritin is more common in adolescents (39-57%, compared to 28% in adults and 21% in healthy adolescents), but contradictory iron stores increase after surgery, suggesting the reversal of chronic inflammatory processes may be contributory to falling ferritin levels (2, 22, 26). In one study, at 5 years post-surgery 59% of RYGB and 27% of SG recipients had 2 or more nutritional deficiencies (particularly B12 and iron). No significant changes in serum levels of folate or vitamins A, B1, or D were found between baseline and 5 y after either procedure (35).

Ongoing nutrient monitoring and supplementation are important to minimize the occurrence and impact of nutritional deficiencies. Risk factors associated with specific deficiencies included surgery type, female sex, supplementation intake, weight regain, and for females, pregnancy (35). Serious complications such as refeeding syndrome, beriberi or vitamin B1 (thiamine) deficiency are extremely rare and case reports described in literature show complete resolution after medical treatment (2).

Dumping syndrome is often seen as a major complication of bariatric surgery and it has been reported in adolescents after RYGB (36). It consists of a combination of gastrointestinal symptoms (abdominal pain, diarrhea, nausea, bloating) and vasomotor symptoms (fatigue, palpitations, hypotension) after eating high-caloric food, and can be divided in early and late dumping. But most patient do not experience any dumping after RYGB, only 12% reported post-prandial fatigue and 7% reported nausea as persisting symptom 2 years after surgery (36). Many patients actually find that the discomfort that follows consumption of high-sugar foods offers a desirable feedback mechanism to help avoidance of unfavorable eating habits.

Gastrointestinal reflux is more common in obesity than in normal weight, and it will significantly improve after RYGB (2). The effects of SG on reflux are not yet completely understood, and some surgeons believe it could cause reflux disease during follow-up (37). But more long-term research is necessary to make any conclusions on this matter.

Obesity is associated with an increased risk of esophageal, thyroid, colorectum, breast, endometrium, cervix, ovary, kidney, stomach, liver, gallbladder and pancreas cancer (38). Adequate surgical treatment of obesity in adolescents thereby reduces the duration and degree of exposure to this risk factor. There are no numbers in adolescent cohorts, but in adults a study mentions a one-third reduction in overall cancer risk among women across a median ten-year follow-up, and another reported 60% fewer deaths from cancer, and 40% fewer deaths from all causes, after a mean of 7 years (2).

Short term psychosocial outcomes after bariatric surgery have been positive, with significant reduction of symptoms of anxiety, depression and anger, alongside improvements in self-esteem, self-concept and overall mood (39). But mental health problems can persist in adolescents after bariatric surgery despite substantial weight loss (18). Although bariatric surgery can improve many aspects, alleviation of mental health problems should not be expected, and a multidisciplinary bariatric team should offer long-term mental health support after surgery. Methods for identifying those at greatest risk of psychosocial impairment should be a major focus of future research.

A multidisciplinary approach

All articles and specialists agree that a distinguished multidisciplinary, pediatric and family centered approach, different from established adult models, is necessary when offering bariatric surgery in adolescents with morbid obesity (8, 20). A well-qualified multidisciplinary team (MDT), routinely engaged in the evaluation and surgical management of severely obese adolescents that follow an established clinical pathway, will generate positive and sustained outcomes.

The "core" team members consist of five members: a (pediatric) surgeon with bariatric surgery experience, a pediatrician with an interest and experience in pediatric obesity, a pediatric psychologist with expertise in adolescent and family treatment and experience treating eating disorders, a certified pediatric dietician, and an administrative program coordinator. Additional desirable team members include: a psychiatrist, a physical activity specialist, a nurse practitioner, a social worker, a gastroenterologist with expertise in fatty liver disease, a pediatric endocrinologist with experience in diabetes and dyslipidemia, and other pediatric specialists such as an orthopedic surgeon and a gynecologist.

The surgeon can be a pediatric surgeon, an adult surgeon, or a combination of both. The optimal surgical training and bariatric experience for surgeons who offer bariatric services to adolescents is unknown, but sufficient experience and a high volume program will lower the complication rates. Dual operating between pediatric and bariatric surgeons seems the best option to minimize the impact of learning curve on mortality and morbidity (2).

Challenges

One of the most challenging questions is from what age we can propose surgical treatment for obesity in children. In the adult population, the age of onset of obesity, years of obesity, and preoperative BMI, and the Edmonton obesity staging system (EOSS) score are related to postoperative results. Patients with a greater preoperative BMI and older age have less good results. A high BMI and EOSS score are related to a higher risk for postoperative complications. Also, the earlier morbid obesity is developed in life, the more risk these patients will have a higher EOSS scores (≥2) later in adult life (40).

We know that obese adults who were overweight or obese as children have increased risks of T2DM, hypertension, dyslipidemia, and carotid-artery atherosclerosis. These risks however, become similar to the normal weight population if these children become nonobese by adulthood (41). So this calls for an early active surgical approach in obese treatment-resistant adolescents.

But it is extremely difficult to predict the exact response of a patient on the proposed surgical treatment. The Swedish AMOS study showed a greater variability in weight outcome in adolescents, compared with adults, which may indicate greater phenotypic heterogeneity and/or a greater need for postoperative support to optimize outcomes (23). It will be essential to characterize and understand the factors responsible for this individual variation in response, to pave the way for precision medicine (4).

The practice of precision medicine accounts for an individual's genes, environment, and lifestyle when deciding upon treatment type and intensity in order to optimize benefit and minimize risk. Obesity is a complex disease with many biopsychosocial determinants which all need to be taken into account when an individualized treatment plan is developed (42). More and especially long term research will guide us to the right timing (age) and indications (weight, comorbidities, and person-specific characteristics) to propose bariatric surgery, and to allow for a perfect patient selection. Some interesting domains in obesity research such as gut microbiota composition, genetics testing, hormonal deregulation (leptin and ghrelin; influence on hunger and satiety) and the inflammation and metabolic changes after surgery are gaining popularity and this will hopefully give new insights in the pathology and aid in the developing of new treatment modalities of pediatric obesity.

Patients also need to be adequately prepared and evaluated before planning any type of intervention. There is no consensus on the optimal medical, psychological, and nutritional requirements during the pre-operative, immediate post-operative, and long-term phases to achieve a desirable outcome. Ideally, a regulated approach with recognized surgical centers should exist, with the necessary surgical volume to reduce complications, but mostly with a dedicated and experienced team to take on all layers of obesity in adolescents. Excellence in clinical outcomes must be the goal and, therefore, monitoring and analysis of outcomes through data collected for prospective research studies or quality assurance programs is indispensable.

Some ethical considerations should also be taken into account when treating obese adolescents agreeing to bariatric surgery, which consist of a life changing and sometimes irreversible procedure. There are known side effects whose severity is possibly not fully understood by the patient. Lack of maturity and family relations poses a series of challenges with autonomy. Their body will be changed and sometimes body-contouring surgery can be necessary for excess skin problems.

Informed consent and assent can pose predicaments due to the complexity and uncertainty of decision making capacity, and lack of voluntariness due to family bonds. Obesity is considered to be self-inflicted, resulting from lack of self-control, and is subject to prejudice and sentiments of guilt in patients and parents. Parental responsibility and guilt might complicate issues of consent and the assessment of the best interest of the child (43). Also, social aspects of obesity, such as medicalization, prejudice, and discrimination, raise problems with justice and trust in health professionals.

There is also uncertainty about the long term outcomes and complications which implicates a strict follow-up for the rest of their life. Adolescents however, are very unpredictable in their adherence to the postoperative guidelines, dietary changes and taking the necessary supplements (nutrients and vitamins). In the Bariatric Outcomes Longitudinal Database registry (BOLD) concerns were raised since only 37% of the 692 adolescents had available data at the 12-month time period (20). And even in a country where healthcare is free (UK), we see that there is a drop of follow-up from 79.3% at 1-year post-surgery, to 59.1% at 2 years and only 33.3% at 5 years (44).

The general pediatrician

The most effective influence on obese adolescents and their parents is counseling by a primary care provider. Referral for tertiary multidisciplinary care depends heavily on the attitudes of primary care physicians. A survey of pediatricians and family practitioners showed that 84.6% were satisfied with the operative outcomes after referral for bariatric surgery (adult or pediatric), but still 88.5% would be unlikely or would never refer a child for a bariatric procedure, and only 44.3% would be somewhat or very likely to refer an adolescent (45). But new evidence is emerging and there is less reluctance to refer morbidly obese patients to tertiary centers, even though it is still mostly not with the intention for bariatric surgery.

There is no actual threshold in weight or BMI to justify a referral to a tertiary center, in general an early referral is preferred, especially when comorbidities or complex psychosocial problems are present. The pediatrician can be of essential help to educate the patient and the parents on obesity and its complications in general, to assess the readiness of a patient for intensive multidisciplinary management (and possibly a surgical procedure), and to assist in the long term follow-up. And ideally, the general pediatrician should also be included in the multidisciplinary decision making and preparation of the patient and family.

Lifelong treatment adherence is an important requirement for successful long-term intervention with bariatric surgery. Optimal postoperative strategies designed to improve long-term follow-up among adolescent patients is currently lacking, but that's where the primary care physician is mostly needed.

The first 2 years, the postoperative follow-up is intensive, with consultations at 1 month, 3 monthly the first year, and 6 monthly the second year. After this, a lifelong yearly follow-up should be maintained. This yearly control should always include a blood sample (table 3), a thorough history and clinical examination. Monitoring and encouraging therapy compliance with long-term mineral and multivitamin supplementation is extremely important. During the first phase of weight loss, it is important that muscle volume is maintained, and a protein (minimum 30 grams) and vitamin supplement is mandatory to prevent complications. Depending on the patients' daily protein intake, which should be minimum 200 grams of meat (or poultry, fish, eggs), the protein supplement can be stopped. The multivitamin supplement should be continued lifelong.

The potential effects and consequences that any bariatric procedure may have on absorption and action of medications should be carefully evaluated, especially for medications where changes in blood levels may have critical effects on patients conditions or can cause significant adverse events. Anti-inflammatory drugs, salicylates, corticosteroids and other drugs that may cause gastric damage should be avoided in the immediate postoperative course. If any doubt exists on an approach towards a rare complication, deliberation with a specialist or a referral to a specialist center should be undertaken without any doubt.

Table 3: Yearly surveillance for nutritional deficiencies after bariatric surgery.

	Sleeve Gastrectomy	RYGB
Timing	every 3–6 months in the first year every 12 months thereafter	every 3–6 months in the first year every 12 months thereafter
Assessment	CBC, platelets electrolytes, iron, ferritine vitamin B12, folate, vitamin D PTH	CBC, platelets electrolytes, iron, ferritine vitamin B12, folate, vitamin D PTH 24-H U-calcium osteocalcin

RYGB = gastric bypass; CBC = complete blood count; PTH = intact parathyroid hormone; 24-H U-calcium = 24-hour urinary calcium

Conclusion

Bariatric surgery is a proven, effective treatment for severe obesity disease in adolescents, but complications and long term comorbidities do exist. It is not considered as a standard treatment, but can be proposed in extreme cases. Early referral to a multidisciplinary tertiary weight loss center is necessary in all children with morbid obesity when conservative measures are failing.

A multidisciplinary approach is undeniably required to effectively plan a personalized and family-based management, and to optimize preoperative decision making. A thorough physical and psychological work-up is essential in the management of obese adolescents.

The general pediatrician and primary care providers play an important role in the early referral of these patients, the multidisciplinary management, the preparation for a surgical procedure and during the postoperative long-term follow-up.

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Recurrent acute event in an infant

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Keywords

Acute event, infant, toxicology, methadone

Abstract

Acute event (AE) is defined as an unexpected change in an infant's breathing, appearance, or behavior. We report the case of a previously healthy 5-month-old infant, treated with omeprazol for gastro-oesophageal reflux, who presented two subsequent episodes of AE. Cardiopulmonary resuscitation was necessary with admission to a Pediatric Intensive Care Unit (PICU) before complete recovering in 24h. No cause could be identified. Ten days later, another acute event required cardiopulmonary resuscitation in PICU again. Urine toxicology screening detected traces of methadone. Subsequent analyses showed the presence of methadone in all capsules of omeprazol.

Cas Clinique

M. un nourrisson de 5 mois est en voyage en France avec ses parents. Depuis deux jours il est grincheux et somnolent, il semble moins actif et ne réclame plus ses biberons. Il présente une rhinorrhée, une hypersialorrhée et des mouvements de mâchonnement. Après le biberon du matin l'état de M. se dégrade. Il devient peu réactif et hypotonique. Les parents se rendent immédiatement aux urgences pédiatriques les plus proches. Dans la voiture, M. n'est plus réveillable, il présente une respiration bruyante et irrégulière. Sa mère constate que son cœur bat de plus en plus lentement. A l'arrivée aux urgences M. est hypotonique et cyanosé. Un épisode d'hypertonie est observé par l'équipe soignante à l'admission faisant suspecter un épisode convulsif. Des premiers prélèvements sanguins sont effectués (tableau 1) et deux doses de diazépam à 0,5mg/kg par voie intrarectale (IR) sont administrées. Celles-ci causent une majoration de la détresse respiratoire entrainant une bradycardie sévère avec une fréquence cardiaque (FC) à 30 bpm. Une réanimation cardio-pulmonaire (RCP) est débutée avec compressions thoraciques, intubation naso-trachéale et administration d'une dose d'adrénaline à 0,1ml/kg par voie intraveineuse (IV) ainsi qu'une dose de charge de clonazépam à 0,05 mg/kg en IV. M. est ensuite transféré en Unité de Réanimation Pédiatrique. Le premier bilan réalisé aux urgences (biologie complète, recherche de toxiques sanguin et une radiographie de thorax) revient négatif (tableau 1). En hospitalisation, le reste du bilan comprenant une ponction lombaire (PL), des contrôles biologiques, la recherche de toxiques urinaires, une échographie cardiaque, un électrocardiogramme, une échographie abdominale ainsi qu'une résonance magnétique (RMN) cérébrale ne révèle aucune anomalie (tableau 2). L'électro-encéphalogramme (EEG) montre l'absence d'anomalies de nature épileptiques et un tracé lent avec surcharge en rythmes rapides suite à la probable imprégnation médicamenteuse par benzodiazépine. M. ne présente aucun antécédent excepté un reflux gastro-œsophagien pour lequel il reçoit de l'oméprazole (1mg/kg/j). Il reçoit également des gouttes homéopatiques à base de gelsemium sempervirens afin de faciliter l'endormissement (1). M. a pu être extubé 24h après l'incident, n'a jamais nécessité de support hémodynamique, et après avoir retrouvé un état neurologique normal, il est transféré à Bruxelles.

A l'admission à l'Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), M. présente un bon état général. M. est observé pendant 5 jours sans aucun incident excepté quelques pics fébriles (maximum à 38,7°C) et une légère inappétence. Une somnolence progressive s'installe le matin du 5ème jour. A ce moment l'état de l'enfant se dégrade à nouveau avec une altération de la conscience, perte de contact, hypotonie, mâchonnements et pâleur. Les paramètres vitaux de M. restent dans les limites de la normale (FC : 110-120 bpm ; tension artérielle systolique (TAs) minimale : 70 à 90 mmHg ; fréquence respiratoire (FR) : 30-35/min) et un EEG effectué en urgence démontre un tracé de sommeil profond. Il est pris en charge par l'équipe de l'Unité de Soins Intensifs (USI) avec administration de lorazépam pour suspicion clinique de convulsions, provoquant une insuffisance respiratoire avec hypoxie sévère entrainant une bradycardie à 45 bpm. Une RCP est effectuée, M. est intubé et des compressions thoraciques sont effectuées.

Une origine infectieuse a rapidement été écartée : PL et hémocultures négatives, CRP maximale à 25mg/L, leucocytose à 18.000/mm^3 se normalisant progressivement, et une neutrophilie à 3.700/mm^3. L'acyclovir (60 mg/kg/j) instauré en France a donc été arrêté. Seule la présence du virus Parainfluenza A a été mise en évidence dans une aspiration naso-pharyngée, ce qui pourrait expliquer les quelques pics fébriles. Une cause métabolique (type intolérance aux protéines dibasiques avec lysinurie) a été suspectée en raison d'une histoire de cassure pondérale. Le bilan débuté en France et complété à l'HUDERF (dosages d'acides aminée et organiques sanguins et urinaires) s'est révélé normal. Une atteinte neurologique, (type encéphalomyélite aiguë disséminée) a également été exclue. En effet la mise au point neurologique (prélèvements de liquide céphalo-rachidien, RMN cérébrale) s'est avérée normale, excepté de multiples EEG montrant une activité cérébrale lente mais aspécifique. Les échographies cardiaques et les ECG normaux ont permis d'exclure une origine cardiaque. Les recherches de toxiques urinaires et sanguins effectuées à l'USI de l'HUDERF reviendront positives pour de la méthadone (non recherchée précédemment en France) avec un taux sanguin à 126 mcg/L (équivalent à un taux plasmatique thérapeutique pour un adulte traité). Un complément d'anamnèse dirigée est effectuée avec les parents mais se révèle peu contributif et les gélules homéopathiques à base de gelsemium sont rapidement pointées du doigt. Les analyses réalisées sur celles ci ne dévoileront aucune substance toxique et confirmeront les doses homéopathiques du produit. Au contraire, la présence de méthadone dans les gélules d'oméprazole (préparation magistrale) a été confirmée par le laboratoire de toxicologie de l'Institut de Santé Publique. En reprenant l'anamnèse, les parents expliquent qu'il s'agissait d'une nouvelle boîte commencée 3 jours avant le premier incident en France et reprise 48h après son arrivée à l'HUDERF. L'agence fédérale des médicaments et des produits de santé (AFMPS) a été prévenue et une enquête a pu être ouverte.

