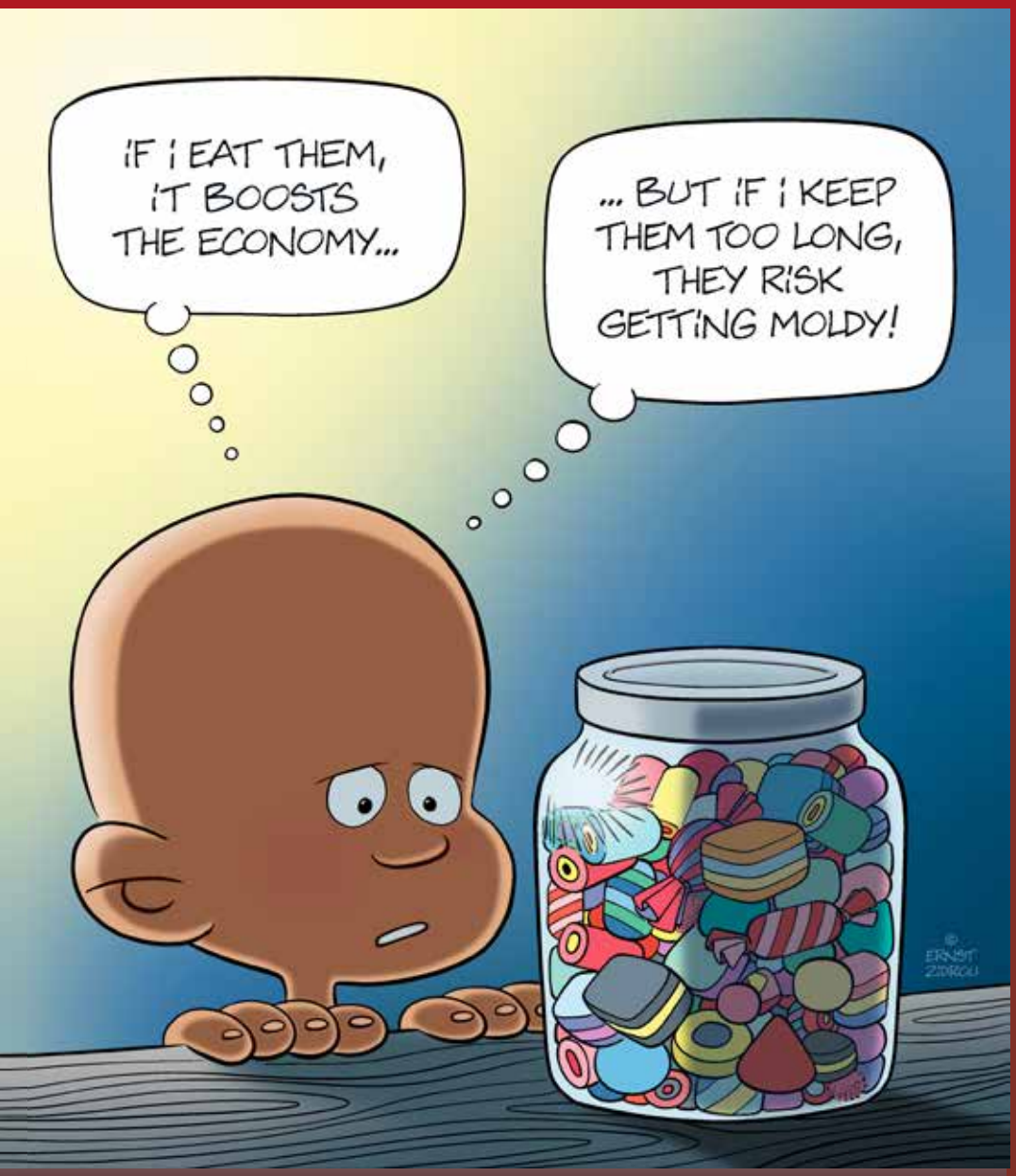
B j P Belgian Journal of Paediatrics

Publication of the Belgian Society of Paediatrics

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

2023 - Volume 25 - number 3 - September



Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

QUARTERLY
ISSN 2466-8907 (printed version)
ISSN 2566-1558 (digital version)

V.U./E.R. C. Chantrain (CHC-Liège), M. Raes (KUL)
UZ Leuven, Herestraat 49, 3000 Leuven
E-mail: BJ-Ped@hotmail.com

Publiekprijs **€ 86,52**

If you don't recommend MenB vaccination to your patients,

who will?

81% van de ouders beschouwt hun arts als een primaire bron van informatie over vaccinatie voor hun kinderen. (n=800)[2]

BEXSERO
Meningokokken groep B-vaccin
(rDNA, component, geadsorbeerd)

BEXSERO is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B.[1]

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN: Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL:** Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd), EU/1/12/812/001-EU/1/12/812/002-EU/1/12/812/003-EU/1/12/812/004. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09. **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING: Een dosis (0,5 ml) bevat:** Recombinant Neisseria meningitidis groep B NHBAfusieeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B NadAeiwit[1,2,3]: 50 microgram • Recombinant Neisseria meningitidis groep B fHbpfusieeiwit[1,2,3]: 50 microgram • Buitenmembraanvesikels (BMV) van Neisseria meningitidis groep Bstam. NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat[2]: 25 microgram • [1] Geproduceerd in E. colicellen door recombinantDNAtechnologie - [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) - [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de volledige SPK. **FARMACEUTISCHE VORM:** Suspensie voor injectie. Melkwitte vloeibare suspensie. **KLINISCHE GEGEVENS: Therapeutische indicaties:** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door Neisseria meningitidis groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening:** Dosering: **Tabel 1. Samenvatting van de dosering: Leeftijd bij eerste dosis:** Zuigelingen van 2 tot en met 5 maanden[a]: **Primaire immunisatie:** Drie doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. - **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b,c]. • **Leeftijd bij eerste dosis:** Zuigelingen van 6 tot en met 11 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 12 tot en met 23 maanden: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 2 maanden. **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]. • **Leeftijd bij eerste dosis:** Kinderen van 2 tot en met 10 jaar: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • **Leeftijd bij eerste dosis:** Adolescenten (11 jaar of ouder) en volwassenen*: **Primaire immunisatie:** Twee doses, elk van 0,5 ml. **Intervallen tussen primaire doses:** Niet minder dan 1 maand. **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]. • [a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. - [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. - [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld. - [d] Zie rubriek 5.1 van de volledige SPK. - * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening: Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties:** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijwerkingen:** Overzicht van het veiligheidsprofiel: De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen: Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥ 1/10) - Vaak: (≥ 1/100, < 1/10) - Soms: (≥ 1/1.000, < 1/100) - Zelden: (≥ 1/10.000, < 1/1.000) - Zeer zelden: (< 1/10.000) - Niet bekend: (kan met de beschikbare gegevens niet worden bepaald). De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar):** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Voedings en stofwisselingsstoornissen: Zeer vaak: eetstoornissen. Zenuwstelselaandoeningen: Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn. - Soms: insulten (inclusief febriele insulten). - Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen: Soms: bleekheid (zelden na booster). - Zelden: ziekte van Kawasaki. Maagdarmstelselaandoeningen: Zeer vaak: diarree, braken (soms na booster). Huid en onderhuidaandoeningen: Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster). - Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar). - Soms: eczeem. - Zelden: urticaria. - Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: koorts (≥ 38 °C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid. Soms: koorts (≥ 40 °C). - Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). **Adolescenten (van 11 jaar en ouder) en volwassenen:** Bloed- en lymfestelselaandoeningen: Niet bekend: lymfadenopathie. Immuunsysteemaandoeningen: Niet bekend: allergische reacties (waaronder anafylactische reacties). Zenuwstelselaandoeningen: Zeer vaak: hoofdpijn. - Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen: Zeer vaak: misselijkheid. Huid en onderhuidaandoeningen: Niet bekend: huiduitslag. Skeletspierstelsel en bindweefselaandoeningen: Zeer vaak: myalgie, artralgie. Algemene aandoeningen en toedieningsplaatsstoornissen: Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise. - Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden). Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België:** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie - Postbus 97 - 1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN:** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië. **DATUM VAN DE GOEDKEURING VAN DE TEKST:** 26/04/2023 (v15). **AFLEVERINGSWIJZE:** Op medisch voorschrift.

References: 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

PM-BE-BEX-ADVR-230001 - Augustus 2023 | VU: GlaxoSmithKline Pharmaceuticals s.a./n.v. Site Apollo Avenue Pascal, 2-4-6 1300 Waver Belgium

GSK

Contents

Pampers
premium protection™

Notre N°1 pour le confort & la protection des peaux sensibles

Le voile DermaComfort éloigne l'humidité et les selles molles de la peau et les retient au cœur du lange.

Voile DERMA COMFORT

50% L'emballage contient 50% de plastique recyclé de source industrielle

- **Micro-aérée pour une peau confortable**
- **Ultra-douce**
- **Indicateur d'urine**
- **Cœur super absorbant**
- **Découpe spéciale cordon ombilical** (Seulement taille 1 & 2)
- **Couche extérieure améliorée, plus opaque, avec des dessins amusants**

OEKO-TEX®
CONFIDENCE IN TEXTILES
STANDARD 100
17.HCH.22181 HOHENSTEIN HTTI
Testé substances nocives, www.oeko-tex.com/standard100

Certifié STANDARD 100 BY OEKO-TEX®
Institut indépendant qui teste la présence de plusieurs centaines de subtances nocives.

Dermatest
Testé cliniquement et dermatologiquement.

0% **0% allergènes de parfum** listés par l'UE.*

70% Nos emballages en carton contiennent **70% de papier recyclé.**

Ensemble, rendons le monde des bébés meilleur.
Rendez-vous sur pampers.be pour en savoir plus.

*Comme règlementé par la réglementation cosmétique de l'UE (CE) No 1223/2009

Version 03/2023

Editorial

Time of saving or saving of time?

At the end of the summer, the Belgian and international press gave wide coverage to the success of the State Bond, which enabled our country to raise almost 22 billion euros. This operation should strengthen the confidence of the markets in our country, proving in particular that Belgium is capable, thanks to the savings of its citizens, of raising large sums of money to finance its debt. It also demonstrates the wealth of our kingdom while revealing the great disparity in the economic reality of Belgian citizens.

Without going into any further economic considerations, these facts struck us on several levels. They confirm that, as well as having a brick in their belly, Belgians have learned to save, to put aside part of their resources to secure their future or to use them later for other projects. This approach is quite legitimate and we certainly don't want to call it into question. We only wonder how to keep it reasonable and how not to tip over into excessive materialism. As Jean de La Fontaine illustrated in his fable, where is the balance between the cricket and the ant? In the 21st century, in a globalized world increasingly confronted with the limits of its natural resources, what message, what nuances should we give our young people?

Today, money is no longer the only asset. The time we spend together, the moments we have for ourselves or for others have become luxuries that we should perhaps integrate them into our savings approach. Just as we can save money to deal with the unexpected or treat ourselves to something out of the ordinary, why not save time to devote to activities and people that are particularly close to our hearts? Is it also time to save, to protect and safeguard natural resources, biodiversity and a pleasant climate, so that we can benefit from them in the future or simply pass them on to next generations?

Besides qualities such as honesty, tolerance, solidarity, respect, gratefulness, we have a responsibility to learn our young people that “thriftiness” or saving-quality (not only financial or economic but in the broad sense of the word) must be one of the fundamental attitudes needed to be developed during growing-up. Our role as educators, parents and youth professionals is certainly to show them the way in this learning process…

With all these questions in mind, we are delighted to present our autumn issue. Several research articles analyze the consequences of COVID-19 lockdown on paediatric activities and pathologies. N. Loumaye and her colleagues assess the repercussions on the attendance to the pediatric emergency department. A. Devos and her team evaluate its impact in perinatology. M. Tretjakova et al. also report a case of acute neonatal encephalopathy associated to SARS-CoV-2. Also in neonatalogy, S. Vanbinst and colleagues studied the feasibility and give their conclusions about the use of a low-cost bubble CPAP system in neonatal medium care units. L. De Cloedt and her team report a case of idiopathic purpura fulminans and provide practical guidelines for diagnosis and treatment.

Many case reports are also published in this issue: the history of a child with failure to thrive that revealed a Niemann-Pick type C diagnosis, a Kinsbourne syndrome as complication of a Mycoplasma pneumoniae infection, an idiopathic infantile hypercalcemia, and another history of severe persistent hypocalcemia in a child with vitamin D deficiency. An unusual presentation of Castleman disease with failure to thrive and hypergammaglobulinemia, a rare case of sporadic colorectal adenocarcinoma and a birth related neonatal rib fracture are also described.

After the summer vacations, we are also proud to highlight the summary of 3 PhD thesis that were presented in 2023: Marine Angé from UCLouvain studied the role of alpha 1 AMPK in sepsis capillary leak syndrome and its potential therapeutic repercussions, Dimitri Declercq from Ghent University analyzed the long-term impact of enteral nutrition and the nutritional status in patients with cystic fibrosis, Daan Van Brusselen also from Ghent University investigated the health impact of air and metal pollution on children in North and South.

We hope you will enjoy reading this issue and on behalf of the entire editorial board, we wish you a sweet and fruitful autumn !

Christophe Chantrain and Marc Raes, Editors-in-chief

Uw vragen of commentaar
Vos questions ou commentaires

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

Comité de rédaction - Redactieraad
M. Raes - C. Chantrain

Gasthuisberg - Kindergeneeskunde

Herestraat 49 - 3000 Leuven
E-mail BJ-Ped@hotmail.com

Attendance to the pediatric emergency department during COVID-19 lockdown

Natacha Loumaye [a], Julia Bokias [b], Mohamed H. Iraki [b], Michele Dramaix [c], Tessa Goetghebuer [a], Elisabeth Rebuffat [a]

[a] CHU Saint-Pierre, Department of Pediatrics, Brussels, Belgium
[b] Erasme Brussels University Hospital, Department of Pediatrics, Université libre de Bruxelles, Brussels, Belgium
[c] Research Center of Health Policy and Systems-International Health, School of Public Health, Université Libre de Bruxelles, Brussels, Belgium
NL, TG an ER contributed equally to this work and share senior authorship

natacha.loumaye@outlook.fr

Keywords

SARS-CoV-2 ; COVID-19 ; pediatric emergency ; collateral damage ; delayed attendance ; diagnoses ; outcome ; side effect.

Abstract

Objectives: SARS-CoV-2 started during the winter of 2019-2020. In Belgium, the first lockdown was instituted between March 18th and May 4th. The attendance to the pediatric emergency department (PED) decreased drastically during this period.

Our study aimed to assess the repercussions of the lockdown on the rate of attendance, evaluate the delay between the onset of symptoms and admission to the PED and the cause of admission in 2020 and 2019.

Methods: This is a retrospective study in a public university hospital in Brussels (CHU Saint-Pierre).

Attendance to the PED during the study period in 2020 (March 18th - May 4th) was compared to the same period in 2019. Chi² test and Mann-Whitney tests were applied and prevalence ratios (PR) with 95% CI were computed. The median of the delay was derived from a survival analysis (Kaplan-Meier) and a log-rank test was used to compare this delay between 2019 and 2020.

Results: During the study period, the number of admissions to PED decreased from 3,087 in 2019 to 783 in 2020 (IR 2020/2019: 0.25, 95%CI: 0.23-0.27). The median delay between the onset of symptoms and the admission to the PED was longer in 2020 than in 2019 (3 days and 2 respectively ($p<0.001$). Children with comorbidities were 1.33 times more likely to attend the PED in 2020 (95%CI: 1.08-1.63).

Intoxication, burns, urogenital and neurological conditions were relatively more frequent, while there were fewer diagnoses of gastrointestinal conditions and fractures in 2020 compared to 2019.

Conclusion: The rate of attendance in PED decreased during the lockdown in 2020 compared to 2019, with a longer delay between the onset of symptoms and the admission to the PED during the lockdown. There is a difference in the distribution of diagnoses in 2020 compared to 2019. This study does not allow us to conclude to any increased morbidity rate but the collateral damage on children should not be overlooked.

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) appeared during the winter of 2019-2020. The number of people infected and the severity of the disease have led to a saturation of the global health care system. Infected patients present with cough, dyspnea, fever, sore throat, rhinorrhea, anosmia, and gastrointestinal symptoms. During the first phase (March to May 2020), children accounted for less than 2% of the positive tests performed globally (1–3). Children were more often asymptomatic or paucisymptomatic compared to adults.(4–7).

To minimize the circulation of the SARS-CoV-2 virus, the government imposed a lockdown. In Belgium, a lockdown was instituted between March 18th and May 4th. The lockdown and its economic consequences limited the access to hospitals and healthcare in general. Most hospital activities were reduced except those in the emergency ward. Many human and material resources were deployed to provide COVID-19 care. It has been already stated elsewhere that non-emergency conditions were delayed (8).

A reduction in the attendance in the pediatric emergency department (PED) was described in many settings (1,9–11). Lazzerini was one of the first to highlight a fall in the attendance in PED in Europe. For example, in Italy, Lazzerini showed a decrease of 73% in the attendance rate in 2020 compared to the same period in 2019 (1). In UK, Isba showed a decrease of 33.8% in the attendance rate in PED in February and March 2020 compared to the same period in 2019 (10).