Après six jours de surveillance intensive et trois jours dans le service des Nourrissons de l'HUDERF, M. sortira d'hospitalisation après récupération clinique complète.

Discussion

Le malaise du nourrisson ou « acute event » (AE) est défini comme un changement brutal de respiration, aspect ou comportement de l'enfant. Les derniers guidelines de l'American Academy of Pediatrics (AAP) redéfinissent les anciennement appelée « apparent life threathening events (ALTE) » en « brief resolved unexplained events (BRUE) » afin de réduire le caractère imprécis et subjectif de cette définition. Les BRUE sont définis comme étant des événements inexpliqués, brefs (moins de 1minute), déjà résolus, survenant chez des enfants de moins de un an et comprenant au moins un des paramètres suivants : cyanose ou pâleur, respiration absente diminuée ou irrégulière, changement de tonus, altération de la réactivité. Les BRUE sont divisés en « high » et « low-risk » (2).Seule la prise en charge de ces derniers a été pour le moment standardisée (2,3). Cependant de nombreux épisodes, dont celui rapporté dans notre cas clinque, ne rentrent pas dans la catégorie de BRUE (événement non résolu lors de l'arrivée des soignants, paramètres vitaux anormaux, etc.). Leur prise en charge reste donc non standardisée et basée sur les anciennes propositions concernant les ALTE. Néanmoins, plusieurs facteurs de gravité sont reconnus pour tout type de AE : l'âge (< 60 jours), la prématurité, les événements récidivants, le recours à une RCP, l'altération des paramètres vitaux, la durée de l'événement (> 1minute), une histoire et un examen clinique suggestifs. Des examens complémentaires (screening toxicologique urinaire par exemple) et une surveillance en milieu hospitalier sont dans ce cas requis. Un diagnostic grave sous jacent est retrouvé 3 à 14 fois plus souvent dans ces conditions.[2,4] Les intoxications seraient responsables d'un faible nombre de malaises graves (8% sur 247) (2,5).La méthadone est un opioïde de synthèse liposoluble, antagoniste des récepteurs NMDA. Elle présente un longue demi-vie, de 8h à 47h, ce qui lui confère une longue durée d'action et explique le délai d'apparition des symptômes lors d'une intoxication. Elle est principalement métabolisée dans le foie et éliminée par les systèmes enzymatiques CYP3A4, CYP26B et CYP2D6 du cytochrome p450, immatures à la naissance, ainsi que le CYP3A7, qui est au contraire présent en taux élevés chez le nouveau-né. L'activité du CYP3A7 décroit au même temps que celle du CYP3A4 augmente. Ceci expliquerait la similitude de certains paramètres pharmacocinétiques, dont la clearance, chez les nourrissons et les adultes, et l'absence de « maturation » avec l'âge (6). Les principaux signes d'une intoxication à la méthadone sont la dépression respiratoire, un coma, un myosis, une bradycardie et un hypotension. La grande biodisponibilité entérale de la méthadone, sa longue demi-vie et le fait qu'une faible dose thérapeutique pour un adulte puisse être létale pour l'enfant, sont de facteurs de gravités de l'intoxication à la méthadone dans la population pédiatrique. Il existe très peu de littérature concernant les intoxications accidentelles d'enfants de parents non traités par méthadone. En effet la majorité d'enfants intoxiqués à la méthadone ont au moins un parent sous traitement (7).Enfin ce cas clinique nous interroge quand à la démarche à suivre face à de tels incidents. Il est primordial de les déclarer. Ceci ayant pour but, non pas de déceler un « responsable » mais de mettre en évidence les mécanismes et différents dysfonctionnements ayant conduit à l'événement. De nombreuses méthodes d'analyses de ces causes profondes (« root causes analysis ») se développent et s'utilisent de plus en plus en milieu hospitalier afin de diminuer ces incidents par une modification des procédures y conduisant (8,9).

Conclusion

En conclusion, ce cas clinique démontre la complexité de la prise en charge des malaises graves. Suite à la présence de facteurs de gravités, une surveillance hospitalière et des examens complémentaires doivent être effectués. Ceux-ci doivent tout d'abord être ciblés, en fonction de l'histoire et de la présentation clinique, mais, si aucun diagnostic n'est mis en évidence, ils doivent rapidement être étendu afin d'exclure d'autres hypothèses diagnostiques. Le screening toxicologique des urines doit faire partie d'un premier bilan pour ces malaises avec signes de sévérité, et cela même en l'absence de facteurs cliniques ou anamnestiques suggestifs.

Table 1: BILAN CHU BESANÇON

A. : Bilan aux urgences	
1. Gazométrie (capillaire)	
pH	7,33 (7,37-7,43)
pCO2	76 cmH2O (50-57)
Bicarbonates	30,4 mmol/L (23-27)
BE	1,4 (-2,00-2,00)
Lactates	2,20 mmol/L (0,30-2,50)
2. Biologie	
Hb	10,7 g/dL (9,5-13,5)
Plaquettes	472 G/L (200-500)
Globules blancs	18,03 G/L (6,00-17,50)
Neutrophiles	2,70 G/L (1,50-8,50)
Lymphocytes	13,67 G/L (2,70-12,60)
Sodium	136 mmol/L (136-145)
Potassium	4 mmol/L (3,5-5,1)
Chlorures	102 mmol/L (98-107)
Bicarbonates	21 mmol/L (21-32)
Protéines totales	60 g/L (64-82)
Glucose	234 mg/dL (74-106)
Calcium	2,35 mmol/L (2,12-2,52)
Urée	7,5 mg/dL (7-18)
Créatinine	0,38 mg/dL (0,30-0,85)
ASAT	50 UI/L (13-7)
ALAT	45 UI/L (12-78)
γGT	27 UI/L (15-85)
Phosphatases Alcalines	596 UI/L (150-900)
CPK	140 UI/L (39-308)
CRP	< 2,9 mg/L (0,0-8,0)
3. Screening toxicologique sanguin	
Antidepresseurs	Recherche négative
Benzodiazépines	Recherche négative
Paracétamol	7,3 mg/L (0,0-0,0)

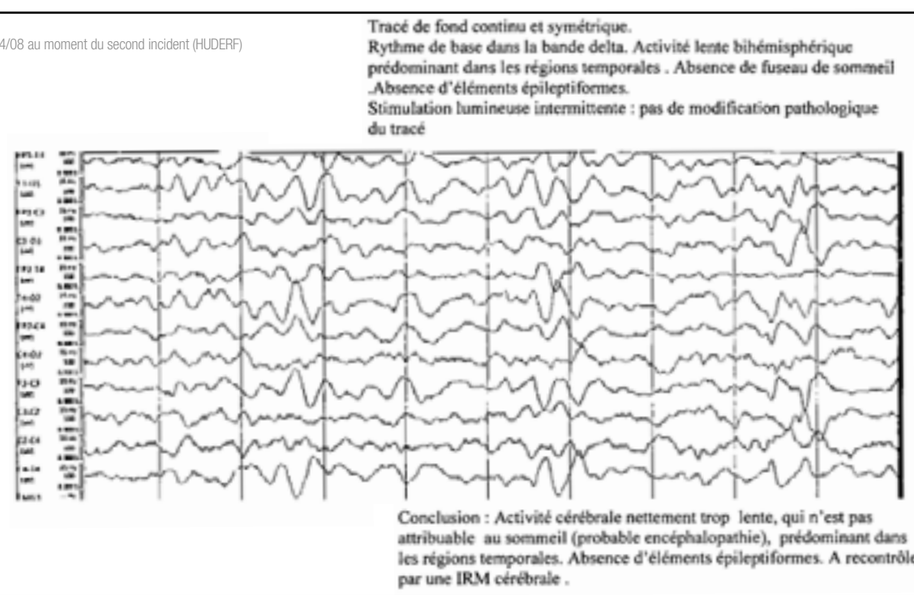
B : Bilan hospitalisation	
1. Ponction lombaire	
Globules rouges	15860 /mm^3 (0-5)
Leucocytes	18 /mm^3 (0-5)
Protéines	0,59 g/L (0,15-0,45)
Glucose	56 mg/dlL (40-71)
Culture en aérobiose	Négative en 48h
2. Biologie (biochimie)	
Sodium	134 mmol/L (136-145)
Potassium	3,9 mmol/L (3,5-5,1)
Chlorures	102 mmol/L (98-107)
Bicarbonates	23 mmol/L (21-32)
Protéines totales	55 g/L (64-82)
Albumine	31 g/L (34-50)
Glucose	196 mg/dL (74-106)
Calcémie corrigée	2,43 mmol/L (2,5-6,6)
Urée	5,4 mg/dL (7-18)
Créatinine	0,19 mg/dL (0,30-0,85)
ASAT	48 UI/L (13-7)
ALAT	47 UI/L (12-78)
CRP	25,8 mg/L (0,0-8,0)
Acide lactique	1,8 mmol/L (0,40-2,00)
3. Screening toxicologique urinaire	
Antidepresseurs	Recherche négative
Benzodiazépines	Recherche positive [1]
Opioïdes (méthadone)	Non recherchés

Table 2: BILAN HUDERF

Bilan malaise	
1. Gazométrie (capillaire) H0	
pH	7,32 (7,37-7,43)
pCO2	43 cmH2O (50-57)
Bicarbonates	22 mmol/L (23-27)
BE	-3,9 (-2,00-2,00)
Lactates	0,9 mmol/L (0,30-2,50)
2. Gazométrie (capillaire) H4	
pH	7,35 (7,37-7,43)
pCO2	45 cmH2O (50-57)
Bicarbonates	24 mmol/L (23-27)
BE	-1,8 (-2,00-2,00)
Lactates	1,11 mmol/L (0,30-2,50)
2. Biologie H12	
Hb	11,3 g/dL (9,5-13,5)
Sodium	137 mmol/L (136-145)
Potassium	4,4 mmol/L (3,5-5,1)
Chlorures	101 mmol/L (98-107)
Bicarbonates	23 mmol/L (21-32)
Protéines totales	55 g/L (64-82)
Calcium	2,4 mmol/L (2,12-2,52)
Urée	6 mg/dL (7-18)
Acide urique	4,2 mg/dl
Créatinine	0,16 mg/dL (0,30-0,85)
ASAT	37 UI/L (13-7)
ALAT	26 UI/L (12-78)
γGT	18 UI/L (15-85)
Bilirubine totale	<0,2 mg/dl (0,2-1 ,2)
3. Screening toxicologique urinaire H12	
Amphétamines	Recherche négative
Benzodiazépines	Recherche positive 1
Cannabis	Recherche négative
Cocaïne	Recherche négative
Méthadone	**Recherche positive**
Cannabis	Recherche négative
4. Dosage sanguin H12	
Méthadone	**126 mcg/L**

1 : recherche positive en benzodiazépine suite à l'administration de celles ci pendant les RCP.

Figure 1. EEG du 4/08 au moment du second incident (HUDERF)



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Article

Progressive pneumonia with pleural effusion and pneumomediastinum as presenting symptom of a hypopharyngeal perforation in a one year old boy.

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Keywords

Hypopharynx, pyriform sinus, esophagus, perforation, trauma, minimal invasive surgery, mediastinitis, drainage

Abstract

Perforation of the upper aerodigestive tract is a rare but potentially life-threatening condition. Hypopharyngeal perforation is in most cases the result of an iatrogenic injury (endotracheal intubation, nasogastric tube placement, endoscopy, …), although foreign bodies, penetrating injuries (falling with a long foreign body in the mouth), blunt trauma or barotrauma have also been identified as possible causes. This case report describes an atypical presentation of a pyriform sinus perforation in a young child.

Introduction

Pediatric oropharyngeal trauma is underreported since it often occurs unwitnessed and physicians are only consulted in case of associated symptoms as bleeding, dysphagia or pain (1). Occurring most frequently in toddlers falling with a long object in the mouth, most oropharyngeal lesions will heal spontaneously, but some lesions can lead to severe complications (1). Described complications are internal carotid artery damage leading to neurological symptoms or severe infections leading to sepsis, toxic shock and even death (1,2). Perforations of the hypopharynx and cervical esophagus are rare, especially in children and most often caused by iatrogenic injury. It has been described as a result of endotracheal intubation, nasogastric tube placement and endoscopy and also as a result of foreign bodies lodged in the pyriform recess, due to penetrating injuries caused by a fall with a long object in the mouth, and as a consequence of a blunt trauma with important acceleration/ deceleration (2-5). In children, however, non-accidental trauma needs to be considered when patients present with such a lesion (6,7). Only 2% of the nonaccidental trauma in children will involve the pharynx, hypopharynx and esophagus (8).

The signs and symptoms of a hypopharyngeal or cervical esophageal perforation may be subcutaneous emphysema, dysphagia, stridor, pain and later on sepsis. Pneumomediastinum but also pneumoperitoneum should also raise suspicion. Due to the atypical symptoms, a high degree of suspicion is necessary to diagnose a perforation of the hypopharynx or cervical esophagus.

Case presentation:

A previously healthy 19 months old boy presented with acute onset fever, one-time vomiting and mild dyspnea. A generally ill condition and a mild tachypnea were observed. Blood analysis revealed high leukocytosis 32640/ µL and increased C-reactive protein (CRP) 15 mg/L. Plain chest radiography showed mild bilateral peribronchitis. The toddler was admitted to the general pediatric ward and treated with high-dose intravenous amoxicillin at a dosage of 200 mg/kg/day. He developed spiking fever and increasing oxygen dependence. Blood analysis the following day revealed a normalization of the leukocytosis, yet a massive increase in CRP 480 mg/L. A control chest radiography showed increasing infiltration of the right upper lobe and the left lower lobe, but also pneumomediastinum continuing up into the neck, see Figure 1. The boy was transferred to the pediatric intensive care unit (PICU) with suspicion of necrotizing pneumonia.

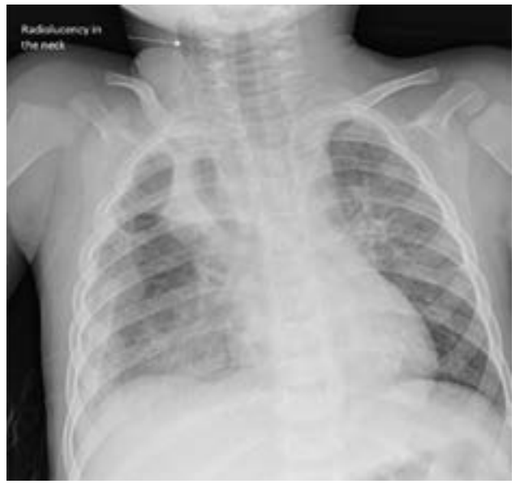
At PICU admission, the patient was stable with moderate respiratory distress. He was treated conservatively with antibiotic switch to high-dose amoxicillin-clavulanic acid at a dosage of 150 mg/kg/day and continuation of oxygen by high flow nasal cannula.

One day later, the young patient developed a tension pneumothorax necessitating urgent placement of a pigtail chest drain with drainage of air and purulent fluid. Since he recovered quickly, oral feeding was resumed the day after the chest-tube placement. The ingested yoghurt immediately appeared in the chest drain. Urgent Computer Tomography (CT)-scan of the neck and chest revealed mediastinitis with air trapping in the neck and mediastinum without pneumothorax or evidence of bronchial injury. Lung parenchyma and esophagus appeared normal. An upper gastrointestinal contrast radiography series showed a contrast leak from the esophagus into the mediastinum, see Figure 2. Endoscopic exploration under narcosis revealed an extensive pyriform sinus tear, see Figure 3. Intravenous antibiotics were switched to piperacillin-tazobactam and fluconazol. After multidisciplinary team discussion, surgical drainage of the mediastinum was performed via a small right cervical incision, leaving a mediastinal drain on suction. Two days later, video-assisted thoracoscopic empyema drainage was necessary because of stagnation of the clinical evolution, and two drains were left in the pleural space. The patient remained ventilated for ten days with a nasogastric tube on suction. Enteral feeding was started two weeks later by nasogastric tube after the confirmation of spontaneous closure of the pyriform sinus tear by both laryngoscopic examination and videofluoroscopic swallow study. After four weeks, the boy was able to eat a normal mixed diet.

Despite thorough and repeated history taking of the parents as well as at the child's day-care, there has never been clarity about the etiology of the boy's hypopharyngeal perforation. An accidental fall with a piece of cutlery in the mouth was suspected.

The patient was followed up at our pediatric multidisciplinary outpatient follow-up clinic. Normal respiration, swallowing, feeding and growth without sequelae were seen at the last control 10 months after the initial presentation.