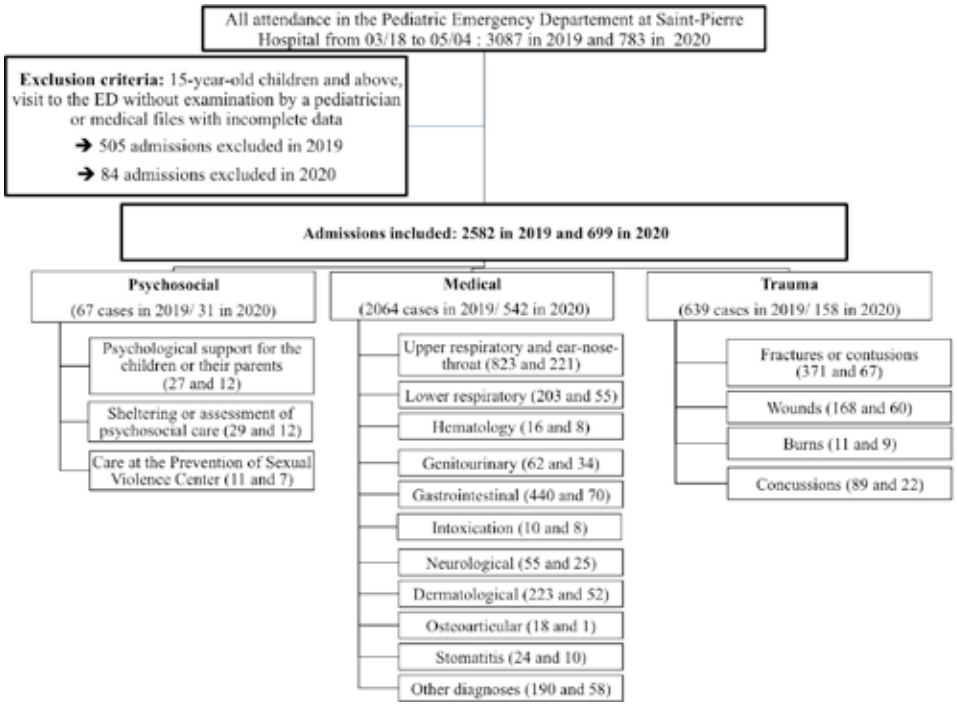
Feral et al. alerted to possible collateral damage leading to lack of diagnostic and care (12). Increased rate of severe pathologies (like urinary tractus, abdominal emergency, stroke, heart disease) has been demonstrated in the adult population during the lockdown period compared to March and April 2019 (13,14). Disruption of childhood vaccination campaigns raised the fear of resurgence of other vaccine preventable infectious diseases (8).

This lockdown had an impact on the circulation of other viruses involved in respiratory or gastrointestinal pathologies. The political measures prohibited the practice of sports in clubs and closed schools, which could have modified the traumatology encountered in pediatric emergencies.

Our study aimed to observe changes in incidences of PED visits in CHU Saint-Pierre between 2020 and 2019. The primary objective is to assess the repercussions of the lockdown in 2020 on the rate of attendance to PED. In secondary objectives, we aimed to evaluate the delay between the onset of symptoms and admission to the PED and the cause of admission in 2020 and 2019.

Figure 1:
Flow chart of medical file selection.

All causes of admission to pediatric emergency department were classified in psychosocial, medical and trauma categories. The subcategories of diagnoses are presented in this figure.



Materials and methods

We conducted a retrospective cohort study in the PED of CHU Saint-Pierre, the national reference center for the management of highly contagious respiratory viruses. This public university hospital is located in Brussels downtown.

In Belgium, the lockdown was instituted between March 18th and May 4th which is the study period. All attendance data to the PED during the study period in 2020 and 2019 were reviewed. Exclusion criteria were: children older than 15-years, visit to the PED without examination by a pediatrician and medical file with incomplete notes. The number of admissions was counted after applying these exclusion criteria. In our hospital, children can receive nursing care in the pediatric emergency room every morning for 2 hours. These admissions of children without a consultation by a pediatrician were not counted as emergency room visits. Some patients with pediatric chronic diseases are seen in the PED after they turn 15 years old. These patients older than 15 years were not counted as emergency room visits in PED (age limit of 15 years based in Belgium on the Royal Decree of 13 July 2006).

The flow chart of the medical file selection is shown in Figure 1.

The first author, NL, collected the data with the help of co-authors JB and MI. The information was stored in a coded Excel file. The following data were extracted from the medical file on the computer system Xperia: age, sex, comorbidity, date of attendance, date of the onset of symptoms, date of the admission to the PED, additional laboratory and radiologic investigations, diagnosis at discharge, discharge disposition (return home; hospitalization; transferred to Intensive Care Unit (ICU); death). In each patient's file, the date of onset of symptoms was recorded as reported by the child caregiver. The delay between the onset of symptoms and the admission to the PED was the difference in days between the date of symptom onset and the date of admission to the PED.

For our secondary objective, the cause of admission to the PED was classified into psychosocial, medical or trauma categories. Each category was divided into diagnostic subcategories according to a classification created for this study (Figure 1). Comorbidities were classified as allergy, respiratory disease, genetic disease, renal disease, hematologic disease, cardio-vascular disease, premature birth and neurological disease. Comorbidities included those identified in previous visit notes and those highlighted in the emergency department visit during the study period.

The classification system used to categorize reasons for admission was established at the time of application to the ethics committee. The subcategory for stomatitis was added after the first two weeks of coding. Previous records were reanalyzed with this new category.

A composite marker was used to determine appropriate visits to the PED, including children needing further examinations or surgical advice, children referred to the PED by a physician and children requiring hospitalization (15).

The institutional ethics committee approved this study on May 14th 2020.

Statistical analysis

The study focuses on the analysis of the year 2020 compared to 2019. To ensure that 2019 was representative of years prior to COVID-19, the PED attendance rates in 2020 were also compared to PED attendance in 2017 and 2018. The number of PED admissions was compared over the same period between 2017 and 2020. With the exception of the PED attendance rate, no further analysis was done on the patients included in 2017 and 2018.

Attendance rate ratios, exact 95% confidence intervals (95% CI) and mid p-values were computed.

Comparison of the admissions to the PED between 2019 and 2020 was performed after exclusion of the children older than 15 years or with missing data (Figure 1). Chi-square test and Mann-Whitney tests were used to calculate prevalence ratios (PR) with 95% CI.

The median of the delay between the onset of symptoms and admission was derived from a survival analysis (Kaplan-Meier) and a log-rank test was used to compare this delay between 2019 and 2020.

All tests were two-tailed and the significance level was set at alpha = 0.05. Statistical analysis was performed with Stata/IC15.0 and Jamovi 1.1.9.0. The graphics were generated with GraphPad Prism 8.4.3.

Results

Between March 18th and May 4th, the incidence of PED visits was 783 in 2020 compared to 3,087 in 2019, representing a decrease of 75% in 2020. The daily incidence decreased from 66 patients in 2019 to 17 patients in 2020. The daily incidence during the study period was similar in 2017, 2018 and 2019. The attendance rate in 2020 compared to 2019 showed an IR (incidence ratio) = 0.25 (95%CI: 0.23-0.27). The attendance rate was also significantly lower in 2020 compared to 2018

and 2020 compared to 2017 IR=0.26 (95%CI: 0.24-0.28) and IR =0.26 (95%CI: 0.24-0.28) respectively.

Table 1 shows the number of attendance to PED in 2019 and 2020, globally and in each diagnostic category. We can see that the absolute numbers of admissions in each category (psychosocial, medical or trauma category) were lower in 2020 compared to 2019. However the relative rate in attendance for a psychosocial condition was higher in 2020 than in 2019 (4.4% versus 2.6%, 95%CI: 1.13-2.59).

Table 1: Comparison of admission to PED from 03/18/2019 to 5/04/2019 and from 03/18/2020 to 5/04/2020.

The absolute number of admissions in each category was lower in 2020. In proportion, it appeared that psychosocial condition was more frequent in 2020 compared to 2019 while trauma and medical conditions were less frequent.

	Cohort 2019 n (%)	Cohort 201920 n (%)	Prevalence Ratio (95% CI)
Admission to the PED (n)	2,582	699	
Patients (n)	2,422	639	
Number of visits to PED [a]			
1	2,282 (94.2%)	587 (91.9%)	0.69 (0.54-0.88)
2	122 (5.0%)	47 (7.4%)	1.45 (1.03-2.06)
>2	18 (0.7%)	5 (0.8%)	1.03 (0.38-2.77)
Admission for psycho-social condition	67 (2.6%)	31 (4.4%)	1.71 (1.13-2.59)
Admission for medical condition	2,064 (79.9%)	542 (77.5%)	0.97 (0.93-1.01)
Admission for trauma condition	639 (24.8%)	158 (22.6%)	0.91 (0.78-1.06)

a p=0.073 (Chi²)

Table 2: Characteristics of the study population attending Pediatric Emergency in 2019 and 2020.

Comorbidities were classified in allergy, respiratory disease, genetic disease, renal disease, hematologic disease, cardio-vascular disease, preterm and neurological disease categories.

	Cohort 2019 2,422 patients	Cohort 2020 639 patients	p–value	Prevalence Ratio (95% CI)
Median age (P25-P75) (years)	3.1 (1.1-7.7)	2.7 (1.1-7.0)	0.188	
Gender M (n, %)	1,346 (55.6%)	335 (52.4%)	0.155	0.94 (0.87-1.02)
Comorbidities (n, %)	294 (12.1%)	103 (16.1%)	0.008	1.33 (1.08-1.63)
Median* delay between the onset of symptoms and the admission to the PED (P25-P75) (days)	2 (1-4)	3 (1-5)	<0.001	

* Survival analysis (K-M); log-rank test.

The characteristics of children attending PED in 2020 and 2019 were compared (Table 2). The presence of comorbidities was proportionally 1.33 times more frequent in 2020 than in 2019 (95%CI: 1.08-1.63). The median delay between the symptom onset and the admission to the PED was longer in 2020 than in 2019 (3 days and 2 days respectively (p<0.001). Figure 2 shows the difference in delay between the symptom onset and the admission in 2020 and 2019 by admission category. The increase in delay in 2020 is statistically significant for global admission, upper respiratory infections and gastrointestinal conditions.

The ratio of proportions of admission for each category in 2020 versus 2019 is presented in a Volcano Plot in Figure 3. Urogenital, neurological conditions, intoxication and burns were relatively more frequent in 2020 compared to 2019, while the gastrointestinal conditions and fractures were relatively less frequent in 2020 than in 2019. There were no statistically significant differences for the other conditions.

Details of additional investigations performed at the PED are shown in Table 3. The proportions of blood test, urinalysis, and nasopharyngeal swabs were higher in 2020 than in 2019 but the proportion of imaging was not significantly different.

The rate of appropriate emergency visits as defined by Ben Ahmed was similar in 2019 and 2020 (54% and 58% respectively; PR= 1.07; 95%CI: 0.99-1.15) but PED discharge was more often followed by a pediatric visit in 2020 than in 2019. (15) Moreover the proportion of patients hospitalized was higher (16.2% in 2020 versus 9.4% in 2019; PR=1.72; 95%CI: 1.40-2.11), except to the ICU (0.4% and 0.5%; PR=0.85; 95%CI: 0.24-2.98), the median length of hospitalization was similar in 2020 and in 2019 (2 days in 2019 and 2 days in 2020, p-value<0,001).

PCR for identification of SARS-CoV-2 was performed only in children who were hospitalized (n=113). Ten (8.8%) swabs were positive, with only 3 patients presenting upper or lower respiratory symptoms.

No diagnosis of Multisystem Inflammatory Syndrome in Children (MIS-C) was made during the study period.

Discussion

This study compares the rate of attendance to PED in 2020 and 2019. We report that the number of pediatric admissions was 4 times lower in 2020 compared to the years 2017, 2018 and 2019, similarly to reports from Italy, Ireland, USA and United Kingdom (1,9,10,11,16). Prior to the pandemic, a decrease in ED attendance was described in the literature following natural disasters and during the financial crisis (17–19). Although the daily number of patients attending the ward in 2020 is small, the difference with 2019 undoubtedly reflects the situation in 2020. Comparisons in terms of diagnoses and time from symptom onset to consultation are impacted by the small size of the 2020 cohort. The statistical power is dependent on the sample size.

When comparing the characteristics of children attending PED in 2020 and 2019, those attending in 2020 have higher rates of comorbidities, probably because parents of children with comorbidities are more prompt in seeking medical care and would be less likely to postpone medical visits. Vulnerable children were more affected. Patients with chronic conditions accounted for 27.8% of PED visits in 2020 compared with 23.7% in 2017, 2018 and 2019 (16).

The delay between symptom onset and ward attendance was longer in 2020 than in 2019. Mc Donnel has suggested that some hospitalizations can be avoided if patients are admitted to the ED without delay (11). We observed an increase in the hospitalization rate. Possible causes are: parental fear of nosocomial SARS-CoV-2 infections, the difficulty in accessing hospital care due to lockdown measures and the closure of hospital beds. Indeed, one of the two pediatric hospitalization units has been converted into an adult ICU unit. The closure of the temporary hospitalization room in the PED also had an impact on the hospitalization rate in 2020 for inpatient care of less than 24 hours.

During the 2020 study period, more follow-up visits were scheduled after hospitalization. The hypothesis of increased follow-up is related to the shorter hospital stay in 2020. Additional pediatric follow-up appointments were scheduled to prevent clinical deterioration at home.

Finkelstein et al compared PED attendance in Canadian tertiary hospitals in a 2018-2020 cohort and during the first wave. Finkelstein showed an increase in the proportion of children hospitalized in ICU and non-ICU

Figure 2:
The difference of the mean number of days between the onset of symptoms and the admission in 2020 and 2019 was reported by subcategories.

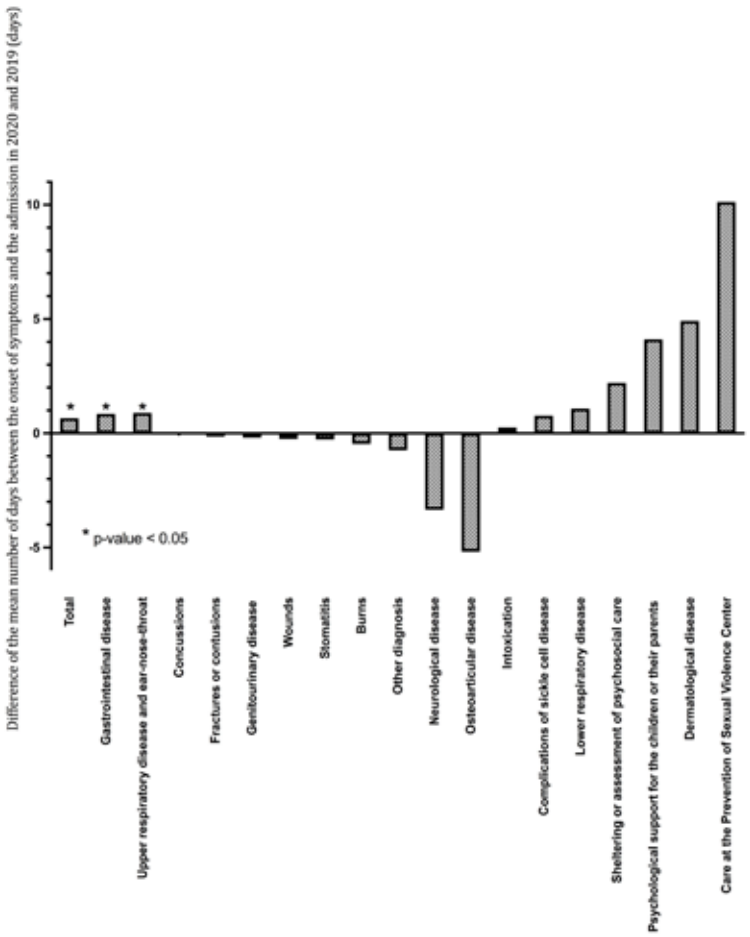


Table 3: Comparison of investigations performed in the emergency department in 2019 and 2020.

	Cohort 2019 N= 2,582 admissions	Cohort 2020 N= 699 admissions	Prevalence Ratio (95% CI)
Nasopharyngeal swabs (n, %)	268 (10.4%)	128 (18.3%)	1.76 (1.45-2.14)
SARS-CoV2 positive swabs (n, %)	NA*	10 (1.4%)	-
Blood test (n, %)	399 (15.5%)	147 (21.0%)	1.36 (1.15-1.61)
Urine test (n, %)	237 (9.2%)	93 (13.3%)	1.45 (1.16-1.81)
Chest imaging (n, %)	145 (5.6%)	42 (6.0%)	1.07 (0.77-1.49)
Other imaging (n, %)	328 (12.7%)	82 (11.7%)	0.92 (0.74-1.16)
Referred by a physician to the PED (n, %)**	340 (13.2%)	105 (15.0%)	1.14 (0.93-1.40)
Hospitalization rate (n, %)	243 (9.4%)	113 (16.2%)	1.72 (1.40-2.11)
ICU* transfers (n,%)**	13 (0.5%)	3 (0.4%)	0.85 (0.24-2.98)
Pediatric follow-up medical appointments (n, %)	511 (19.8%)	208 (29.8%)	1.50 (1.31-1.73)
Appropriate visits in PED (n, %) #	1,395 (54.0%)	403 (57.7%)	1.07 (0.99-1.15)

* NA= Not applicable **PED = Pediatric Emergency Department *** ICU = Intensive Care Unit

This marker included children who had been referred by a physician to the PED and those who needed additional examinations, surgical advice (wound, fracture) or hospitalization.

during the first wave but with a similar lengths of stay. There were no differences in mortality between two groups. This author concluded that Canadian children were sicker during the early-pandemic period, even though there were no differences in mortality or length of stay (20). The results of our study must be put into perspective with this Canadian study. The absence of deaths and the stable proportion of ICU admissions do not allow us to conclude that there is a higher morbidity and mortality rate during our study period.

The parents had the possibility to call the PED for a telephone advice during the different years studied. The number of telephone calls did not increase significantly (personal communication).

General practitioners were mainly overwhelmed by the adult patient population. Private pediatricians continued their practices and helped to filter out visits to the PED. Although, the population attending the Saint-Pierre public hospital is not used to going to see a pediatrician or a general practitioner before going to the emergency room.

Walk-in consultations were maintained during the pandemic but the number of regular pediatric consultations was reduced. Our hospital's pediatricians have been working as part of the adult emergency team.

The rate of appropriate emergency department visits was about 50% in 2019 and 2020. However, this rate is lower than that found in a Belgian study carried out in 2010 (60%), but higher than in the USA (42%) or in Italy in 2010-2011 (43%) (15,21–24).