Figure 1. Plain chest radiography at the time of referral: presence of infiltration in the upper and lower lobe and pneumomediastinum with radiolucency in the neck.



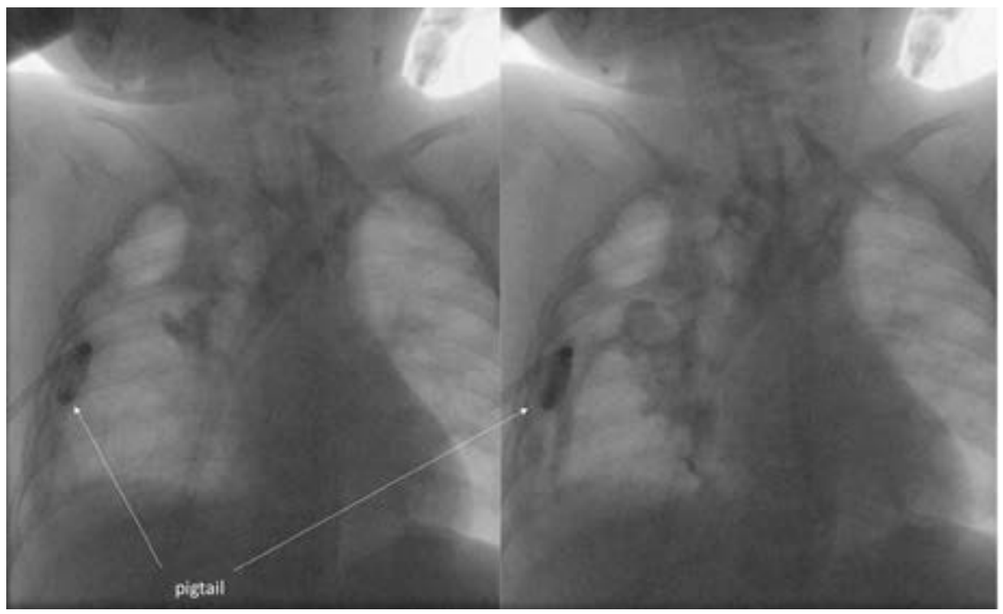
Discussion:

The clinical signs and symptoms of a perforation of the hypopharynx or cervical esophagus include dysphagia, stridor and pain. Due to the opening towards the mediastinum, these patients are at risk for severe infections and sepsis eventually with fatal evolution (2). Although this lesion occurs as a result of iatrogenic injury in 68% of cases, it remains also important to consider hypopharyngeal perforation in patients with emphysema or pneumomediastinum with out-of-hospital registrations (2). Other etiologies may be accidental penetrating trauma as a result of fall with a long object in the mouth, a sharp foreign body lodged in the pyriform sinus or blunt trauma (3-5). The blunt trauma associated with acceleration/deceleration, a direct blow to the neck or strangulation will compress the laryngeal cartilage against the vertebral bodies eventually leading to perforation (5). In infants and small children child abuse should also be considered, especially in the absence of a history of clear trauma (6,7).

The treatment of a perforation of the hypopharynx or cervical esophagus is still under debate. Described treatment options range from conservative expectant management using broad-spectrum (prophylactic) antibiotics and withholding oral feeding to surgical interventions. Different types of interventions have been described: primary repair, surgical drainage and/or placement of transcutaneous drains. A literature review from 1990 recommended expectant management for tears less than 2 cm that were limited to the pharynx (2). More recent studies demonstrated increased morbidity and mortality if surgical treatment was delayed for more than 24 hours (2,10). In a retrospective review of all their treated cases, Zenga et al. demonstrated in 2015, that not only size and location should be considered in the treatment discussion: based upon the evolution of 28 patients, they concluded that patients who had eaten between the time of perforation and diagnosis, who had a diagnostic delay of 24 hours or more and those that show signs of systemic toxicity, were at higher risk of failing conservative management and in these patients surgical drainage should be considered (2). They also advocated an aqueous swallow study five to seven days after the injury before resuming oral intake (2).

The young patient presented here had a diagnostic delay of more than 24 hours, had eaten (yoghurt) between the perforation and diagnosis and presented with signs of systemic toxicity. After multidisciplinary team discussion, he was treated successfully with mediastinal drainage via a limited right cervical incision. The development of empyema in the right chest necessitated video-assisted thoracoscopic drainage two days later.

Figure 2. Upper gastrointestinal contrast radiography series: contrast leaking along the esophagus before deviating to the right side towards the pigtail drain.



Conclusion:

Perforations of the hypopharynx or cervical esophagus are rare, especially in young children, and can be potentially life-threatening. Different treatment options are available but depend on the time to diagnosis and clinical evolution of the individual patient. The young patient presented here healed well and without sequelae after minimally invasive surgical treatment.

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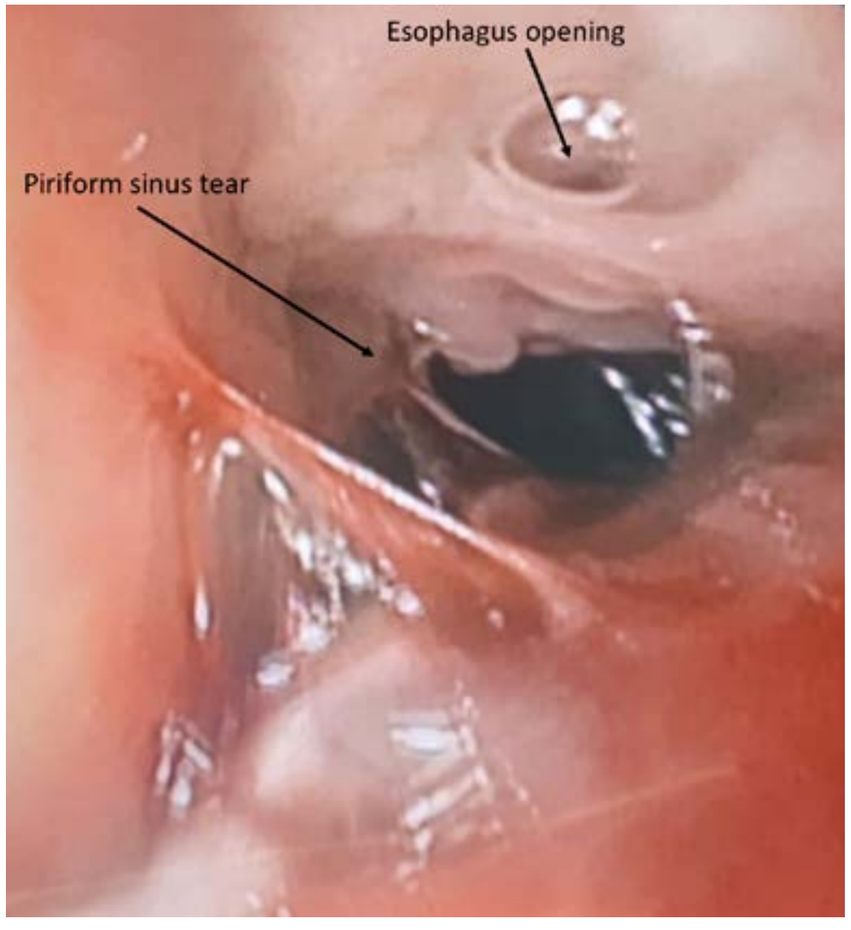
Figure 3. Endoscopic view on the pyriform sinus tear



Survey about the alcohol consumption by minors in Flemish youth movements

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Keywords

alcohol consumption, minors, youth movements

Abstract

Background Alcohol consumption and intoxication amongst Belgian minors is a major and even growing problem. It can have harmful consequences in various areas of physical and mental health. Young people are a high-risk group, because they are in an age-period of intense somatic and psychological changes.

Methods This study is an explorative cross-sectional analysis based on an online survey. Leaders of 14 to 16-year-olds within the two biggest youth movements in Flanders were questioned voluntarily and anonymously.

Results Of the 476 respondents, 84% (n=400) indicated that 14 to 16-year-olds have ever been consuming alcohol at the youth movement. In the majority of the cases, this is only done on special occasions. They mainly drink beer (84.3% (n=401)), on average 2-3 glasses. However, 'binge-drinking' is also observed. The questioned young adults agreed that there should be clear rules about alcohol consumption. Nevertheless, half of the respondents think that their youth movement should tolerate occasional consumption within this age group, since it is a protected environment to guide young people in drinking alcohol.

Conclusion The majority of the Flemish adolescents who attend a youth movement drinks alcohol before the age of 16. This research shows that preventive measures of the youth movements for alcohol consumption are not yet fully utilized.

Introduction

Many studies have shown the harmful effects of alcohol on health. No organ system is spared from the negative impact of alcohol, e.g. liver damage, chronic kidney disease, cardiovascular and respiratory effects, mental and cognitive consequences, ...[1] Because the consequences often correlate with the duration of alcohol intake, consumption by young people causes an additional long-term risk. Serious consequences are also possible in case of acute intake, such as increased aggression with interpersonal violence, delayed reflexes resulting in traffic accidents and convulsions or coma at very high intake. An extreme variant of alcohol consumption is 'binge drinking': drinking a large quantity of alcohol in a short period of time. This is defined as follows: drinking at least five glasses within two hours for men and at least four glasses for women.[2]

Alcohol consumption and intoxication amongst Belgian minors is a major and even growing problem.[3] Moreover, young people in Belgium are frontrunners within Europe regarding 'binge drinking'.[4] Data from the Intermutualist Agency (IMA) show that in 2017 at least 2334 young Belgian people aged from 12 to 17 ended up in an emergency department after alcohol abuse.[5] Although Belgian legislation prohibits alcohol under the age of 16, an epidemiological study by the Flemish Expertise Centre for Alcohol and Other Drugs (VAD) demonstrates that 80% of 15 to 16-year-olds have ever consumed alcohol.[6,7]

Young people are more vulnerable to the effects of alcohol. Compared to adults, they reach a higher blood alcohol concentration at the same intake. On the short term, this may imply a quicker development of black-outs or a faster loss of consciousness. The long-term consequences are also numerous: an increased risk of developing chronically problematic alcohol consumption or a tobacco and drug addiction and the development of various cancers. Lasting learning and memory problems can occur because the hippocampus and prefrontal cortex shrink due to alcohol consumption. Both environmental and genetic factors have an impact on these effects.[8-10]

Risk factors for alcohol (ab)use are determined by environment and genetic interactions, but also by development-related issues. As adolescence progresses, the social and psychological influence of friends and surroundings increases. Specifically, adolescents are very sensitive to group pressure.[11-15] This sense of group feeling dominates very strongly within youth movements, especially since they have often grown up together during childhood. The youth movement provides a setting where young people are taken away from parental supervision on a weekly basis and they come under the responsibility of young adults.

The aim of this explorative study is to provide insight into the drinking behaviour of the Flemish youth aged 14 to 16 years, in the absence of parental supervision, such as within a youth movement. With this accurate study, further extensive research may be conducted within other similar environments in which young people find themselves (school, sports club, etc.). The outcome of such research may serve as a basis for further specific prevention within the context of alcohol policy, both general policy and the the policy within youth movements.

Methods

Research design

In order to describe the prevalence of alcohol consumption within the age group 14 to 16 years in the youth movement, we conducted an exploratory cross-sectional study using an online survey. The questionnaire was submitted to leadership of 14 to 16 year old members of the two largest youth movements in Flanders, the Chiro and the Scouts respectively. After approval by the Research Ethics Committee UZ/KU Leuven (MP009660), the questionnaire was sent out to 1937 leadership. Participation in the study was completely voluntary and anonymous.

Design survey

The questionnaire included anonymous demographic data (age, gender, number of years of leadership and leadership of a boys and/or girls group) and eight multiple choice questions about alcohol consumption of 14 to 16-year-olds within the youth movement. The ninth question consisted of four sub-questions based on a 5-point Likert scale. In these questions we surveyed the attitude of the leadership towards alcohol consumption amongst minors.

Statistical analysis

We used IBM SPSS Statistics 25.0 for data cleaning and analysis. Incomplete or inaccurate questionnaires were excluded. Afterwards, the answer options were categorized and the results were analysed using frequency tables. Subsequently, using Chi-square tests, we examined whether there were statistically significant links between the categorical variables ordered in cross tables.

RESULTS

The questionnaire was completed by 34% (n=663) of the leaders. With a confidence level of 95%, the margin of error for this survey was 3%. After data-cleaning, 476 usable questionnaires remained. The final response rate was 24.6%.

Table 1 shows the demographic analysis of the respondents. Of all respondents, 28.8% were leaders of a youth movement group with only girls as members, 15.8% of a group only for boys and 55.5% were leaders of a mixed youth movement group.

Table 1 Demographic data of the questionnaire respondents.

	N	*%*	*mean*	*Median*	*St. Dev.*
Age	476	100	20.9	21.0	1.82
16	1	0.2			
17	3	0.6			
18	32	6.7			
19	63	13.2			
20	101	21.2			
21	106	22.3			
22	70	14.7			
23	59	12.4			
24	28	5.9			
25	6	1.3			
26	5	1.1			
27	1	0.2			
28	1	0.2			
Gender	476	100			
Female	269	56.5			
Male	207	43.5			
number of years of leadership	476	100	3.8	4.0	1.57
1	28	5.9			
2	78	16.4			
3	115	24.2			
4	106	22.3			
5	77	16.2			
6	41	8.6			
7	31	6.5			
Gender of the youth movement group	476	100			
Female	137	28.8			
Male	75	15.8			
mixed	264	55.5			

Analysis of alcohol consumption

Table 2 demonstrates that 84% of the leaders replied positively when asked whether alcohol had ever been consumed by 14 to 16-year-olds within their youth movement. In 80.8% of the groups, this occurs only on special occasions, but with 19.2% rather on a regular basis. Occasions of alcohol consumption within the youth movement are: during camp (1 evening at camp 26.3% or several evenings at camp 44.9%) or at a party of their youth movement (46.8%). The drink that is mainly consumed is beer (84.3%). To a lesser extent wine (10.3%), spirits (5.3%) or strong beers (1.3%). According to almost half of the respondents (47.3%), the minors usually drink 2-3 glasses of beer or wine on the above-mentioned occasions. 13.2% of the respondents mentioned that >/= 4-5 glasses of beer or wine were drunk by on each occasion.

Table 2 Descriptive statistical analysis of alcohol consumption.

Did 14 to 16-year-olds ever drink alcohol at the youth movement?	Yes	No				
N (476)	400	76				
%	84	16				
How often do 14 to 16- year-olds drink alcohol?	Rarely – Never	Occasionally	Regularly	Monthly	Weekly	
N (476)	196	189	70	19	2	
%	41.1	39.7	14.7	4	0.5	
On what occasions does this happen?	Never	1x at camp	Several times at camp	youth movement party	Several times at camp + parties	During weekly meetings
N (476)	80	125	44	53	170	4
%	16.8	26.3	9.2	11.1	35.7	0.8
What's being drunk?	Normally never alcohol	Beer	Beer and Wine	Beer and strong beers	Beer, wine and liquor	
N (476)	73	329	43	6	25	
%	15.3	69.1	9.0	1.3	5.3	
How many glasses of beer/ wine at a time?	0 glasses	Max. 1 glass	2-3 glasses	4-5 glasses	>5 glasses	
N (476)	72	116	225	49	14	
%	15.1	24.4	47.3	10.3	2.9	

Consequences of alcohol consumption

Table 3 shows that with 84.9% of the respondents, there has never been an unwanted incident after consuming alcohol by 14 to 16-year-olds at the youth movement. 5% reported that there had ever been an accident, 1.1% mentioned loss of consciousness by minors and 0.6% of the respondents noted alcohol intoxications. Furthermore, young people secretly drink alcohol at the youth movement sometimes. According to 24.6% of the leadership this happened only once. 18.1% of them catch young people secretly drinking alcohol at least once a year. 51.1% replied that they had never experienced this before. The majority (21.2%) indicated that if they would catch a young person drinking alcohol, they would take the alcohol, have a constructive conversation, followed by a first time warning and afterwards, they would inform the parents.

Attitude of young adults towards alcohol consumption amongst minors

The leadership's attitude towards alcohol consumption amongst minors was questioned by four statements (table 4). The answers were divided about the first statement: 'It is good that 14 to 16-year-olds occasionally drink alcohol at the youth movement. This is how they learn to deal with alcohol.'. The majority agreed with the following statement: 'As a group, we are aware of the vision/rules on alcohol consumption of our overall organization'. 73.1% respondents believe that there should be clear rules on alcohol consumption amongst minors in the youth movement. More than half of the management shares the opinion that it is important that parents are involved in determining their child's alcohol consumption within the youth movement.

There was a statistically significant relationship (p=0.004) between gender and the answer to the first statement: women were more likely to disagree; men to agree. No statistically significant link was found between gender and answers to the other statements. Moreover, the outcome of the survey demonstrated a significant relationship (p<0.001) between the answer to this first statement and the groups where alcohol was ever drunk by 14 to 16-year-olds: leaders of those groups were more likely to agree with this statement and vice versa. No statistically significant

link (P=0.21) was shown between gender of the youth movement group and the alcohol consumption ratio by 14 to 16-year-olds in that group.

Table 3 Consequences of alcohol consumption.