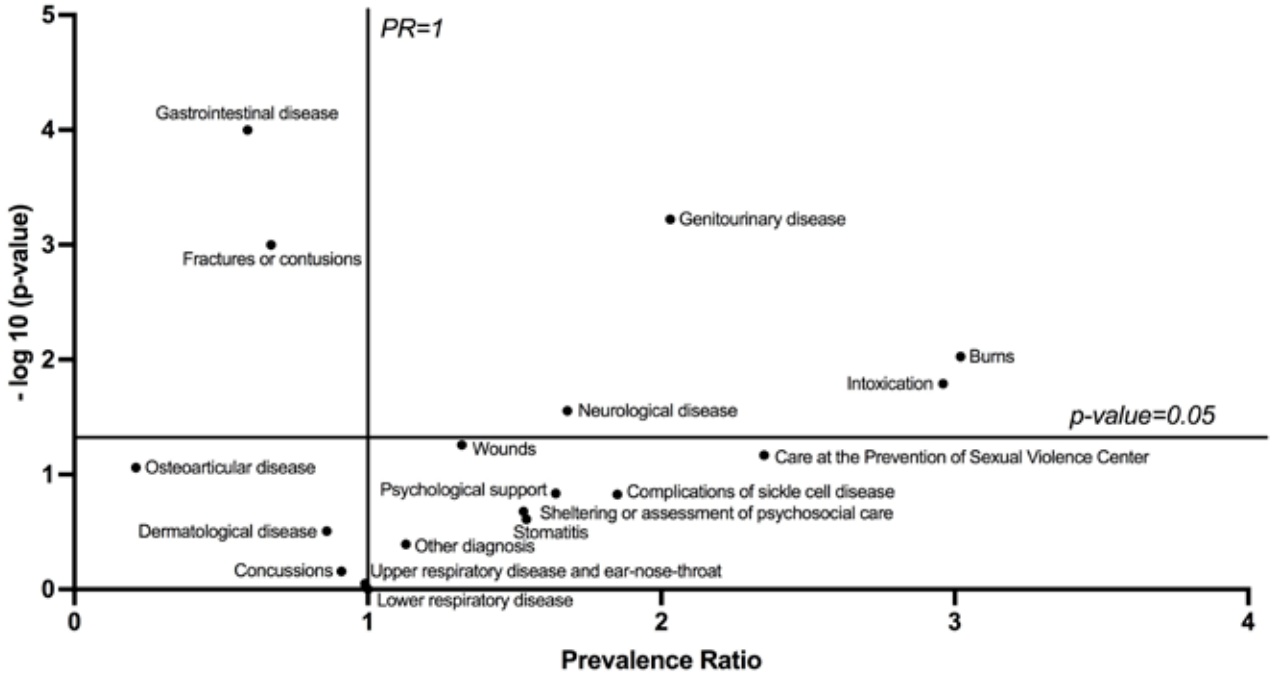
Despite a decrease in the absolute number of visits for PED, the proportion of diagnosis categories changed in 2020. It appears that the proportion of admission for burns was higher in 2020 than in 2019 but the absolute number of burns was similar. However, in Ireland, the proportion of injuries and intoxications was similar in 2018, 2019 and 2020 (25). The lower rate of fractures and contusions is probably due to the cessation of sports practice, school closures, playground closures, but also a reduction in road traffic accidents due to teleworking (9,11). Urogenital conditions were relatively more frequent, while gastrointestinal conditions were less frequent. This is probably related to the restriction of contacts due to confinement, which may affect the rate of gastroenteritis but not urinary tract infections. In adults, one study reported more severe urinary tractus infection but fewer ED visits in 2020 compared to 2019 (13). A Canadian multicenter study reached the same conclusions regarding the significant decrease in gastroenteritis diagnoses. This study included cohorts with larger daily visits than our study (22,654 admissions in 2019 and 7,535 in 2020) (26).

The COVID-19 crisis and its impact on the economy led to an increased risk of mental illness, domestic violence and child abuse (27–31).

While admissions for psychosocial conditions were relatively more frequent in 2020 than in 2019, it is likely that the real number of cases of child abuse or psychological distress in 2020 was even higher (32). The number of traumatic injuries caused by physical child abuse in 2020 is twice to the number in 2019 and 2018 (8, 4, and 3 cases respectively) (33). The Centers for Disease Control and Prevention showed that the proportion of mental health–related visits in PED increased in 2020 compared to 2019 (+24% for children aged 5-11 years, and +31% for children aged

Figure 3: Volcano plot of Prevalence ratio to Pediatric Emergency Department by clinical categories in 2020/2019.

The dots in the upper left side show a significant decreased in proportions (PR <1 and p-value <0.05) for gastro-intestinal conditions and fractures in 2020. The dots in the upper right side show a significant increase in proportions in 2020 (PR >1 and p-value <0.05). Urogenital, neurological conditions, intoxication and burns were relatively more frequent in 2020 compared to 2019. The dots below the horizontal row are not significant; there were no significant differences for the other conditions.



12-17 years) (34). During this pandemic, the overloaded medical teams, the reduced number of pediatric consultations, as well as the modified calendar of medical appointments, compromised good support for patients. School closures also reduced the number of alerts for child abuse alerts by teachers (35,36). CHU Saint-Pierre hospital is a reference center for sexual violence in Brussels and is one of the two reference centers for child abuse. During the lockdown period, the number of child abuse reports was much lower than in the previous year (141 versus 215) (Vanthournout, SOS enfant, personal communication). The number of calls to the dedicated crisis line to help children in the French-speaking region of Belgium was similar. (6,668 during the period studied in 2020 and 6673 in 2019). However, the proportion of calls for maltreatment has almost doubled (18.8% for the whole of 2020 versus 10.8% in 2019). (Courtoy, Ligne écoute téléphonique 103 Ecoute Enfant, personal communication).

Finally, we have identified few COVID-19 patients in our study. According to the guidelines of the Belgian Health Care , nasopharyngeal swabs for SARS-CoV-2 PCR were performed only in case of hospitalization. Indeed, the COVID-19 cases were underestimated, we see only the tip of the iceberg. In a Greek study, no SARS-CoV-2 was detected in PED during the first wave (0/60 tests). However, during the second containment, the positivity rate increased to 23% (69 positives out of 299 tests) (37). According to Belgian data , there were 600 cases of COVID-19 in children under 19 years of ages during the period between March 18th and May 4th, including 233 cases were in children under 10 years of age. In the Brussels region, there were 65 cases of COVID-19 in children under 19 years of age from March 18th to April 5th, 2020.

To our knowledge, there is no Belgian publication on PED attendance during COVID-19.

The children suffered more from the collateral damage and other pathologies than from COVID-19 in 2020. One of the lessons of our study is to better understand what diagnoses are encountered in the event of a lockdown and how to improve the management and referral of these patients in the future. Targeted prevention campaigns could be disseminated during a future pandemic. Knowing the type and proportion of diagnoses will allow better allocation of personnel and resources in the event of a future health crisis.

This study has some limitations. Data were collected retrospectively for both years. This mono-centric study took place in the national reference center for the management of highly contagious respiratory viruses in Belgium. Therefore, due to the fear of SARS-CoV2, attendance at this hospital cannot reflect the attendance at another hospital. The number of patients attending the ward every day in 2020 is small, but it reflects the situation in 2020. The difference is undoubtedly statistically significant between the number of attendance in 2020 compared to 2019 or 2020/2018 or 2020/2017. Changes have been observed, but a causal link could not be formally demonstrated. This study does not allow us to conclude an increased morbidity rate due to the lockdown. Furthermore, an assessment of long-term morbidity in the post-COVID period cannot be derived from an analysis of emergency department admissions in 2020. To better assess the long-term impact of this pandemic, epidemiological studies on the health of children attending schools and health prevention centers are needed.

Pediatric studies are a small part of the scientific literature. All of the studies used in the discussion were small and of short duration in 2020. The SARS-CoV-2 virus had different variants over the next two years. The mutations have resulted in a variety of COVID-19 impairments and severities. Most of the studies that contribute to this discussion are focused on the first wave.

Moreover, we may have missed some relevant studies by including only English language publications.

Conclusion

In conclusion, as observed in many other countries, the rate of attendance at the PED of CHU Saint-Pierre decreased during the lockdown in 2020 compared to the same study period in 2019. The delay between the onset of symptoms and the admission to the PED was longer, and the hospitalization rate was higher during the lockdown. There is a difference in the distribution of diagnoses in 2020 compared to 2019.

This study highlights the implications of the lockdown on various aspects of the pediatric care.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES

1. Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health. 2020 May;4(5):e10–1.
2. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020 Oct;146(4):e2020009399.
3. Pecoraro L, Dalle Carbonare L, De Franceschi L, Piacentini G, Pietrobelli A. The psychophysical impact that COVID-19 has on children must not be underestimated. Acta Paediatr. 2020 Aug;109(8):1679–80.
4. Safadi MAP. The intriguing features of COVID-19 in children and its impact on the pandemic. J Pediatr (Rio J). 2020 May;96(3):265–8.
5. Pavone P, Ceccarelli M, Taibi R, La Rocca G, Nunnari G. Outbreak of COVID-19 infection in children: fear and serenity. Eur Rev Med Pharmacol Sci. 2020;24(8):4572–4575.
6. Zachariah P, Johnson CL, Halabi KC, Ahn D, Sen AI, Fischer A, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. JAMA Pediatr. 2020 Jun 3;e202430.
7. Boast, A, Munro A, Goldstein H. An evidence summary of Paediatric COVID-19 literature. Don't Forget the Bubbles, 2020.
8. Shepherd J, Friedland G. Preventing COVID-19 Collateral Damage. Clin Infect Dis. 2020 Sep 12;71(6):1564–7.
9. Comelli I, Scioscioli F, Cervellin G. Impact of the COVID-19 epidemic on census, organization and activity of a large urban Emergency Department. Acta Bio Medica Atenei Parm. 2020;91(2):45.
10. Isba R, Edge R, Jenner R, Broughton E, Francis N, Butler J. Where have all the children gone? Decreases in paediatric emergency department attendances at the start of the COVID-19 pandemic of 2020. Arch Dis Child. 2020 Jul;105(7):704.1-704.
11. McDonnell T, Nicholson E, Conlon C, Barrett M, Cummins F, Hensey C, et al. Assessing the Impact of COVID-19 Public Health Stages on Paediatric Emergency Attendance. Int J Environ Res Public Health. 2020 Sep 15;17(18):6719.
12. Feral-Pierssens AL, Claret PG, Chouihed T. Collateral damage of the COVID-19 outbreak: expression of concern. Eur J Emerg Med. 2020 Aug;27(4):233–4.
13. Borgmann H, Struck JP, Mattigk A, Wenzel M, Pilatz A, Kranz J, et al. Increased Severe Adverse Outcomes and Decreased Emergency Room Visits for Pyelonephritis: First Report of Collateral Damage during COVID-19 Pandemic in Urology. Urol Int. 2021 Jan 6;1–7.
14. O'Brien CM, Jung K, Dang W, Jang HJ, Kielar AZ. Collateral Damage: The Impact of the COVID-19 Pandemic on Acute Abdominal Emergency Presentations. J Am Coll Radiol. 2020 Nov;17(11):1443–9.
15. Benahmed N, Laokri S, Zhang WH, Verhaeghe N, Trybou J, Cohen L, et al. Determinants of nonurgent use of the emergency department for pediatric patients in 12 hospitals in Belgium. Eur J Pediatr. 2012 Dec;171(12):1829–37.
16. DeLaroche AM, Rodean J, Aronson PL, Fleegler EW, Florin TA, Goyal M, et al. Pediatric emergency department visits at US children's hospitals during the COVID-19 pandemic. Pediatrics. 2021;147(4).
17. Keenan HT, Marshall SW, Nocera MA, Runyan DK. Increased incidence of inflicted traumatic brain injury in children after a natural disaster. Am J Prev Med. 2004 Apr;26(3):189–93.
18. Raker EJ, Zacher M, Lowe SR. Lessons from Hurricane Katrina for predicting the indirect health consequences of the COVID-19 pandemic. Proc Natl Acad Sci. 2020 Jun 9;117(23):12595–7.
19. Gkentzi D, Katsoula V, Fouzas S, Mentis M, Karatza A, Dimitriou G. Economic Recession and Attendances in the Pediatric Emergency Department. BioMed Res Int. 2019 Feb 10;2019:1–7.
20. Finkelstein Y, Maguire B, Zemek R, Osmanlliu E, Kam A, Dixon A, et al. Effect of the COVID-19 Pandemic on Patient Volumes, Acuity, and Outcomes in Pediatric Emergency Departments: A Nationwide Study. Pediatr Emerg Care. 2021 Aug;427–34.
21. Kubicek K, Liu D, Beaudin C, Supan J, Weiss G, Lu Y, et al. A Profile of Nonurgent Emergency Department Use in an Urban Pediatric Hospital: Pediatr Emerg Care. 2012 Oct;28(10):977–84.
22. Poku BA, Hemingway P. Reducing repeat paediatric emergency department attendance for non-urgent care: a systematic review of the effectiveness of interventions. Emerg Med J. 2019 Jun 21;emermed-2018-207536.
23. Seguin J, Osmanlliu E, Zhang X, Clavel V, Eisman H, Rodrigues R, et al. Frequent users of the pediatric emergency department. CJEM. 2018 May;20(3):401–8.
24. Vedovetto A, Soriani N, Merlo E, Gregori D. The Burden of Inappropriate Emergency Department Pediatric Visits: Why Italy Needs an Urgent Reform. Health Serv Res. 2014 Aug;49(4):1290–305.
25. Dann L, Fitzsimons J, Gorman KM, Hourihane J, Okafor I. Disappearing act: COVID-19 and paediatric emergency department attendances. Arch Dis Child. 2020 Aug;105(8):810–1.
26. Goldman RD, Grafstein E, Barclay N, Irvine MA, Portales-Casamar E. Paediatric patients seen in 18 emergency departments during the COVID-19 pandemic. Emerg Med J. 2020 Oct 29;emermed-2020-210273.
27. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. Child Adolesc Psychiatry Ment Health. 2020 Dec;14(1).
28. Bradbury-Jones C, Isham L. The pandemic paradox: The consequences of COVID-19 on domestic violence. J Clin Nurs. 2020 Jul;29(13–14):2047–9.
29. Fontanesi L, Marchetti D, Mazza C, Di Giandomenico S, Roma P, Verrocchio MC. The effect of the COVID-19 lockdown on parents: A call to adopt urgent measures. Psychol Trauma Theory Res Pract Policy. 2020 Aug;12(S1):S79–81.
30. Feltman DM, Moore GP, Beck AF, Siffermann E, Bellieni C, Lantos J. Seeking Normalcy as the Curve Flattens: Ethical Considerations for Pediatricians Managing Collateral Damage of Coronavirus Disease-2019. J Pediatr. 2020 Oct;225:233–8.
31. Fiorillo A, Gorwood P. The consequences of the COVID-19 pandemic on mental health and implications for clinical practice. Eur Psychiatry. 2020;63(1).
32. Crawley E, Loades M, Feder G, Logan S, Redwood S, Macleod J. Wider collateral damage to children in the UK because of the social distancing measures designed to reduce the impact of COVID-19 in adults. BMJ Paediatr Open. 2020 May;4(1):e000701.
33. Kovler ML, Ziegfeld S, Ryan LM, Goldstein MA, Gardner R, Garcia AV, et al. Increased proportion of physical child abuse injuries at a level I pediatric trauma center during the Covid-19 pandemic. Child Abuse Negl. 2021 Jun;116:104756.
34. Leeb RT, Bitsko RH, Radhakrishnan L, Martinez P, Njai R, Holland KM. Mental health–related emergency department visits among children aged< 18 years during the COVID-19 pandemic—United States, January 1–October 17, 2020. Morb Mortal Wkly Rep. 2020;69(45):1675.
35. Garstang J, Debelle G, Anand I, Armstrong J, Botcher E, Chaplin H, et al. Effect of COVID-19 lockdown on child protection medical assessments: a retrospective observational study in Birmingham, UK. BMJ Open. 2020 Sep;10(9):e042867.
36. Teo S, Griffiths G. Child protection in the time of COVID-19. J Paediatr Child Health. 2020 Jun;56(6):838–40.
37. Kostopoulou E, Gkentzi D, Papasotiriou M, Fouzas S, Tagalaki A, Varvarigou A, et al. The impact of COVID-19 on paediatric emergency department visits. A one-year retrospective study. Pediatr Res. 2022 Apr;91(5):1257–62.

HET BELANG VAN HYDRATATIE VOOR ZUIGELINGEN TIJDENS DE WINTERPERIODE

Voor baby's en jonge kinderen is het heel het jaar door fysiologisch belangrijk om voldoende vocht in te nemen. Dit vraagt echter extra aandacht in het winterseizoen, wanneer er een verhoogd risico is op vele infecties waarvan de belangrijkste symptomen verband houden met uitdroging.[1,2]

De lichaamsmassa van pasgeborenen bestaat voor zo'n 75% uit water. Dit percentage neemt in het eerste levensjaar snel af tot 60%, en blijft gedurende de hele kindertijd tot de adolescentie relatief stabiel. De geleidelijke rijping van de nierfunctie tegen de leeftijd van 2 jaar en een hogere verhouding tussen lichaamsoppervlak en lichaamsmassa, waardoor meer water via de huid verloren gaat, verklaren gedeeltelijk waarom de behoefte aan water bij kinderen groter is dan bij volwassenen.[1]

De EFSA (European Food Safety Authority) heeft de adequate inname voor verschillende leeftijdsgroepen vastgesteld (tabel). De behoeften kunnen echter van kind tot kind verschillen, en een adequate inname moet soms aangepast worden aan de mate van activiteit en aan omgevingsfactoren zoals warmte en vochtigheid.[3]

De aanbeveling van de EFSA inzake adequate waterinname voor zuigelingen van 0 tot 36 maanden.