Has There ever been an unwanted incident after drinking alcohol by 14-16 year olds?	Never	Accident	Physical aggression	Verbal violence	Destruction of material	Alcohol intoxication	Loss of consciousness	Several of the above
N (476)	404	24	4	16	11	3	5	9
%	84.9	5	0.8	3.4	2.3	0.6	1.1	1.9
How often is a young person caught by secretly drinking alcohol?	Never	One time	1x/year	Several times/ year	weekly			
N (476)	245	117	86	27	1			
%	51.5	24.6	18.1	5.7	0.2			
what is the leader's reaction after that?	Is accepted	Taking alcohol + conversation + warning	Taking alcohol + conversation + warning + parents informed	Parent informed + suspension	Conversation + punishment	Never happened		
N (476)	7	187	112	12	76	82		
%	1.5	39.3	23.5	2.5	16	17.2		

Table 4 Attitude of adolescents towards alcohol consumption amongst minors.

	Strongly disagree (1)	*rather disagree (2)*	*neutral (3)*	*rather agree (4)*	*strongly agree (5)*
It is good that 14 to 16- year-olds occasionally drink alcohol at the youth movement. This is how they learn to deal with alcohol.					
N (476)	90	117	83	134	52
%	18.9	24.6	17.4	28.2	10.9
As a group, we are aware of the vision/rules on alcohol consumption of our overall organisation.					
N (476)	10	41	50	144	231
%	2.1	8.6	10.5	30.3	48.5
We think it is important that there are strict rules at the youth movement concerning alcohol consumption among minors.					
N (476)	9	7	19	93	348
%	1.9	1.5	4.0	19.5	73.1
It is important that parents have a say in their child's alcohol consumption within the youth movement.					
N (476)	22	71	122	143	118
%	4.6	14.9	25.6	30.0	24.8

Discussion

A large majority (84%) reported that 14 to 16-year-olds once consumed alcohol in the youth movement. According to VAD data from 2015-2016, the average starting age for alcohol consumption is 14.3 years in Flanders. A survey conducted by the VAD within Flemish schools shows that 36.2% of 12 to 14-year-olds and 75% of 14 to 16-year-olds have ever consumed alcohol.[16] A World Health Organization (WHO) report shows that the global average age for starting alcohol consumption is before the age of 15. The percentages are clearly highest in Europe.[17] In our study we could not demonstrate a statistically significant difference between alcohol consumption in male, female or mixed youth movement groups (p = 0.21). According to VAD data from 2016-2017 boys in secondary school drank more frequently and more consumptions than girls.[6] Our study revealed that beer is predominantly consumed, but 5.3% of the leaders mentioned that the 14 to 16-year-olds occasionally drink spirits. In the VAD study is indicated that strong drinks are drunk by <4% of the minors.[18]

One eight of the respondents mentioned that >/= 4-5 glasses of beer or wine were drunk by minors on each occasion. This is defined as 'binge drinking'.[2] The European Survey Project on Alcohol and Drugs (ESPAD) is a survey conducted every four years amongst 15 to 16-year-olds in 36 European countries. In 2015, 'binge drinking' was observed in 37% of boys. This percentage was slightly lower amongst girls of that age group.[19] The fact that so many minors are exposed to binge drinking is alarming. The consequences of alcohol consumption are related to the quantity that is consumed. After 1 to 3 standard glasses of alcohol, the inhibitions disappear and memory disorders or blackouts can occur. After 4 to 7 glasses, balance disorders may appear, movements become less coordinated and information is more difficult to store in the cognitive system. Increased alcohol consumption leads to stronger narcotic effects and raised risk of unconsciousness.[20]

Based on our survey we can conclude that the acute consequences of drinking alcohol remain limited. Nevertheless, accidents (5%), loss of consciousness (1.1%) and alcohol intoxications (0.6%) happened amongst 14 to 16-year-olds after drinking alcohol at the youth movement. Alcohol users, including young people, often underestimate alcohol-related harm.[21] Their brains are in full development and as a result they react more impulsively and often begin to show risky behaviour, such as excessive alcohol consumption.[11] Due to the neural changes, the young people are temporarily more sensitive to certain effects of alcohol, such as the rewarding effects. This further stimulates consumption. During puberty there are also changes in their social context: the known shift from parents to peers as the first source of support.[22]

Accordingly, several studies showed that one of the most important predictors for drinking behaviour amongst young people is peer influence.[23] Recent research has shown the comparatively strong influence of peers compared to parents and family.[24] Positive alcohol-related attitudes are enhanced when alcohol is talked about positively in peer groups. This may lead to an increase in alcohol consumption.[25] Mostly, the adolescents see their leaders as an example. Therefore, they will rather accept advice from them than from their parents during this period of their lives.[22] In this way, leaders of the youth movement can play an important role in the prevention of excessive alcohol consumption amongst young people.

We used a series of statements to explore the perspectives of the young adults supervising the young people, since they can have a major role in prevention. A large majority of the leaders stated that they were familiar with the rules of the coordinating organisations, in particular the rules that completely ban alcohol consumption amongst <16-year-olds. However, the results show that on special occasions the leaders ignore these rules for a while and allow alcohol consumption. Nevertheless, almost all respondents found it important to have clear rules on alcohol consumption within the group. Because of the adolescent's sensitivity towards the opinions of peers, nearly half of the interviewed leaders believe that the youth movement is a good and protected environment to guide young people in drinking alcohol. It is noteworthy that a link could be shown between the gender of the respondent and the answer to this statement. Especially men appeared to agree with this. It is also notable that mainly groups where this age group had ever drunk alcohol, agreed with this statement. They may be right if we bear in mind that alcohol use can be understood as a developmental tool during an adolescent's search for autonomy and self-reliance. Increased parental supervision and the imposition of restrictions on adolescents can have a negative impact on this developmental task.[25]

However, in order to raise awareness amongst young people with a chance of effective success, it is necessary to adjust young people's views on alcohol. In Belgium, adolescents come into contact with alcohol from an early age. Therefore, it is necessary to make them aware of the harmful effects and all possible (negative) consequences of alcohol consumption already from late childhood onwards.[22] In this context it is also interesting to point out a study from the USA which shows that punishing alcohol consumption is not recommended, but this subject has not yet been sufficiently studied. Hitherto, it can be said that it is more important to inform young people about the harms of alcohol consumption and to teach them in a positive way how to reduce these harms.[26]

Within the youth movements, the coordinating organizations have already taken steps towards more prevention of alcohol consumption by minors. In their awareness-raising actions, they try to introduce their members to the subject playfully. 'Chirojeugd Vlaanderen', for example, offers the 'Sixpack game' for this purpose.[27] The effectiveness of game elements within alcohol prevention by youth movements goes beyond the scope of this article, but would offer an interesting new perspective on the attitude of youth movements towards alcohol consumption.

Limitations

Our survey did not consist of a validated/standardized questionnaire, because they did not correspond to the purpose of our study. Secondly, there is a chance of 'selection bias' because of voluntary participation of the respondents. Another inherent weakness of our research is the chance of 'memory bias'. Self-reporting - including underestimating or overestimating events - influences the formulation of answers. Finally, 'response bias' must also be taken into account: respondents could consciously or unconsciously give socially desirable answers to personal questions. The latter was guarded by guaranteeing strict anonymity.

Conclusion

Because the consequences of alcohol consumption are still underestimated and there is a social acceptance by society, young people have a positive view towards alcohol consumption. Youth movements can have a crucial role here. Although some initiatives have already been undertaken within youth movements, the results of the study show that preventive measures are not yet fully implemented. Further awareness-raising of young people about alcohol consumption is needed. More in-depth research on drinking experiences of young people within the youth movement or within different contexts of leisure would be a valuable contribution to this topic.

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Management of arteriovenous malformations in pediatric population: about two cases

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Keywords

arteriovenous malformations – pediatric – intracerebral hemorrhage

Abstract

We report 2 cases of hemorrhagic presentation of brain arteriovenous malformations (AVMs) in the pediatric population and their management. AVMs are sporadic congenital abnormalities developing between the 3rd and 8th weeks of intrauterine life. In spite of their congenital origin, only 18- 20% of cerebral AVMs are diagnosed during infancy and childhood and are symptomatic after 15 years. This could be due to the fact that most pediatric AVMs are only detected after rupture. Incidence represents 0.1 to 4% of the general population. The prevalence is estimated to be between 0.06 and 0.11%. This risk is higher within the first 5 years after diagnosis. Several morphologic AVM characteristics are associated with hemorrhagic AVM presentation, including small AVM size, deep venous drainage, and the presence of associated arterial aneurysms. Intracranial hemorraghe is the presenting clinical manifestation in 75-80% of pediatrics patients. Upon initial diagnosis of intracerebral hemorrhage on non-contrast CT, workup and treatment should be initiated without delay. Multimodality therapies are currently available. In most cases, the complete cure requires several interventions.

Introduction

The annual incidence of brain arteriovenous malformations (AVMs) in the general population is estimated between 0.1 and 4% with an annual hemorrhage rate between 2 and 10% and a 50% risk of neurological morbidity (1). The re-rupture rate is estimated to be 2–4% resulting in a mortality rate up to 25% (1). This risk is higher within the first 5 years after diagnosis. In comparison with the adult population, the literature regarding pediatric presentation is scarce. However, AVMs reportedly carry a higher rate of rupture in children than in the adult population. Several morphologic AVM characteristics are associated with hemorrhagic AVM presentation, including small AVM size, deep venous drainage, and the presence of associated arterial aneurysms. We report 2 cases of hemorrhagic presentation of brain AVMs in the pediatric population and their management.

Clinical Cases

Case 1: A 15-year-old girl was referred from another institution with acute unilateral headache, left hemianopsia, vision disorders and vomiting, without alteration of consciousness. Unenhanced brain CT (computerized tomography) showed a large right parieto-occipital hematoma (Figure 1). A cerebral digitalized subtraction angiography (DSA) was performed and confirmed the presence of an AVM (Figure 2). Embolization achieved the immediate angiographic cure of the lesion. At follow-up, the only residual symptoms are reading difficulties. Follow-up DSA at 3 months identified a tiny early venous drainage so that additional stereotactic radiosurgery by gamma knife was performed (Figure 3).

Case 2: A 11-year-old girl presented with acute onset of headache, vomiting and alteration of consciousness. Brain CT revealed a massive ventricular hemorrhage without edema (Figure 4). She was intubated and an external ventricular drain was placed. Brain MRI (Magnetic Resonance Imaging) and DSA identified a deeply located brain AVM. Immediate embolization was performed, allowing to occlude 80% of the nidus and several AVM related aneurysms, suspected to be the cause of the hemorrhage (Figure 5). Additional gamma-knife radiosurgery has been planned as well. The patient keeps a discrete lower left limb paresis.

Discussion

AVMs are sporadic congenital abnormalities developing between the 3rd and 8th weeks of intrauterine life. They result from the persistence of a connection between one or several arteries and one or several veins without interposition of the capillary bed. Annual incidence represents 0.1 to 4% of the general population (1). The annual prevalence is estimate to be between 0.06 and 0.11% of the general population (2). Despite their congenital origin, only 18- 20% of cerebral AVMs are diagnosed during infancy and the cerebral AVMs are only symptomatic after 15 years (1). This could be due to the fact that most pediatric AVMs are only detected after rupture.

Initial hemorrhage risk factors include the size (small), a previous history of hemorrhage, deep-seated or infratentorial AVMs, deep venous drainage, female sex, associated aneurysms, and diffuse AVM morphology. Only deep AVM location and exclusive deep venous drainage showed an independent effect on both initial and follow-up hemorrhage. Initial hemorrhagic presentation appears to be the strongest predictor for subsequent hemorrhage in untreated AVM patients.

The overall risk of hemorrhage from an untreated AVM in all age groups is estimated to be between 2 and 10% yearly, but the actual rupture risk may differ between distinct patient subgroups. They tend to rupture more frequently in children than in adults (1).

The symptoms at the time of presentation are various. Intracranial hemorrhage is the presenting clinical manifestation in 75-80% of pediatrics patients (2). Symptoms of congestive heart failure (18%) predominate in the newborn whilst neurological symptoms such as stroke, seizures or hydrocephalus (36%) occur more commonly in infants and older children (2). The diagnosis is based on DSA. A DSA should be performed when a cerebral hemorrhage is seen on CT scan.

Multimodality therapies are currently available. In most cases, the complete cure requires several interventions. The Spetzler-Martin grading system classifies AVMs based on location, size, and draining venous system, and it is used to assess the patient's risk of neurological deficit after open surgical resection. Surgery is less often performed and reserved to cases where hematoma removal is necessary. If high intracranial pressure is present, an external ventricular drainage or an evacuation of the hematoma must be performed, possibly including removal of the AVM.

One or several trans arterial or rarely transvenous embolizations reduce the risk of bleeding and are associated with another therapy in case of AVM remnant, most often stereotactic radiosurgery (Gamma-Knife). Gamma Knife is a device used for neurosurgical treatments in stereotaxic radiosurgery, delivering a high dose of ionizing radiation in a very localized manner. This strategy is efficient and associated with low morbidity and mortality rates. Recommendations promote early treatment intervention in patients presenting with AVM hemorrhage, particularly in those harboring additional morphologic risk factors. Prospective data on treatment-related AVM morbidity, however, are lacking. There are 2 main types of embolizing agents: particles which are the most widely used embolizing agents (non-spherical particles, microspheres), and liquids (glues, gels, sclerosing agents, viscous emulsions) (3).

Conclusion

Upon initial diagnosis of intracerebral hemorrhage on non-contrast CT, work-up and treatment should be initiated without delay. MRI and arteriography should proceed in the management. Intensive care and monitoring are indicated. Depending of the location of hemorrhage, if high intracranial pressure is present, an external ventricular drainage or an evacuation of the hematoma must be performed, possibly including removal of the AVM as well. In other cases, embolization reduces the risk of rebleeding. Stereotactic radiosurgery is possible mostly in case of AVM remnants after embolization. Prospective data on treatment-related AVM morbidity, however, are lacking.

Figure 1. Unenhanced brain CT at admission (axial MPR): right parieto-occipital hematoma

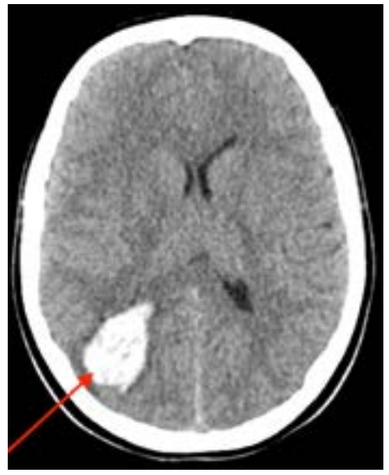


Figure 2. Pre-embolization DSA (frontal view) showing an early venous drainage

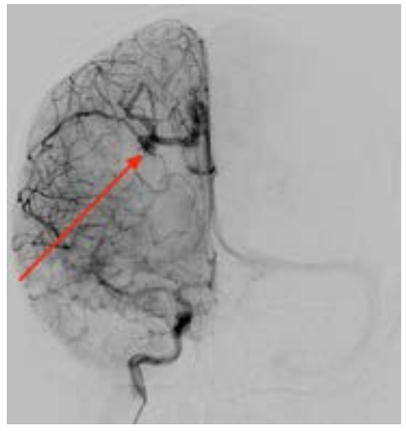


Figure 3. Post-embolization DSA (frontal view) showing complete angiographic obliteration

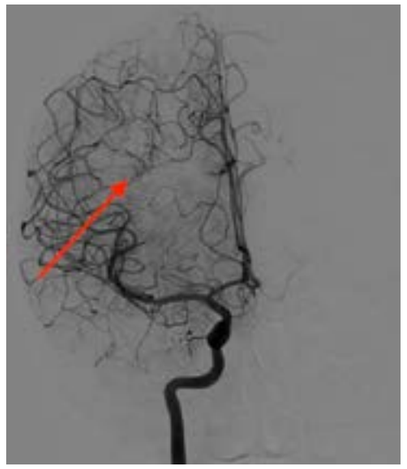


Figure 4. Unenhanced brain CT at admission (sagittal MPR): massive ventricular hemorrhage

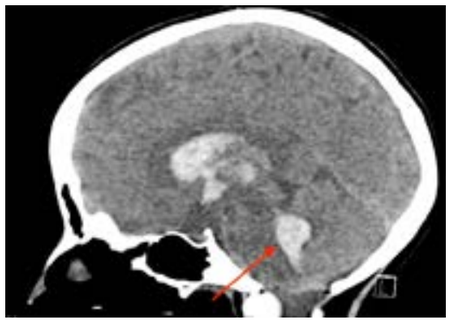
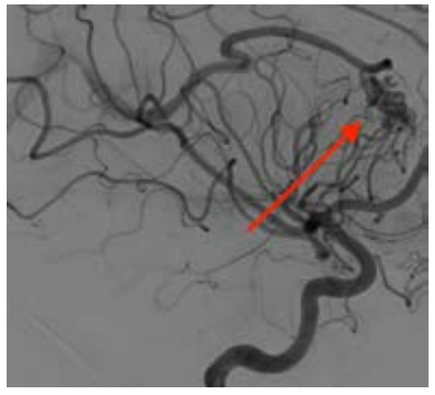


Figure 5. Pre-embolisation DSA (oblique view) showing the nidus and the deep venous drainage



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A rare presentation of congenital spinal dermal sinus

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Keywords

Dysraphism, spinal dermal sinus, paediatric neurosurgery, case report

Abstract

A spinal dermal sinus is a regularly occurring type of spinal dysraphism, predominantly localized in the lumbosacral region. Early detection is essential to prevent complications, e.g. infections. We present a neonate with a congenital skin defect near the left scapula. MR-whole spine demonstrated a low cervical spinal dermal sinus, dorsal deviation of the dural sac and tethering of the myelum. Low cervical and paravertebral position is very unusual. Patient was referred to a paediatric neurosurgical centre for surgical correction. Early diagnosis of spinal dermal sinus is crucial as earlier surgery is more successful in preventing irreversible neurological damage.