Leeftijdsgroep	Adequate inname
0-6 maanden	100-190 ml/kg in de vorm van melk
6 tot 12 maanden	800-1000 ml/dag
1 tot 2 jaar	1100-1200 ml/dag
2 tot 3 jaar	1300 ml/dag

Baby's en jonge kinderen zijn bijzonder vatbaar voor diarree en uitdroging door hun hogere stofwisseling, hun onvermogen om hun behoeften kenbaar te maken of zichzelf te hydrateren, de hevigere transpiratie in de eerste levensmaanden of ziekteprocessen die leiden tot vochtverlies.[4]

Uitdroging bij zuigelingen: pas op voor winterziektes

In de meeste gevallen is uitdroging bij kinderen het gevolg van gastro-enteritis, een veel voorkomende ziekte tijdens de wintermaanden met symptomen die vochtverlies bevorderen: diarree, braken en koorts.[4]

Virale infecties, waaronder infecties met het rotavirus, norovirus en enterovirus, zijn verantwoordelijk voor 75 à 90% van de gevallen van besmettelijke diarree. In het geval van een bacteriële infectie zijn de belangrijkste ziekteverwekkers Salmonella, Shigella en Escherichia coli.[4]

Voldoende hydratatie van de lichaamsweefsels is essentieel voor de gezondheid en het leven. Een verlies van lichaamsgewicht, dat overeenkomt met een verlies van lichaamswater, van ongeveer 1% wordt normaal gezien binnen de 24 uur gecompenseerd. Bij gebrek aan compensatie en als het verlies aan lichaamsvocht blijft toenemen, treden er beperkingen op van de fysieke en cognitieve prestaties, de thermoregulatie en de cardiovasculaire functie. Een verlies van 10% of meer van het lichaamsvocht kan fataal zijn.[3]

Aanbevelingen voor het drinkwatergebruik van zuigelingen

Water dat over het algemeen geschikt is voor zuigelingenvoeding omvat bronwater dat voldoet aan de veiligheidsnormen en commercieel flessenwater (natuurlijk bronwater of behandeld water met een laag mineraalgehalte).[5] Bij de keuze van de bron van het water dat gebruikt wordt als drank of bij de bereiding van flesvoeding, moet men erop letten dat het een minimum aan nitraten bevat, een mogelijke bron van vergiftiging.[6] In elk geval moet het water dat gebruikt wordt voor zuigelingenvoeding gesteriliseerd worden voor kinderen jonger dan 4 maanden.[5]

In geval van vochtverlies tijdens ziekte (koorts, diarree ...) valt moedermelk of zuigelingenvoeding te verkiezen boven water, om een verstoord elektrolytenevenwicht te voorkomen. Orale rehydratietherapie kan nodig zijn.[5]

Water is essentieel voor het leven, en ook voor de ontwikkeling van zuigelingen. Het aanleren van gezonde drinkgewoontes is belangrijk vanaf de kindertijd, aangezien veel van het voedingsgedrag dat in de kindertijd aangeleerd wordt, blijft bestaan tot de volwassenheid. Kinderen die weinig water drinken, zullen ook als volwassenen weinig water drinken, met mogelijke invloed op de gezondheid van de nieren en de stofwisseling en op cognitieve en stemmingsstoornissen.[1]

Referenties:

1. Bottin J. H. et al., Hydration in Children: What Do We Know and Why Does it Matter? Annals of Nutrition & Metabolism 2019; 74(3): 11–18. **2**. Childhood winter illnesses - Knowing what to do. NHS. **3**. Scientific Opinion on Dietary Reference Values for water. EFSA Journal 2010; 8(3): 1459. **4**.Vega R. M. et Avva U., Pediatric Dehydration [Updated 2022 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436022/ **5**. Nutrition Guideline: Healthy Infants and Young Children – Water. Alberta Health Services, November 2013. P 6.1.1-6.1.5. https://www.albertahealthservices.ca/ **6**. Greer F. R. et Shannon M., American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Committee on Environmental Health. Infant methemoglobinemia: the role of dietary nitrate in food and water. Pediatrics 2005; 116(3): 784-786

COVID-BIRTH study : Perinatal Impact of Maternal Covid-19

Anne Devos [a], Bieke Bollen [b], Anne Smits [c], Kristel Van Calsteren [d], Francesca Russo [d], Titia Hompes [e], An Eerdekens [c]

[a] University Hospitals Leuven, Department of Pediatrics, Leuven, Belgium
[b] Faculty of Medicine, Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[c] University Hospitals Leuven, Neonatal Intensive Care unit, Leuven, Belgium
[d] University Hospitals Leuven, Department of Obstetrics and Gynaecology, Leuven, Belgium
[e] University Hospitals Leuven, Universitary Psychiatric Centre, Leuven, Belgium

anneke_d92@hotmail.com

Keywords

Covid-19; SARS-CoV-2; pregnancy; breastfeeding; mental health; perinatal impact; neonate.

Abstract

The perinatal impact of maternal COVID-19 disease and the hygienic and social distancing measures taken during the epidemic remain unclear. In this prospective study, the impact of SARS-CoV-2 infection and the social distancing measures on parental anxiety, depression and bonding in COVID-19 positive and COVID-19 negative pregnancies were evaluated.

We recruited pregnant women at delivery in a university hospital in Belgium between April and December 2020, both SARS-CoV2 negative and confirmed (current or previous) SARS-CoV2 positive during pregnancy. Baseline clinical information was retrieved from the patient's medical file. Women received questionnaires electronically at birth (Day 0-3) and 6 weeks after delivery.

In total, 240 individuals were included at delivery and 37 (15%) of them were COVID-19 positive pregnancies. No significant differences on maternal, neonatal, or breastfeeding outcomes between the COVID-19 positive and negative group were observed. Pregnancy, breastfeeding and neonatal outcome data were similar compared to reference values before COVID-19.

Elevated Edingburg Postpartum Depression Scale scores (>13) were seen in 11% of our patients. This number was significantly higher compared to data in pregnant women at the same hospital before the COVID-19 pandemic. Elevated GAD-7 (Generalized anxiety disorder score) was documented in 13.5% of all included patients. More than half of all women reported that the epidemic had an impact on the support they received post-partum.

It appears that the COVID-19 epidemic has a serious impact on the mental well-being of pregnant women and mothers. It is important to further explore the risk-benefit analysis of future measures during the epidemic.

Introduction

With over 600 million cases worldwide, as of March 2023, coronavirus infectious disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) set up a global public health crisis (1).

The impact of SARS-CoV-2 infection during gestation remained unclear at the beginning of the pandemic. The possibility of vertical transmission of SARS-CoV-2 has been a point of debate (2-6). Although rare, vertical transmission is possible, with the highest risk in the third trimester of pregnancy (7-9). The effect of the COVID-19 pandemic and its consequences on maternal and neonatal outcomes continued to be a knowledge gap (10-13). This uncertainty brought fear among healthcare providers and pregnant women.

Pregnancy, delivery of a baby, and early motherhood are crucial moments in the life of a woman. For the infant, the first 1000 days of life have been acknowledged as the base for mental and physical health in later life (14). When pregnancy and birth occur in uncertain times, when social distancing is the norm, when no visits are allowed, when thoughts of fear were overall present, it is unknown how these events affect mother-infant bonding, parental stress, breastfeeding rates, health problems during infancy and neurodevelopmental outcome of the infant (14). Different studies and reports addressed these indirect but potentially harmful consequences of the COVID-19 pandemic on pregnant women and neonates (15,16).

During the pandemic, the focus of healthcare and its resources shifted to the acute care of infection. A survey in the United Kingdom, conducted in maternity services, showed a reduction in both antenatal and postnatal appointments, as well as a shift to remote consultation methods (16). While these measures will likely protect both patients and staff against the acute effects of the virus, it remains essential to monitor pregnancy, maternal and neonatal outcomes during these challenging times. Reduced access to antenatal and postnatal care may impact the ability to screen for physical, psychological, and social problems. The risk-benefit analysis of these measures must be evaluated, as they risk amplifying and accentuating existing health and socio-economic inequalities (16,17).

A matched-control study in the United States of America showed acute traumatic stress symptoms in almost 50% of COVID-19 positive women in response to childbirth. They were twice as likely to have no visitors during delivery and hospitalisation and were separated more from their newborns in comparison with COVID-19 negative women (13). In addition, a Turkish cross-sectional study found pregnant women at high risk of antenatal depression during the COVID-19 pandemic (Edinburgh depression score >13) (18). A review including twelve studies about the impact of COVID-19 on breastfeeding plans showed positive experiences (increased time at home) as well as negative experiences (separation from newborn, decreased professional and family support, fear of vertical transmission). An Italian study showed a decrease in exclusive breastfeeding during lockdown and home confinement in non-infected mothers (19,20). Furthermore, breastmilk substitute companies capitalized on the uncertainty and fear among mothers during the COVID-19 pandemic by spreading debatable health claims and misinformation. These tactics violated the International Code of Marketing of Breast-Milk Substitutes (21).

The purpose of this study was to obtain greater insight in the perinatal impact of maternal COVID-19. Primary objectives were to examine the association between COVID-19 infection and the social distancing

measures on parental anxiety, depression, and mother-child bonding. Secondary, we wanted to assess the association between the COVID-19 pandemic and the measures of social distancing on breastfeeding outcomes, breastfeeding complications and health complications in the neonatal period in COVID-19 positive pregnancies, as well as in COVID-19 negative pregnancies.