Introduction

A congenital dermal sinus is a tract lined by epithelial cells from the skin into the underlying structures, which can end anywhere between skin and thecal sac. A dermal sinus terminating in the intrathecal space is called a spinal dermal sinus (1,2). The development of meningitis and abscesses is known as a serious complication (1). Multiple other anomalies (for example, tethered cord and inclusion tumours) are associated with a spinal dermal sinus and can cause neurological impairment themselves (1,2). Therefore, early recognition and treatment are essential (3). We present a low cervical spinal dermal sinus in a neonate, a rather rare phenomenon.

The patient was born by vaginal delivery at 36 weeks plus one day, a spontaneous preterm birth, after an uncomplicated pregnancy with normal ultrasound examinations. The patient did well after birth (Apgar scores were maximal) and had a birth weight of 1918 grams (percentile 2,3). On physical examination a single umbilical artery and a small skintag between both nipples were visible. During inspection of the back, a skin defect near the left scapula was seen (figure 1).

Ultrasound of this defect showed a spinal dermal sinus and a magnetic resonance (MR) scan was performed for more detailed imaging. This showed agenesis of processus spinosi and transversi from C4 to C7, dilatation of the dural sac and tethering of the cervical myelum. Dorsal from the myelum a small lesion (circa five millimetres) was present, suggesting a demoid cyst. The further course of the spine showed no anomalies (figure 2A and 2B). Surgical correction was planned once patient reached the age of six months. Prior to the surgery patient was followed-up ambulatory. Initially, she had adequate growth and development. When she was three months old, we noticed a delay in development and some minor dysmorphias (frontal bossing, large anterior fontanel, low set ears). It was unclear whether this was associated with the aforementioned spinal dermal sinus. Microarray investigation and whole exome sequencing showed no anomalies.

At the age of seven months patient underwent surgical correction of the spinal dermal sinus in a neurosurgical hospital for children (figure 3). Surgery was originally planned at the age of 4,5 months, but was delayed due to patient's illness at that time. The entire spinal dermal sinus was removed by taking away the skin fold near the left scapula and by subsequently dissecting the connection into the intrathecal space. A small and expected dermoid cyst at the end of the sinus was also removed and the myelum was released, which is clearly visible on the postsurgical MR-scan (figure 2C). Surgery and recovery were uncomplicated. After surgery, the delay in motor development continued to exist. When our patient was eleven months old, she was unable to sit independent and she could not roll over from tummy to back. The most recent MR-scan (one year after surgery) showed signs of hypotrophy of the funiculus lateralis, which can be associated with injury of the corticospinal tract. No retethering was seen. At two years follow-up, the patient could speak single words but was not able to walk independently. There was an asymmetry in arm movement (left arm favoured over right). She was referred to a paediatric neurologist, who diagnosed limited motor function of the right arm, presumably due to residual damage of the right corticospinal tract. The patient had a wide based gait and preferred bottom shuffling. There was no evidence of hypo-, hyperreflexia or pathological reflexes. The patient continued physical and occupational therapy at a rehabilitation centre.

Discussion

Epidemiology and pathophysiology

A spinal dermal sinus is a type of spinal dysraphism that occurs in one out of 2500 live births (1). The connection between skin and intrathecal space is formed by incomplete separation of neuro-ectoderm and cutaneous ectoderm during the third to eighth week of pregnancy. This is most likely, a consequence of incomplete disjunction and can occur at every level of the spine (1,2-4). Most spinal dermal sinuses are lumbar, lumbosacral or sacral (80-95%). Cervical and thoracic spinal dermal sinuses are rare (1-10%), and literature consists of predominantly case reports and (small) case series (1-3,5). Most are located in the midline, but paravertebral localisation is possible, as in our patient (2). The combination of a cervical and paravertebral localisation is very unusual and has not been described in previous case series (1-3,5). Other abnormalities like inclusion tumours (lipoma, dermoid, epidermoid), split cord malformations, tethered cord and missing vertebral arches are associated with the presence of a spinal dermal sinus (2,4,6). Associations with specific DNA mutations are not described in literature to our knowledge (1-7).

Symptoms

More than 90% of spinal dermal sinuses are diagnosed in response to cutaneous anomalies, such as sinus ostium, hemangioma, meningocele, dimple,

Figure 1. This picture was made serveral hours after birth and shows the appearance of the spinal dermal sinus near the left scapula.

hypertrichosis or cerebrospinal fluid fistula. Abnormal neurological examination (especially in older age) is common (1-3,5). Pain, scoliosis, urinary incontinence and constipation are other reported symptoms. Presentation with (recurrent) meningitis is not uncommon (1). Abnormalities during neurological examination are more often seen after the age of one year and are caused by consequences of associated neurological anomalies (tethered cord, inclusion tumours) or complications of infections (meningitis, abscesses) (3,5). The infection rate in patients older than one year is significantly higher than in younger patients (1). Diagnosis is usually (and preferably) made during infancy, however, diagnoses until the age of 55 years are described in literature (3,5).

Sacral dimple

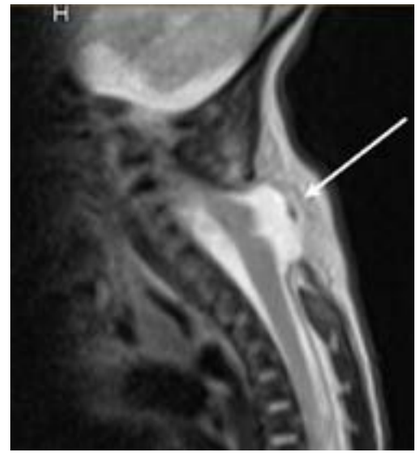
A sacral dimple occurs in 4% of neonates and is not a part of the spectrum of spinal dermal sinuses. Sacral dimples are shallow, blind ending, not associated with cutaneous abnormalities and/or spinal pathology and are therefore harmless. A dimple is typically found within the gluteal cleft, while spinal dermal sinuses usually are localized above. When sacral dimples show cutaneous abnormalities (for example hypertrichosis), further investigations are necessary (1,3).

Diagnosis and treatment

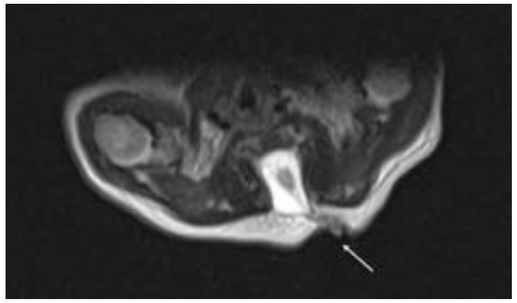
Although a spinal dermal sinus can be diagnosed by ultrasound at very young age, MR-scan is the preferred imaging modality (1,5). MR-scan allows diagnosis of other abnormalities of the spine (1). As a spinal dermal sinus conveys risk of infectious complications with possible irreversible neurological damage, surgery is indicated preferably within 12 months after birth (1,5). The procedure includes excision of the whole sinus tract and the associated inclusion tumour (present in 50% of the cases). Surgical outcome is generally favourable: pre-operative abnormalities of neurological examination (mainly progressive sensorimotor loss of function) improve in 45-80% of the patients and remain stable in the remaining patients. Postoperative neurological deterioration is rarely described in literature, in line with our clinical experiences (2,3,5,7). Risk groups for irreversible neurological damage include older age combined with motor weakness and concurrent urological anomalies (10-41%) (2,3,5,7). The increased risk with advanced age reflects the impact of associated anomalies as tethered cord or infectious complications (2,3,7).

Figure 2. Magnetic resonance whole spine

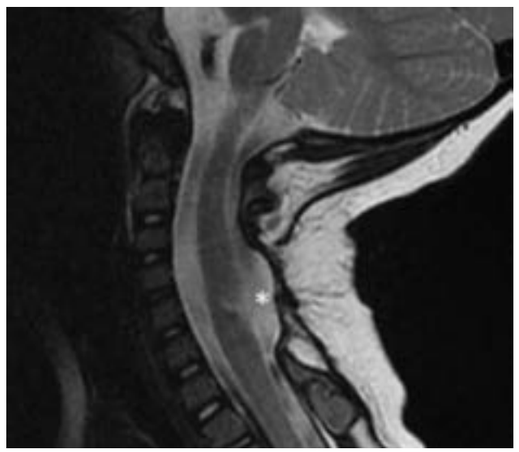
A. Sagittal T2 image, illustrating the absent spinous processes from C4 to C7. The dural sac deviates dorsally (arrow). The myelum is distorted and pulled dorsally by tethering.



B. Transversal T2 image, illustrating the low cervical spinal dermal sinus tract (arrow).



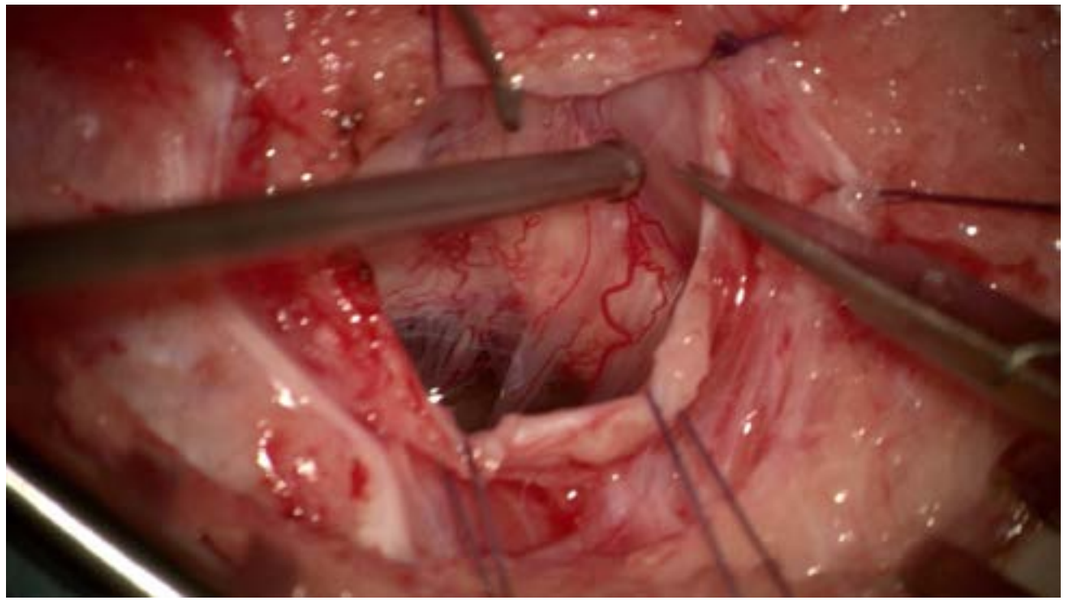
C. Postoperative sagittal T2 image. Tethering has been resolved, liberating the myelum. There appears impression of the myelum at the right with probable hypotrophy of the lateral funiculus (asterisk).



Conclusion

As our case shows, spinal dermal sinuses can develop at all spinal levels and can be localised off-midline. Therefore, the whole spine must be thoroughly examined for their presence. Early diagnosis of spinal dermal sinus is crucial as earlier surgery is more successful in preventing irreversible neurological damage. Ideally, diagnosis is made before the age of twelve months.

Figure 3. Peroperative image before untethering. The dura is preparated and positioned with sutures. The myelum is horizontal in this image. The spinal tract resulted into tethering of the spinal cord. As a result, nerve roots (projecting vertically) are pulled to the patients left side (upward in the image).



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Article

Some trainees are more equal than others - The paediatric residency payment gap, as illustrated in a cross-sectional study in Flanders

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Keywords

Residency, trainees, working conditions, pay gap, salary

Abstract

Objective:
In Belgium, medical doctors in specialty training are employed under a distinct statute (sui generis). Recent polls showed relevant heterogeneity in adherence to employment contracts, wages, and social benefits. We aimed to study the wages, working conditions and fringe benefits and identify this heterogeneity among Flemish paediatric trainees.
Methods:
We conducted a cross-sectional study among approximately 200 trainees in paediatrics in Flanders. By an anonymized survey, wages, working conditions and fringe benefits were collected.
Results:
Fifty-four surveys were completed, containing data from a quarter of all trainees. Data concerned employment regimens from 21 hospitals. The median gross and net monthly salary were, respectively, €3175.55 (IQR 3031.5-3365) and €2400.52 (IQR 2265.5-2645). Only minimal effect of seniority could be found. The median extra salary for all earnings besides the standard income was €311.16 per month, an additional income of 15%. The median net income per hour (€9.23) just exceeds the nationally fixed minimum wage. Fringe benefits were infrequently provided.
Interpretation:
The trainee in paediatrics in Flanders is being paid disproportionately and unfairly. The roots for this inequity can be traced back to an outdated statute, an inadequate legal framework and a weak position on the labour market. With this detailed survey, we found relevant heterogeneity in trainees' incomes, with unevenly provided fringe benefits, lack of transparency and misinformation being frequently present.

Introduction

At the four Flemish universities (Ghent University, KU Leuven, University of Antwerp and Free University of Brussels), around 200 physicians are under training to become a qualified paediatrician. These four universities give shape to the basic medical curriculum with a uniform training program, after which the universities are also responsible for the five-year paediatrics training program. During this period, trainees are employed in their own university departments or in district hospitals (within and outside linguistic and national borders). An annual permutation is present according to the tide of the academic years. The diversity between these different training centres contributes to the broad base that is required in becoming a paediatrician (1).

The social statute under which these all medical trainees have been employed in Belgium, the so-called sui generis statute, which is in place since April 1, 1983, was initially created as a temporary measure, but continues until today. The sui generis, which is in place for all medical trainees in Belgium, implies a partial employee statute, especially with regard to social securities (e.g. unemployment benefits, pension acrrual, etc. are not embedded in the minimum wage conditions). In exchange, limited taxes are payed. After more than 35 years, the minimal social protection contained in this unique statute seems outdated, especially taking into account the important socio-economic developments in the health care sector and a constantly changing society. Several interest groups (2-4 have therefore critically examined this statute and have questioned its further existence in recent years.

The working conditions of the trainees in Belgium were specified in multiple legal provisions (including ministerial decree Colla (30/04/1999) Article 5 on equitable compensation and by the law of 12/12/2010 Article 5-7 on the maximum working hours and additional working hours). Additionally, attempts to regulate these legal provision in practice have been performed by university training centres with ongoing quality control monitoring and efforts to improve on the work-life balance of trainees. Nevertheless, a recent survey (2) revealed important heterogeneity in complying with these conditions. In addition, legal gaps persist allowing for a penalty-free interpretation of the employment contract. It is furthermore important to mention that the trainee is employed in various hospitals during his/her training program and that, for practical reasons, filling in these internships is not always done with full input (or permission) from the individual trainee.

To gain insights into the current employment conditions of paediatric trainees, a survey was conducted concerning wages, working conditions and fringe benefits within this professional group in Flanders and Brussels.

Material and methods

An electronic survey was drafted and sent out by junior representatives of the Flemish Association for Paediatrics (Jong VVK). From December 2018 onwards, the surveys were distributed by e-mail via the Flemish universities and the Jong VVK members among their fellow trainees. The survey consisted of three parts. The first part explored general data such as university and number of years in training, the current hospital of employment, if and how working hours were registered, which type of on-call schedule applied and whether the trainee agreed to the arrangement with regard to the so-called opt-out (extra compensation for extended duty hours from an average of 48 to 60 hours per week). Part two asked for net and gross wages (both basic and total wages), and extra earnings for participating in on-call duties and opt-out. The respondents were able to enter these manually, but a module was also provided to upload scans of payslips and/or quarterly or annual overviews (after anonymizing). Part three questioned any alternative compensations (fringe benefits) such as vacation salary, end-year bonus, commuting fees, training budget, and insurances. It was permitted to enter data retrospectively (a maximum of one year in the past), for example to provide data from several training centres. Before analysis, all data were anonymized.

Large variation appeared on how the salary was calculated between the training centres. Therefore, the focus in the analysis was put on the gross basic monthly wages (most uniformly stated on the salary slips and contracts) and the net total monthly wages including all extras such as on-call duty or opt-out compensation or any other incomes after deduction of taxes (the amount received on the bank account).

Both parametric and non-parametric statistical tests were used after control of normality (Shapiro-Wilk test). The parametric independent t-test and one-way ANOVA (both also after checking homogeneity in variances with the Levene's test) and the non-parametric Mann-Whitney U and Kruskal Wallis test were used.

Results

Demographics

Fifty-four surveys were completed by 48 unique trainees in paediatrics, of which 6 of them thus entered data from two hospitals (see Table 1). Half of the surveys were completed by trainees from the Ghent University (27/54; 50.0%). With 14 questionnaires, the University of Antwerp provided a quarter (14/54; 25.9%) of the answer. To a lesser extent, data were available from Brussels (7/54; 13.0%) and Leuven (6/54; 11.1%). About half of the respondents (26/54; 48.2%) worked in one of the 4 university hospitals, the majority of which in the Ghent University Hospital (13/26; 50%). The other half provided data from one of 17 non-university, district hospitals. The respondent's average seniority was 2.98 years of training. One third (21/54; 38.9%) of the data came from juniors (≤ 2nd years).

Wages

Half of the respondents (31/50; 57.4%) indicated that seniority was taken into account when calculating their salary. A quarter (15/50; 27.8%) of trainees did not know whether seniority was accounted for. Two Dutch colleagues specifically noted that their years as a "free assistant" (so-called ANIOS statute in the Netherlands) were not counted for in Belgium. Previous years in a research setting were also only partly counted for according to the respondents.

Working hours were not registered in almost half of the trainees (24/52; 46.2%). Two trainees indicated that only their hours on-call were registered, while for one colleague every hour was accounted for except the on-call hours. More than 9 out of 10 trainees consented with the rules regarding opt-out and all respondents participated in on-call duties, 86% (43/50) of whom were staying in the hospital for the night. Of the 4 trainees who indicated that they did not participate in the opt-out, 2 worked in a Dutch hospital.

Income details were provided on 47 employment regimens (Table 2). The median gross basic monthly wage and net total monthly wage was €3175.55 (interquartile range (IQR) 302.00) and €2400.52 (IQR 369.74), respectively. A wide spread in the various salary scales was found, including variations within the same university (IQR 202.39 to 577.91) or depending on the years

Table 1. Demographic variables of the cohort of paediatricians in training studied

Demographics		n	%
University	Ghent University	27	50.0%
	Free University of Brussels	7	13.0%
	University of Antwerp	14	25.9%
	KU Leuven	6	11.1%
Current employer or internship	University hospitals	26	48.1%
	UZ Gent	13	24.1%
	UZ Antwerpen	6	11.1%
	UZ Brussels	4	7.4%
	UZ Leuven	3	5.6%
	District hospitals	28	51.9%
	ZNA Paola	5	9.3%
	Amphia Breda	2	3.7%
	ZNA Jan Palfijn	2	3.7%
	Serruys Ostend	2	3.7%
	AZ Groeninge Kortrijk	2	3.7%
	AZ Maria Middelares Ghent	2	3.7%
	ZP De Haan	2	3.7%
	HHZH Lier	2	3.7%
	AZ Delta Roeselare	1	1.9%
	Our Lady of Aalst	1	1.9%
	Chirec Brussels	1	1.9%
	AZ Klina	1	1.9%
	ZOL Genk	1	1.9%
	HHZH Mol	1	1.9%
	RZ Tienen	1	1.9%
	Virga Jessa Hasselt	1	1.9%
	AZ Turnhout	1	1.9%
Paying agency	My current employer	48	88.9%
	My university	5	9.3%
	I do not know	1	1.9%
Seniority (years in training)	1	14	25.9%
	2	7	13.0%
	3	8	14.8%
	4	17	31.5%
	5	7	13.0%
	6	1	1.9%
	Average (SD)	2.98 (1.5)	
Seniority is reflected in my salary	Yes	31	57.4%
	No	4	7.4%
	Do not know	15	27.8%
Working hours	Full registration	25	48.1%
	Partial registration	3	5.8%
	No registration	24	46.2%
On-call duties	Sleeping-in	39	78.0%
	From home	7	14.0%
	Both	4	8.0%
Opt-out	Yes	47	90.4%
	No	5	9.6%

in training (IQR 255.07-420.0). The differences between the P95 (the highest-earning trainees) compared to the P5 (those with the least profit) was €713.79 net per month. The wealthiest 5% had a salary that was at least 134% of the 5% of trainees that earned least. When the net basic monthly salary and the net total monthly salary were both provided (n = 25), the median difference between the two was €292.32, corresponding to what the trainee thus is earning extra per month for all services that are not included in the basic wages, i.e. on-call duties. The difference between the P95 and P5 on this additional income is €627.30. If we consider a working week of 60 hours (as is consented with the opt-out in most), the trainee in Flanders earns a median net €9.23 per hour (IQR €1.42).

There is an increase in median salary from the first to the fifth year of training of 8.1% gross and 11.0% net (as plotted in Figure 1). Per year of seniority there is thus an median net salary increase of €48.95 per month. The

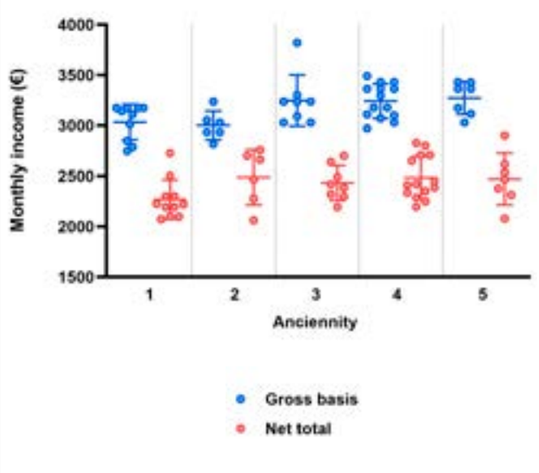
Table 2: Salary of the investigated cohort of paediatricians-in-training

Salary	Basic gross		Total net	
n	46		47	
	Median	IQR	Median	IQR
Salary	€3,175.55	€302.00	€2,400.52	€369.74
Per training year				
1	€3,112.25	€387.35	€2,225.19	€255.07
2	€2,983.15	€120.79	€2,565.14	€420.00
3	€3,238.09	€208.57	€2,404.15	€255.28
4	€3,239.81	€265.44	€2,418.02	€370.82
5	€3,365.00	€310.92	€2,469.92	€300.63
6	€3,723.74	-	€2,497.61	-
Sig *	<0.05		0.107	
Per university				
Lowest median	€3,092.19	€284.39	€2352.89	€311.68
Highest median (gross)	€3238,84	€189,45	€2,421.00	€577.91
Highest median (net)	€3,054.79	€165.21	€2,662.56	€202.39
Sig *	<0.05		0.183	
Guard services				
Sleeping-in (or both)	€3,176.55	€333.5	€2,452.92	€359.56
From home	€3,087.25	€144.05	€2,225.19	€170.03
Sig **	0.425		<0.001	
Opt-out				
Yes	€3,175.55	€270.50	€2,387.65	€286.05
No	€3,365.00	€791.5	€2,763.87	€481.42
Sig **	0.345		0.160	
Working hours				
Full registration	€3,175.55	€310.56	€2,452.92	€350.00
Partial registration	€3,397.09	€63.30	€2,301.92	€27.94
No registration	€3,143.00	€223.84	€2,387.30	€311.37
Sig *	0.114		0.409	
Number of fringe benefits				
1-2	€3,158.44	€333.5	€2,326.44	€348.62
> 2	€3,238.09	€303.33	€2,492.67	€287.11
Sig **	0.265		0.122	

* Kruskal Wallis

** Mann-Whitney U

Figure 1. Evolution of the basic gross and total net income including all additional salary, as a function of seniority. Plot displaying the gross basis (blue) and net total (red) for 47 employment regimens. Median and interquartile ranges are shown.



differences in salary as a function of seniority are significant for the gross basic salary (P <0.05), but not for the net total salary (P = 0.107). A post-hoc analysis showed statistical significant differences in the gross wages for each of the two junior years in comparison with each of the three senior years (individual Mann-Whitney U tests P<0.05). Besides for the differences between first and fourth year of training (P<0.05), the net wages did not significantly differ. More than a quarter (15/50; 27.8%) of the trainees did not know whether seniority was accounted for in their income.

A difference in salary was noted depending on which of the 4 universities the trainee was associated with. The difference in gross salary was statistically significantly different between the universities (P <0.05). The median net salary differed from a minimum of €2352.89 to a maximum of €2662.56 when we compare the wages of trainees to the four training centres. Although we have to take the limited sample size of these subgroups into account, the differences between the universities cannot be explained by the proportion of younger students (the university with the highest net salary even had the largest percentage of first and second years).

Performing sleep-in duties (as opposed to being on-call from home) causes the trainees to improve their median monthly salary by €227.73 (P = 0.001). The small group that did not fall under the rules of opt-out was too heterogeneous to carry out a statistically valuable analysis (and also contained some outliers). Even taking seniority into account, the net monthly wages of two trainees working in the Netherlands (without opt-out and thus with a maximum of 48 working hours per week) were €316.61 higher than their Belgian colleagues, almost all of whom complete a 60-hour week (P <0.05).

Fringe benefits

A minority of trainees (8/51; 15.7%) indicated they have a separate budget for training. An end-year bonus and vacation salary were only provided in respectively 4 and 1 trainee (both out of 51 respondents). Six out of 10 trainees benefit from a bicycle fee (32/51; 62.7%) and the same number of trainees indicate that they do not receive a compensation for commuting with the car (31/51; 60.8%). A public transport subscription was refunded in a quarter of respondents (12/51; 23.5%). Hospitalization insurance is the only insurance that is provided in at least half of the trainees by their employer. Generally, trainees were not well informed, as except for hospitalization insurance (where only 3 trainees indicated they did not know if they had it), for all other fringe benefits at least 15.7% of trainees indicated not to know if they could make use of it (up to 47.1% in training budget). Fringe benefits are summarized in Table 3. Trainees that had fewer fringe benefits had (although not statistically significant) lower wages than colleagues with multiple additional benefits.

Table 3: fringe benefits and alternative reimbursements of the cohort paediatricians in training studied

Fringe benefits and alternative fees	Yes		No		I do not know		Total
	n	%	n	%	n	%	n
Training budget	7	15.6%	18	40.0%	20	44.4%	45
Vacation salary	1	2.2%	34	75.6%	10	22.2%	45
End-year bonus	4	8.9%	33	73.3%	8	17.8%	45
Commuting fees							
Bike	28	62.2%	9	20.0%	8	17.8%	45
Car	8	17.8%	28	62.2%	9	20.0%	45
Public transport	10	22.2%	18	40.0%	17	37.8%	45
Insurances							
Civil liability	18	40.0%	14	31.1%	13	28.9%	45
Hospitalization	24	53.3%	19	42.2%	2	4.4%	45
Additional pension ("group insurance")	7	15.9%	26	59.1%	11	25.0%	44

Discussion

This cross-sectional study presents local differences in working conditions and the social statute among paediatric trainees in Flanders, Belgium. A big variation in the salary of trainees could be observed, irrespective of the university or the hospital of employment. Discrepancies could not be explained by a difference in job content. Seniority does not result in a significant wage increase, despite the meaningful increase in knowledge, skills and responsibilities over the years. Seniors tend to work more independently, treat patients with more severe or critical conditions and often participate in the supervision of their junior peers.

The net hourly salary, which does not exceeds 10 euros, is less than what could be expected for a well-educated employee performing physically and emotionally stressful work, frequently during the night hours. Although the starter salary is in the same range of fellow employees with an academic master's degree in Belgium (5)(), this comparison obviously does not account for a working week of 60 hours. In many cases it was difficult to calculate the net monthly wage from the gross monthly wage. was obtained and calculations made on the payslips were often not clear or verifiable. The extra net salary for all additional performances outside the standard working week is limited (around 10% extra).The course of the traineeship might be associated with certain uncertainties. Across all disciplines, it is a trajectory that is frequently characterized by changing (annual) plans, and governmental, university or local policy shifts. Moreover, the quality of training is unfortunately not the only concern as training content is biased by the need to fill in departments, hospitals and on-call duties. As such, the trainee is often performing tasks that not lead to a direct gain in knowledge or skills. On the other hand, (thorough and high-qualitative) training might be worth a fortune if sufficiently provided. Supervising on the trainee's tasks, providing teaching on up-to-date and evidence-based knowledge and skills and – in the end – being acknowledgeable for his/her clinical activities are important efforts that should always be prominently present in the trainee-trainer relationship. If, during the ever busy clinical tasks, these challenging demands are largely met, the net salary will certainly not be the only "benefit" at the end of the month. As such, these efforts should be appreciated separately and in addition to the net salary or the inevitable daily tasks without direct impact on clinical knowledge or skills.

About a quarter of the paediatricians-in-training in Flanders was reached with this survey. Although this could be regarded as an underrepresentation, it should be noted that data were obtained from over 20 different training centres. To our knowledge, this is the most extensive and detailed income-related survey among medical trainees. In 2002, a questionnaire was conducted among 42 responding gastroenterology trainees from 10 different European countries (monthly income ranging from €767 to €2180) (6). A recent summary paper reported on wages of medical trainees in 8 European countries (7). In those countries, the local economic situation can partly explain differences in wages. The employer or paying agency can be the university, the local hospital, the supervising department or the government.

The small sample size in this cohort did not allow a sub-analysis per year of accomplished traineeship or between different training settings. Furthermore, no account was taken of household members as dependents, which could have influenced net wages. To correct for these possible differences, future research could account for cumulative wages for the entire traineeship.. In this survey, no inquiries were made of performances delivered. Such analyses traditionally focus on the (usually ample) working hours per week, although we argue that physical and mental workload deserves at least as much attention. This information could add additional value to the data, although we believe that not only the standardization of payment conditions, but also workloads should be a priority for coming years. It is obvious that a better pay cannot justify for violating applicable work regulations (such as the maximum number of hours per week). In addition, important indirect data are available in the analysis that the remuneration of the trainee cannot be fair, given that half of the respondents indicated that working hours were not registered or that on-call duties were not settled for. Lack of registration not only impedes supervision of compliance with maximum working hours, but also makes a fair salary, corresponding with the performances delivered, challenging. Except for employment in an (assigned) hospital - under the aegis of the supervisor - there are, moreover, few alternative (attractive) career options for the trainee, and compared to graduated medical specialists, who enjoy an exclusive position on the labour market, a trainee is not competitive and easier to replace. Although the trainee is indispensable in many hospitals, it seems evident that these aspects are at the root of the pay gap with highly educated employees in other sectors (including those in a so-called junior position). Concerning this subject, dissatisfaction among medical trainees on the working conditions already culminated in strikes in the UK in 2016 (8) and in Poland in 2017 (9). Despite such initiatives in the past, based on the data presented in this survey, unfair working conditions and unexplainable variation are still found in a cohort of paediatric trainees in Flanders.

Several reasons might be suggested for the observed variations in working conditions, that should contribute to the "lessons learned". First of all, especially in Belgium, trainees in medical specialties enjoy a historically weak position at the negotiating table concerning their social statute.Altough several interest groups have achieved unseen successes in the past, for example by limiting working hours, salary conditions can still be improved, as can be appreciated by this study. The inherent temporary statute of the trainee undoubtedly includes some disadvantages. Employers might have little drive to satisfy such "passers-by" with competitive wages and fringe benefits while having few other career options, on the other hand. In addition, there is a possible conflict of interests due to the dual function of employer and educational supervisor by the same person or organization. Future initiatives should tackle the above mentioned issues and provide more equitable and fair working conditions with attention for competitive wages and appropriate fringe benefits and social rights. It is moreover of importance that future studies are conducted among similar groups of trainees and data is being published on their working conditions in Europe and abroad.

Conclusions

The paediatric trainee in Belgium is disproportionately and unfairly compensated for his extensive professional activities. The underlying sui generis statute, the inadequate legal framework and the weak and non-vacant position of the trainee on the labour market are visible in this analysis, with heterogeneity in wages and providing fringe benefits, even within this single specialty. The individual trainee is not well informed about his working conditions and there is a lack of transparency regarding the salary.

A trainee of the same level should enjoy the same training in one hospital as in the other, bear the same workload and responsibility, and thus be paid the same. As a variation on the timeless quote from "Animal Farm" by the masterful hand of George Orwell, regarding the current situation, we can conclude that "All trainees are equal, ... but some are more equal than others".

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Article

Umbilical Venous Catheter-Related Complications: A Retrospective Study at the University Hospital of Leuven

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Keywords

neonates, umbilical venous catheters, CLABSI, portal vein thrombosis

Abstract

Background: Assess the complication rate of umbilical venous catheters (UVC) in newborns and identify risk factors, useful for prevention.

Design and methods: A retrospective observational study at the Neonatal Intensive Care Unit (NICU) of the University Hospitals of Leuven, based on the admissions from January 2016 until December 2016. Central line-associated bloodstream infection (CLABSI) was defined as one positive blood culture in a symptomatic neonate 48 hours after placement and up to 48 hours after removal of the umbilical venous catheter. Portal vein thrombosis was defined as the formation or presence of a blood clot in the vena portae, diagnosed by ultrasound. Descriptive statistics were used to calculate incidences. The significance of results was valuated with Pearson's chi-squared test and Fisher's exact test.

Results: In 291 neonates, i.e. 58.2% of all neonates, an UVC was inserted on admission. Primary outcome was defined as the incidences of central line-associated bloodstream infection (CLABSI) and thrombosis. Thrombosis was the highest reported complication with an incidence of 3.4%. In children, examined by abdominal ultrasound, the incidence of portal vein thrombosis increased to 10.3%. Extremely low birth weight (ELBW, birth weight ą1000grams) was a significant risk factor (RR = 6.8; 95% CI: 1.9 to 23.9) compared to neonates with a higher birth weight. The second most frequent complication was CLABSI with an incidence of 2.4% or 3.8 per 1000 catheter days. ELBW was again a significant risk factor compared to neonates with a higher birth weight (RR = 6.53; 95% CI: 1.53 to 27.78).

Conclusion: Neonates weighing 1000 grams or less had the highest risk of developing CLABSI or thrombosis during UVC use. Lack of screening for portal vein thrombosis possibly causes an underestimation of the incidence of thrombosis. Improvements can be made regarding prevention and follow-up of UVC-related complications.

Introduction

The first report on the use of umbilical venous catheters was in 1947 for exchange transfusions in neonates with erythroblastosis fetalis.[1] Nowadays, use of central venous catheters is a common practice in a modern neonatal intensive care unit (NICU) and possibly a life-saving treatment. Umbilical venous catheters (UVC) are frequently used because of their easy and painless access. Indications for insertion are the administration of fluids, parenteral nutrition, blood products or medication and monitoring of the central venous pressure. Besides the many advantages, UVCs can also be the cause of serious complications, such as portal vein thrombosis and central line-associated bloodstream infection (CLABSI). In neonates, CLABSI is not easily diagnosed and defined, resulting in a reported wide incidence range (6-34.5%[2-7]). Recent studies showed that by screening for portal vein thrombosis, remarkable high numbers of incidence (up to 43%[8-11]) are found in neonates with an UVC. Portal vein thrombosis can have long-term consequences that can become visible long after the event without any earlier signs, such as portal hypertension and esophageal varices. To prevent these complications and their consequences, it is important to have surveillance data and to provide a protocol for treatment and follow-up.

In the University Hospital of Leuven, around 600 neonates are admitted at the NICU on a yearly basis. This article reports a retrospective study about the incidence of UVC-related complications and possible associated risk factors.

Materials and Methods

i. Setting and study population:

This retrospective, observational study was conducted at the University Hospitals Leuven after approval of the ethics committee of KU Leuven (number: MP002380). Inclusion criteria were all patients admitted at the NICU between January 1th 2016 and December 31th 2016, who received an UVC. That year 519 neonates were hospitalized and 302 of them received an UVC (58.2%). Eleven patients were excluded because they deceased within 48 hours and no conclusion could be made regarding the UVC (n = 6) or because they were transferred to another center with the UVC in situ and no further information was documented (n = 5). This led to a total study population of 291 neonates with 297 UVCs.

All UVCs were inserted by neonatologists or pediatric residents. Indications for an UVC according to our protocol are neonates <34 weeks gestational age and critically ill infants. If the patient requires long-term IV therapy, a peripherally inserted central catheter (PICC) is placed before day 7. To estimate the insertion length of the catheter, the Shukla-Ferrara formula was used [(Birth weight x 3 + 9)/2+1].[12] The position of placement of the catheters, which was evaluated with thoracoabdominal radiograph (AP and LL views), was considered appropriate when the tip was located before the cavo-atrial junction (upper border T9 - lower border T10).[12] If the catheter was too high or intrahepatic, the standard procedure was to retract the catheter into the correct position or into the low pre-hepatic position without a new control radiograph. At the time of the study, all UVCs were polyurethane 4 Fr double lumen catheters (VygonÒ).

ii. Data collection:

Data were retrospectively collected from the electronic medical files of all subjects. Demographic data included birth weight, gestational age and sex. Catheter characteristics were defined as catheter days (calendar days on which an UVC was in situ), insertion in another center, concomitant umbilical arterial catheter use, malposition, initial tip position and reasons for removal of the catheter. The reasons for removal were grouped in elective (end of therapy, switch to another type of venous catheter) and non-elective reasons (suspicion of local or systemic infection, leakage, accidental removal, occlusion, dislocation, necrotizing enterocolitis (NEC), and thrombosis). All patient files were screened for complications. Lab results and radiographic examinations were retrieved. In case of CLABSI, the catheter day of positive blood culture, germs and tip culture were collected. In case of thrombosis, the position and degree of occlusion of the thrombus, the follow-up and therapy were recorded. There was no systematic screening for thrombosis. Ultrasounds performed during hospitalization in the NICU were reviewed and the indication was noted. Other outcomes were documented including NEC, intraventricular hemorrhage (IVH) > grade II, liver damage and cardiac complications such as arrhythmia, pericardial effusion and cardiac tamponade.

iii. Definitions:

For this study the definition of umbilical venous catheter-associated infection was based on the Centers for Disease and Control (CDC) definition[13]. CLABSI was defined as one positive blood culture in a neonate showing clinical signs of sepsis 48 hours after placement and up to 48 hours after removal of the UVC. Blood cultures in the first 48 hours were considered as congenital infections transmitted by delivery from the mother and were not registered. All blood cultures in the NICU are taken with an aseptic procedure. After UVC removal, a tip culture was not routinely performed; therefore, a positive tip culture was not part of the requirements. Portal vein thrombosis was defined as the formation or presence of a blood clot in the vena portae, diagnosed by ultrasound performed during the hospitalization.

iv. Data analysis:

Descriptive statistical analyses were made using SPSS StatisticsÒ version 25. Incidences of complications were measured in percentages. For CLABSI a second measurement was documented as infections per 1000 catheter days. Different categories based on birth weight were made for analysis. To assess the statistical significance between differences of categorical variables, Pearson's chi-squared test was used. If the expected count of one or more cells was less than 5, Fisher's exact test was performed. A p value of less than 0.05 was considered significant. The mean and standard deviation was used for values who followed a normal distribution. Otherwise the median is shown.

Results

i. Patient characteristics:

In the 12-month study period, 302 out of 519 admissions (58.2%) received an UVC. 291 met the inclusion criteria in whom 297 catheters were placed. In the study population the mean birth weight was 2167 grams (± 951grams) and the mean post menstrual age was 33 weeks (± 4 weeks) (Table 1).

ii. Catheter characteristics:

The total catheter duration of the 297 UVCs was 1,844 catheter days with a mean of 6.2 days per catheter (range 1-15). Most of the catheters were placed in the University Hospitals Leuven, with exception of 6.1% of catheters who were inserted externally before transfer of the infant. Only 24.6% of catheters had a correct initial position on the first thoracoabdominal radiograph, 39.7% was located intrahepatic, 23.9% intracardiac, 8.4% pre-hepatic and 3.4% in other positions. Standard procedure in the hospital was to retract the intrahepatic catheters into a pre-hepatic position. So, half of the catheters were in the high position and half in the low position after correction. In 43.1% patients with an UVC, an umbilical arterial catheter was inserted simultaneously. 53.2% of catheters were removed electively (Table 2). Two third of the patients needed further intravenous therapy after removal, mostly through a PICC or peripheral venous catheter.

iii. Primary outcomes:

CLABSI had an incidence of 2.4% of all patients or 3.8 per 1000 catheter days. Subgroups were created according to birth weight categories (Table 3). The incidence was significantly higher in infants with extremely low birth weight (ELBW) £1000 grams (10.3%, p = 0.026). Median day of onset of CLABSI was day ten (range 4-11). Cultured germs were coagulase negative staphylococci in 71.4% (*Staphylococcus epidermidis*, *Staphylococcus hominis* and *Staphylococcus capitis*) and other gram-positive bacteria in 28.6% (*Bacillus cereus* and *Streptococcus gordonii*). Only in four out of seven patients the tip of the UVC was cultured. Two cultured tips were positive and two negative, but the latter were taken after the start of antibiotics. In this group of seven patients with CLABSI, eight UVCs were placed. Two of them were inserted in another hospital.

Portal vein thrombosis, was seen in 3.4% of patients with an UVC. Only in 33.3% of patients an abdominal ultrasound was performed, usually early in hospitalization. The median day on which the thrombus was detected was day 5.5. Ultrasounds were mostly performed as screening for congenital disorders or abdominal complaints such as melena or vomiting (Table 4). Two of our patients with a thrombosis had unexplained thrombocytopenia, in one patient no blood could be aspirated through the UVC on insertion. These findings raised questions whether a thrombosis had occurred. The other patients underwent an ultrasound for reasons unrelated to the thrombosis. In the population in which an ultrasound was performed the incidence increased to 10.3%. In ELBW infants a higher incidence was reported: 13.3% in the total subgroup and 40.0% in the subgroup who had an abdominal ultrasound (Table 5). In the ten patients with a portal vein thrombosis 12 UVCs were placed of which nine in the low position (eight intrahepatic and one pre-hepatic) and three in the correct position before the cavo-atrial junction. The difference was not statistically significant (p = 0.075). The thrombi were located in the left branch of the vena portae (n = 9) or in the ductus venosus (n = 1). None of the thrombi were symptomatic during NICU hospitalisation. Seven of the thrombi were occlusive (including the one located at the ductus venosus); in five patients anticoagulation therapy was given according to the hospital's protocol. One patient had a severe NEC at the time and could not start the therapy. During hospitalization, two patients were screened for coagulation disorders; both were normal. Later follow-up for an extensive coagulation screening was not systematically done. Follow-up ultrasound of the liver (median time four months after the event) showed that only two out of ten patients had a complete normal ultrasound. Anomalies consisted of hyperreflective lesions (n = 6), a hypertrophic arteria hepatica (n = 4), hepatomegaly (n = 1) and persistent absence of flow in the left branch of the vena portae (n = 1).

Two patients have experienced both a CLABSI and portal vein thrombosis.

iv. Secondary outcomes:

Less frequent complications possibly associated with malpositioned umbilical venous catheters, were also examined in this study. Intraventricular hemorrhage > grade II had an incidence of 3.1% in the premature newborns (<36weeks). Liver damage documented on ultrasound other than thrombosis occurred in 1.8% of patients. NEC appeared in 1% of neonates. Arrhythmia occurred in 0.7%, no other cardiac complications were noted.

Discussion

Catheter-associated bloodstream infection is the most frequently reported complication of umbilical venous catheters, with incidence varying between 6 and 34.5% or 7.2 to 20.0 per 1000 catheter days2-7. There is a large range due to differences in populations (eg. ELBW infants) and definitions of CLABSI (eg. clinical sepsis vs. laboratory-confirmed bloodstream infection). The CLABSI incidence reported in this study is lower than in other studies. There are possible explanations of the low CLABSI incidence: the mean catheter time was relatively short and our study population was not limited to VLBW infants known to have a higher CLABSI incidence. Median onset of CLABSI was on day ten, proving an appropriate aseptic insertion procedure in the hospital. Causative organisms were as expected from the literature: coagulase negative staphylococci and other gram positive bacteria. The incidence rates in neonates weighing 1000 grams or less was much higher compared to neonates with higher birth weights proving this to be a significant risk factor. Other risk factors not proven significant were repetitive catheter placements, line manipulations and insertion in referring hospital. The latter might be because these neonates had an unexpected problem at birth requiring urgent and maybe less sterile placement of an UVC before transfer to the University Hospital. We are confident that all registered infections are nosocomial in origin since there were no bacteria found associated with neonatal sepsis and the time-range of positive blood culture was day 4-11.

The second most important complication is portal vein thrombosis with incidence varying between 3% and 43 % depending on whether a screening protocol is present.[8-11,14-15] In this study an incidence of 3.4% was found, compatible with these numbers. However, incidence increased to 10.4% in the subgroup in which an ultrasound was performed. Since there was no systematic screening, the actual incidence will probably be higher. Thrombi were first detected by ultrasonography on median day 5.5, similar with the study from *Dubbink-Verheij et al.* where day six was the median.[16] For thrombosis the incidence rate in neonates weighing 1000 grams or less was again significantly higher compared to neonates with higher birth weights. Incidence was as high as 40% in this group if they received an abdominal ultrasound. In this study polyurethane UVC's were used. There is no reported difference in outcome between the use of PVC catheters and other materials.[17]

A suggestion for future management is to screen for thrombosis in all neonates with UVC. If high costs are an issue, the cost-benefit ratio could be better by screening only the extremely and VLBW infants. None of the patients were followed up by a pediatric hematologist for coagulation studies and no neonates could be identified with thrombophilia. Portal vein thrombosis associated with thrombophilia is reported in neonates. In case-control studies the odds ratio for children with portal vein thrombosis having an inherited thrombophilic defect compared to controls ranged from 5.47 to 11.9.[18-19] Only one patient had a follow-up with a pediatric hepatologist, even though only two of the patients with a thrombus had a normal follow-up ultrasound of the liver. To prevent long term consequences such as portal hypertension and esophageal varices, another suggestion would be to follow up these patients until regression of the thrombus.

Two patients had both a CLABSI and portal vein thrombosis as complication of UVC-use. The portal vein thrombosis was detected after the onset of sepsis. Correlation between those two complications has been described in literature. Possible pathogenesis is the thrombotic effect of infection resulting from hemostatic anomalies due to systemic inflammation[20].

Other complications, mainly related to malposition of the catheter, are cardiac complications such as arrhythmia and tamponade of which the incidences were low in this study. *Kurtom et al.* described an association between IVH grade III-IV and malposition of an UVC.[21] *Sulemanjii et al.* stated that malposition of the UVC gave a higher risk for NEC (OR: 6.9).[22] Both these complications were rare in this study so no conclusions could be made. According to *Grizeli et al.* 0.8% of patients would have a serious liver complication such as abscess formation or hematomes.[23] Liver damage (anomalies on ultrasound other than thrombosis) in this study was not severe and transient in 1.8% of patients. Some case reports were found, describing pericardial effusion and cardiac tamponade after umbilical venous catheterization, but these did not take place in this cohort.[24-25]

Only 24.6% of catheters were correctly placed on initial radiographic control. According to research, up to 53% should be in the correct position using the Shukla-Ferrara formula[12]. Studies comparing three evaluation methods, namely the Dunn method, the Shukla-Ferrara formula and the revised Shukla-Ferrara Formula, show no significant difference in primary outcome which is correct tip position on radiographic control[12]. These results raise the question if the Shukla-Ferrara formula was systematically and correctly used.

This study has several limitations. The most important one is that this is a retrospective study, relatively small and performed at one center. Secondly, because there was no screening for thrombosis, the incidence could be underestimated. Also, without a positive tip culture, CLABSI could be caused by another catheter if it was in place at the time of the infection. Given the small number of events a multivariate analysis could not be done to identify independent risk factors. We used bi-variate analysis to stratify the incidence by birth weight. The differences in incidence between those birth weight-groups can be confounded by other factors.

Despite these limitations this study offers a good view on incidences of UVC-related complications and can be of help in taking some new measures regarding management for screening and follow-up of the UVC-related complications. Further research in larger population groups are still needed to evaluate the less frequent complications and their possible association with UVCs.

Conclusion

This study shows that thrombosis and infection are important UVC-related complications. Lack of screening for portal vein thrombosis possibly causes an underestimation of the incidence of thrombosis. Neonates weighing 1000 grams or less had the highest risk of developing CLABSI or thrombosis during UVC use. Other possible risk factors inherent to the catheter such as length of catheter stay, catheter manipulations, malposition and externally placed catheters were not proven significant in this study. Screening for thrombosis could identify more patients with this complication. This could lead to better secondary prevention (removal of the catheter) and long term follow up. This potentially leads to an improved outcome for these patients.

Table 1: Patient characteristics

		N	%
Sex	Boys	161	55,3%
	Girls	130	44,7%
Birth weight (grams)	≤ 1000	30	10,3%
	1001 - 1500	58	19,9%
	1501- 2500	99	34,0%
	> 2500	104	35,7%
PMA (weeks)	<30	54	18,6%
	30 - 36	138	47,4%
	>36	99	34,0%

Table 2: Indications for removal of the catheter

		N	%
	Leakage	97	32.2%
	End of therapy	96	31.9%
	Replacement by other catheter	64	21.3%
	Suspected local or systemic infection	18	6.0%
	Accidental removal	17	5.6%
	Occlusion	3	1.0%
	Malposition	3	1.0%
	Thrombosis	2	0.7%
	NEC	1	0.3%
Total		301	100.0%

Table 3: CLABSI per birth weight group

			≤1000 grams	1001 - 1500 grams	
Population	Infections	N	3		1
	% Incidence	42.9%		14.3%	14.3%
		10.0%		1.7%	1.0%
	N	30		58	99
	%	10.3%		19.9%	34.0%

Table 4: Indication for abdominal ultrasound

	N	%
Screening for congenital disorders	47	48.9%
Abdominal complaints	19	19.8%
Abnormal coagulation	8	8.4%
Others	7	7.3%
Hernia (inguinalis, umbilicalis)	5	5.2%
Cholestasis/hyperbilirubinemia	5	5.2%
Screening kidney disorders	5	5.2%

Table 5: Portal thrombosis per birth weight group

		≤1000 grams	1001 - 1500 grams	1501 - 2500 grams	>2500 grams
Thrombosis	N	4	2	1	3
	%	40.0%	20.0%	10.0%	30.0%
	Incidence	13.3%	3.4%	1.0%	2.9%
Population	N	30	58	99	104
	%	10.3%	19.9%	34.0%	35.7%

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Unravelling the genetic cause of life-threatening infections in children

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Introduction

Primary immunodeficiency diseases (PIDs), or inborn errors of immunity (IEIs), are a heterogeneous group of genetically determined diseases involving one or more components of the immune system. The principal hallmarks of these disorders are susceptibility to infections, autoimmunity and higher risk of cancer (1). The great advances of the last decades in human genetics have permitted an acceleration in the discovery of new genes associated with known or new phenotypical PIDs, with the greatest leap determined by the implementation of next-generation sequencing (NGS) in 2009 (2). Since then, more than 200 new genes have been discovered to underlie a primary immunodeficiency, doubling the total number of diseases so far described (3).

One specific point of interest in the research on IEIs has always been the search for genetic, and specifically monogenic, causes of susceptibility to infection (4,5). Aided by the progress in genetic sequencing, the study of subjects affected by unusual, recurrent or severe infections shed light on many different immune mechanisms and defects relevant to human immunity against microbes. In turn, this led to a great change in our perception of what constitutes an immunodeficiency: on one hand, we have "conventional" primary immunodeficiencies, in which rare Mendelian traits confer susceptibility to infection with a multitude of pathogens, in a completely penetrant manner and with a measurable effect on immune cells number or function. Examples of these conventional IEIs are X-linked agammaglobulinemia (Bruton disease), severe combined immunodeficiencies (SCIDs), congenital neutropenia, etc. On the other hand, increased and selective susceptibility to infections with one or a narrow range of pathogens can be referred to as "non-conventional" IEIs, such as invasive Neisseria infections in patients with late complement pathway defects, mycobacterial disease in patients with interferon (IFN)-γ/IL-12 pathway defects, Herpes simplex virus 1 encephalitis in patients with defects of the Toll-like receptor 3 (TLR3) signaling pathway, and chronic mucocutaneous candidiasis (CMC) in patients with defects of T helper 17 function (5-7).

Indeed, a tremendous effort has been devoted to discovering novel genetic etiologies of seemingly fortuitous presentations, such as life-threatening infections in children without a detectable immunological phenotype, and to understanding the underlying mechanisms of these and other non-conventional IEIs. Starting from this framework, our line of research focused on patients, encountered in daily practice, with unexplained phenotypes that could indicate an immune defect, such as severe course of infection, autoinflammation, or syndromic features with immunodeficiency. By following a stepwise approach based on immunological screening followed by genetic testing, mostly with next generation sequencing, and functional analysis of potential mutations, we gained understanding of the mechanisms of immune dysfunctions while making the most efficient use of our resources.

1. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines

In a first project, we studied two children with an unusual infectious presentation: a 7-year-old boy from a consanguineous family suffered from disseminated vaccine-strain measles at the age of 1 year, and a 14-year-old girl from a second family developed viscerotropic vaccine-strain yellow fever at the age of 12 year (8). For the rest these children were healthy and had no complications from other common infections. The younger sister of the first patient also developed measles encephalitis after the first dose of measles-mumps-rubella (MMR) vaccine, and unfortunately died.

In both patients, whole exome sequencing (WES) identified previously not reported biallelic variants in the gene encoding the subunit 1 of the type I IFN receptor (IFNAR1), involved in anti-viral innate and intracellular responses. IFNAR1 combines with IFNAR2 to form the type I IFN receptor, which is activated by IFN-α and IFN-β upon detection of a viral infection. The receptor then signals downstream via adaptor molecules called signal transducer and activation of transcription (STAT), in particular STAT1 and STAT2, which enter the nucleus to initiate the transcription of hundreds of IFN-stimulated genes (ISGs) essential for anti-viral responses (Fig. 1).

These variants were predicted to be pathogenic by in silico prediction tools, so a complete functional analysis was undertaken at the gene, protein and cellular level. We could indeed show how these variants caused the loss of expression and loss of function of IFNAR1, which in turn could not activate the STAT proteins and induce the expression IFN-stimulated genes. This rendered the patients' fibroblasts highly susceptible to viruses in vitro, including vaccine-strain measles and yellow fever. Finally, these defects were corrected by the addition of the wild-type IFNAR1 gene to the patients' cells.

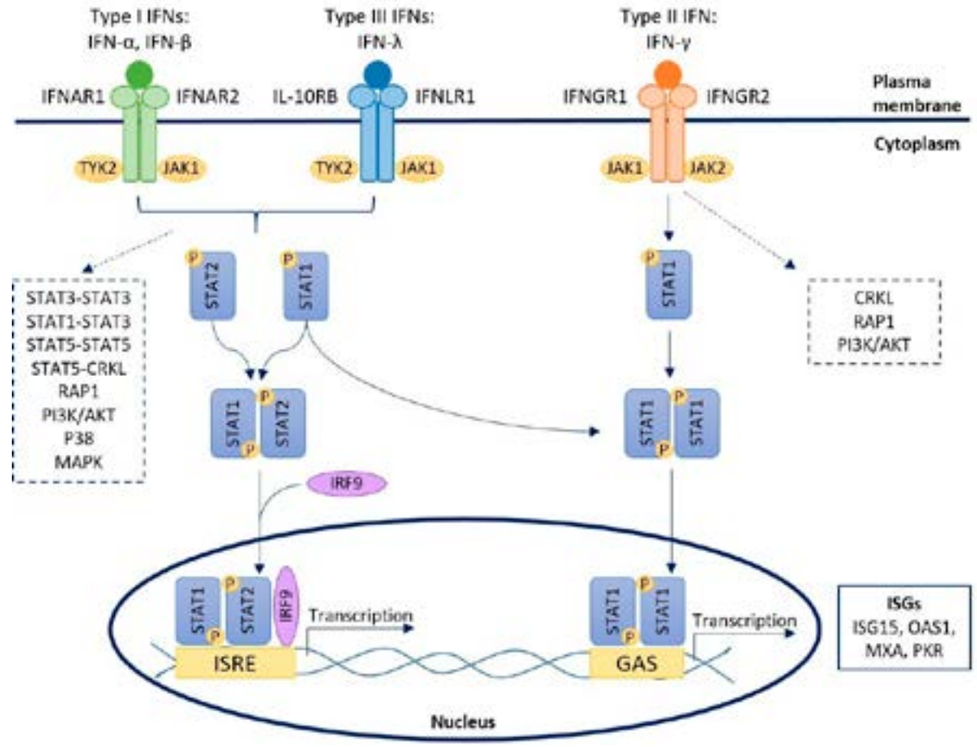
Therefore, we proved that autosomal recessive complete IFNAR1 deficiency results in life-threatening complications of live attenuated viral vaccinations in previously healthy children, but apparently not other severe infections.

2. Clinical, immunological and molecular study of a cohort of patients with STAT2 deficiency

STAT2 deficiency is another autosomal recessive disorder of the type I IFN response. Similarly to IFNAR1 and IFNAR2-deficient patients, these patients present with a characteristic, although not fully penetrant, risk of disseminated disease and encephalitis after inoculation with live MMR vaccine (8-12).

In contrast with IFNAR1 deficiency, they also seem to be susceptible to other viral illnesses and show a more severe phenotype, with a mortality of 19% in childhood. Analyzing sixteen patients from seven unrelated kindreds with 8 different biallelic mutations in STAT2, we found a broader infectious and non-infectious phenotype than previously described, centered on viral susceptibility. In particular, infection with VZV (varicella-zoster virus) (in one case vaccine strain), influenza and enterovirus were prevalent in this cohort. Moreover, several of the patients in our cohort showed a striking inflammatory response during infections. Four patients were in fact diagnosed with atypical Kawasaki disease, three of them after MMR inoculation. Type I IFNs greatly contribute to the regulation of inflammation in human hosts, with both pro- and anti-inflammatory effects. We can speculate that the defect of type I IFN signaling in patients with STAT2 deficiency could in some cases lead to a hyper-inflammatory status, especially when the immune system is challenged

Figure 1: Schematic representation of the three interferon (IFN) receptors and their main downstream signaling pathways.



by microbial stimuli. Recent evidence shows indeed that STAT2 plays a role in the USP18-mediated auto-regulation loop, which controls inflammation (13). STAT2 defects could therefore be responsible for both a defect in the IFN anti-viral response and an uncontrolled IFN activation, leading to inflammation (14,15).

These data indicate a relevant role of type I IFN in the immune response to live vaccine inoculation, also sustained by studies on the mechanism of attenuation of these viruses. The fact that IFNAR1, IFNAR2 and STAT2 deficiencies all result in disseminated vaccine-strain measles while deficiency in IL-10RB, a subunit of the type III IFN (IFN-λ) receptor, has not been reported to produce this infectious phenotype, suggest that type I IFN signaling is more critical for defense against measles vaccine-strain virus than type III IFN signaling (16,17). Moreover, several mechanisms of viral attenuation are based on the loss of IFN resistance or the acquisition of IFN-stimulating properties by the virus, which allow the host to contain the infection (18-22). Therefore, the absence of a functioning IFN pathway in patients with defects of type I and/or III IFN immunity could explain the extreme virulence shown by these live vaccine viruses.

As with other innate immunity defects and IFNAR1 deficiency, once patients reach adulthood they seem to be protected from severe infections (5,6). These findings hint to the fact that the innate compartment of immunity has evolved over a long period of time to form a tightly intertwined network of defense against microbes, where each component overlaps for most of its functions with other parts. This redundancy can guarantee the best defense in case of failure of one component and explains the narrow spectrum of infections experienced by many patients with an innate immune defect.

3. Systemic inflammation and myelofibrosis in a patient with Takenouchi-Kosaki syndrome due to CDC42 Tyr64Cys mutation

Finally, in the last project we tackled another inborn error of immunity presenting with a broader phenotype than previously described (23).

We studied a young woman manifesting intellectual and growth delay, dysmorphisms, macrothrombocytopenia, camptodactyly, brain malformations, hepatosplenomegaly, liver hemangiomas and a large aortic aneurysm. She also suffered from immunodeficiency and severe lung infections, and she died at the age of 26 years from pneumonia complicated by respiratory insufficiency, alveolar hemorrhages, systemic inflammation and sepsis. Using WES, we identified the de novo Tyr64Cys mutation in cell division cycle 42 (CDC42), encoding a small GTP/GDP-binding protein necessary for cell cytoskeleton dynamics. The Tyr64Cys mutation in CDC42 causes Takenouchi-Kosaki syndrome, a rare developmental disorder characterized by intellectual and growth delay, dysmorphisms, macrothrombocytopenia, camptodactyly, structural brain abnormalities with sensorineural deafness, hypothyroidism and frequent infections (24-26). Other mutations in CDC42 have been reported to cause either a spectrum of developmental phenotypes or, for mutations affecting the C-terminal domain of the protein, a syndrome of immune dysregulation with neonatal-onset severe autoinflammation and hemophagocytic lymphohistiocytosis (27-29).

The extended immunophenotyping of our patient showed B cell lymphopenia with increased naïve B cells, decreased naïve T cells, and a global defect of CD8+ T cell activation. Most interestingly, the patient had signs of immune dysregulation and autoinflammation, including myelofibrosis and

upregulation of serum inflammatory cytokines, such as IL-6, IL-18, and CXCL9. These findings expand the phenotypic spectrum of Takenouchi-Kosaki syndrome and link autoinflammation with other CDC42 mutations than those in the C-terminal domain. This case highlights the complex crosstalk between different organs and the central role played by immune components in the homeostasis of multiple systems. It also illustrates the fine tuning required to calibrate the function of most enzymes involved in the immune response. Ultimately, it is another example of the subtle balance between immunodeficiency and excessive inflammation, which can both be present in a single IEI.

Conlcusions

In this thesis I study patients presenting with severe and unusual infections, and I highlight the advantages and limitations of applying NGS to the diagnosis of patients with suspected IEI. The rapid expansion of NGS genetic techniques in recent years has allowed the discovery of hundreds of novel IEIs and has expanded our knowledge the extreme phenotypic heterogeneity and genetic pleiotropy of these disorders.

The discovery and investigation of these and other monogenic disorders give us an incredible insight on the mechanisms of immune responses and allow us to develop new diagnostic and therapeutic approaches. This way, even seminal findings in single patients can improve our understanding of fundamental immunology. Finally, our results lay emphasis once again on the fact that a severe or unusual course of infection in an otherwise healthy child should always be considered as a potential immunodeficiency and studied accordingly.

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Systemic treatments for eczema

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Question

Which systemic immunosuppressive medicine to treat moderate to severe eczema is the most effective and safe?

Context

Eczema is a common and chronic inflammatory disease in both children and adults. It can range from mild eczema with small patches of dry skin to moderate eczema with larger areas of the skin affected which will be redder and can be even swollen. Finally, in people with severe eczema the entire body can be affected with red crusts and broken skin which may ooze fluids. Moderate and severe eczema can significantly impact quality of life.

While there is no cure, treatments that alleviate symptoms are available. The first choice is to apply topical medications such as emollients and corticosteroids to the affected skin. However, if topical treatment is not sufficiently effective, the use of systemic drugs, taken orally or injected, is considered.

Criteria for study selection

The Cochrane review included studies on systemic immunosuppressive medication for moderate to severe atopic eczema. The studies had to compare the medication to placebo or one of the other eligible medications. The main outcomes of interest were the proportions of patients experiencing important positive effects on symptoms, defined as at least a 75% improvement on the Eczema Area and Severity Index (EASI75) or 50% improvement on the Patient-Oriented Eczema Measure (POEM), and the proportion of patients with serious adverse effects or infection at short- and long-term duration.

Summary of the results

The review includes a total of 74 studies with 8177 participants of which about 55% were male and the average age was 32 years (range 2-84 years). Only seven studies with relatively small sample sizes focused on children with ages ranging from 3.6 to 14 years. All trials included patients with moderate to severe eczema with 38% assessing only severe eczema. The trial duration varied from 2 weeks to 60 months with treatment duration varying from single dose to 60 months. Only 33 studies assessed long-term outcomes (5-60 months) with 73 studies measuring short-term outcomes (2-16 weeks).

A total of 29 immunosuppressive medications were tested belonging to three different classes: (1) conventional treatments with most commonly ciclosporin; (2) small molecule treatments including for example phosphodiesterase-4 inhibitors; and (3) biological treatments including most commonly dupilumab but also for example fevipiprant (QAW039).

This systematic review includes a network meta-analysis. This is a statistical analysis in which multiple treatments are compared to one another both through direct treatment comparisons within studies as well as indirect comparisons across studies using a common comparator. Few studies compared different treatments directly to one another (34% with 15% of those testing different doses of the same drug) or included both an active comparator treatment and a placebo (1%), but 65% did compare the active drug to placebo. The network meta-analysis, therefore, allowed the authors to rank the different immunosuppressive treatments although they had not necessarily been tested directly against each other.

The network meta-analysis suggests that dupilumab is ranked first for the effectiveness compared to other biological treatments. Dupilumab increased the proportion of people reaching EASI75 (placebo: 184 per 1000 vs dupilumab: 560 per 1000; risk ratio: 3.04 (95%CI*: 2.51-3.69); high certainty evidence) and improved POEM scores (mean of improving score: placebo 5.18 vs dupilumab: 12.48 (95%CI: 11.79-13.18); high certainty evidence) in the short-term (<16 weeks). We remain uncertain about the effects of dupilumab compared to placebo on EASI75 in the long-term (very low-certainty evidence).

Tralokinumab may be more effective than placebo in achieving short-term EASI75 (placebo: 184 per 1000 vs tralokinumab: 468 per 1000 (95% CI: 223-984) but the supporting evidence is graded as low-certainty and no evidence is available on its effect on long-term EASI75 or short-term POEM. Due to very low-certainty evidence, we remain uncertain of the effect of ustekinumab on either short-or long-term EASI75. No evidence was identified for its effect on POEM scores.

The effects of other immunosuppressive drugs in comparison to placebo on short-term EASI75 remains uncertain as only very low- and low-certainty evidence was available.

During short-term follow-up fewer patients may have had severe adverse events using fevipiprant (QAW039) or dupilumab than using placebo (low- to moderate-certainty evidence). No difference in serious adverse events were found when other systemic agents were compared to placebo (very low- to low certainty evidence). Regarding the potential effect of immunosuppressive agents on risk of any infection, the evidence did not indicate a difference compared to placebo, but this evidence was of low or very low certainty.

Conclusion

Dupilumab is the most effective biological treatment for moderate to severe eczema. It reduces symptoms in the short term compared to placebo and is safer than other treatments in the short term. Unfortunately, due to the lack of data comparing the conventional treatments (e.g. cyclosporin) and newer biological treatments (e.g. dupilumab) for the primary outcomes, it remains impossible to rank the efficacy and safety between these treatments.

Implications for practice

Although eczema is prevalent in children, the evidence remains limited and inconclusive in this population. This review identified only seven studies with ages ranging from 3.6 to 14 years. Several different treatments were assessed with various clinical outcomes. At the moment it is not possible to identify the most effective and safest treatment for children.

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Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema: a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD013206. DOI: 10.1002/14651858.CD013206.pub2

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