Methods

Study-design

A prospective observational study was conducted in the University Hospitals Leuven, a tertiary care university hospital in Belgium. We recruited pregnant women who delivered in the University Hospitals Leuven between April 2020 and December 2020. COVID-19 negative pregnancies were defined as patients with a recent (<1 week) negative polymerase chain reaction (PCR) for SARS-CoV-2 on nasopharyngeal swab or with no recent swab but asymptomatic. COVID-19 positive pregnancies were defined as patients with current or previous SARS-CoV-2 infection confirmed by PCR on nasopharyngeal swab, or with current suspected SARS-CoV2 infection because of suggestive signs and/or symptoms. All patients admitted for delivery were screened for SARS-CoV-2 infection by nasopharyngeal swab, as specified in the standard clinical protocol. This was done either the day before hospitalization in patients with planned deliveries, or at admission in patients with spontaneous labor. As some unscheduled patients might deliver before the results of the test, and since the sensitivity of the PCR test for SARS-CoV-2 is not 100%, symptomatic patients with or without available test results were also included.

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study was approved by the Ethics Committee Research of the University Hospitals Leuven (internal study number S63942). Written informed consent was obtained on admission in labor ward for delivery.

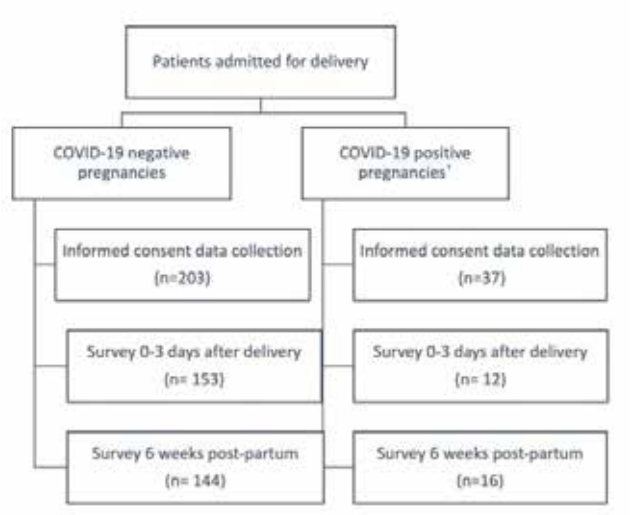
Since this was an observational study and the evolution of the COVID-19 pandemic was still unknown, it was not possible to calculate a required sample size. Sample size was estimated based on the average deliveries per month at our hospitals (200/month), participation rate for questionnaires during pregnancy in other studies (25-40%) and the rate of COVID-19 positivity among patients admitted for delivery at that time (5-10%). We estimated to recruit 540 patients.

An electronic database was set up within the safe environment of a clinical server at the hospital (REDCAP). Baseline clinical information (including demographics, comorbidities, pregnancy history) was retrieved from the patient's medical file at admission. Women received questionnaires electronically on admission, at birth (Day 0-3), and 6 weeks after delivery. They received questions about demographics, education and social environment, medical and obstetrical history, mental health, pregnancy and neonatal complications, as well as COVID-19 related questions (Figure 1). Women who were admitted to University Hospitals Leuven after a stillbirth or a termination of pregnancy due to severe congenital malformations were excluded from the questionnaire part of the study.

Psychological measurements

Parental anxiety, depression and bonding were assessed using the Edinburg Postpartum Depression Scale (EDPS), Mother Infant Bonding Scale (MIBS) and the Generalized Anxiety Disorder-7 (GAD-7). These were included in the questionnaires at birth (day 0-3) and 6 weeks after delivery. The GAD-7 is a valid and efficient tool for screening for GAD (generalized anxiety disorder) and assessing its severity in clinical practice and research. The GAD-7 items include: 1) nervousness; 2) inability to stop worrying; 3) excessive worrying; 4) restlessness; 5) difficulty in relaxing; 6) easily irritated; and 7) fear of something awful happening. The GAD-7 asks participants to rate how often they have been troubled by each of these 7 core symptoms over the past 2 weeks. The total score of the GAD-7 ranges from 0 to 21. A score of 10 or greater on the GAD-7 represents a reasonable cut-off point for identifying cases with GAD. A cut-off of 13 is proposed in pregnancy. The EPDS was developed

Figure 1: Flow chart of participants included in the study



to determine postnatal depression symptoms and the critical cut-off point is 13. It is a self-reporting 10-item scale. The total score ranges between 0 and 30. MIBS is an 8 item self-rating mother-to-infant bonding questionnaire that has been designed to assess the feelings of a mother towards her new baby (22). Breastfeeding outcomes were assessed with focused questions about breastfeeding duration, breastfeeding support, and breastfeeding complications. Infancy health was evaluated with focused questions about growth evolution and hospital admissions.

Data Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26 for Mac. Descriptive statistical analyses were performed for the clinical data. Also, for the data collected by the questionnaire, descriptive statistics (percentages, means, standard deviations, medians, ranges) were used. Summary statistics for all variables were calculated using means and standard deviation for continuous variables, when normally distributed, and frequency and proportions for categorical variables. Pregnancy and neonatal outcome data in COVID-19 positive and negative women were compared with each other and with reference values available from 2019 in Flanders (SPE) (23).Chi-Square and Fisher-exact test were used when comparing proportions between both groups (e.g., COVID-19 positive vs COVID-19 negative patients or reference values from SPE). Unpaired t-test was used to compare means between COVID-19 negative and positive groups. Significance level was accepted if $p < 0.05$.

Results

Baseline data

In total, 240 women were included in our study. Data from the medical records are summarized in Table 1. The medical record was not fully completed for each patient resulting in missing data for some variables. There were significantly more non-Caucasian women in the COVID-19 positive group. There were no other statistically significant differences in baseline demographics between the COVID-19 positive and COVID-19 negative group.

COVID-19 Infection

Thirty-seven of all patients (15.3%) had a current or previous COVID-19 infection. Thirty-four were confirmed by PCR, three had only strong clinical suspicion. Nasopharyngeal swab was used for PCR testing in all cases. Reported symptoms were cough (41%), rhinorrhea (33%), tiredness/lethargy (26%), sore throat (15%), dyspnea (15%), fever (15%), headache (11%). Anosmia was reported in two patients. No gastro-intestinal symptoms were reported. Almost one fifth (18.5%)

had no suggestive symptoms. Three women were hospitalized in the third trimester of the pregnancy due to COVID-19 infection and received intensive care. There was one preterm delivery and one stillbirth after pre-eclampsia and HELPP.

Current Pregnancy and birth

Table 1: Baseline characteristics of patients

	COVID-19 negative pregnancies (n=203)	COVID-19 positive pregnancies (n=37)	P-value*
Age (years)	32±3,6	32±4,3	1.0
Race			
Caucasian	185/194 (95.4%)	30/36 (83.3%)	0.02
Medical History			
None	113/197 (57.4%)	23/35 (65.7%)	0.46
Psychiatric disorders	6/197 (3.0%)	0/35 (0%)	0.59
Conception			
Spontaneous	167/194 (86.1%)	35/36 (97.2%)	0.09
In vitro fertilization (IVF)	6/194 (4.1%)	1/36 (2.8%)	1.0
Pregnancy Complications			
None	119/197 (60.4%)	20/36 (55.6%)	0.58
Gestational diabetes	11/197 (5.6%)	5/36 (13.9%)	0.08
Stillbirth	0/197 (0.0%)	1/36 (2.8%)	0.15
Steroids for fetal lung maturation	7/195 (3.6%)	2/37 (5.4%)	0.63
Delivery Type			
Spontaneous	100/195 (51.3%)	16/37 (43.2%)	0.47
Planned	92/195 (47.2%)	18/37 (48.6%)	1.0
Urgent	3/195 (1.5%)	3/37 (8.1%)	0.06
Anesthesia			
None	30/195 (15.4%)	7/36 (19.4%)	0.62
Spinal/Epidural	163/195 (83.6%)	28/36 (77.8%)	0.47
General	1/195 (0.5%)	1/36 (2.8%)	0.29
Complications at birth			
None	182/195 (93.3%)	32/37 (86.5%)	0.18
Shoulder dystocia	6/195 (3.1%)	4/ 37 (10.8%)	0.06
Postpartum hemorrhage	3/195 (1.5%)	1/37 (2.7%)	0.50
Birthweight (gram)[1]	3287±478	3240±673	0.61
Breastfeeding at birth	162/197 (82.2%)	30/35 (85.8%)	0.81
NICU/Medium care admission	27/197 (13.7%)	9/36 (25.0%)	0.13

[1] *Mean ± SD*
** obtained by t-test for continuous and chi-square or Fisher's exact test for categorical variables*

There were no statistical differences between the COVID-19 positive group and COVID-19 negative group for pregnancy and birth characteristics. Comparing our total population to the reference values of SPE 2019, we saw similar values for most characteristics, including number of spontaneous pregnancies (89.8%, p=0.33) and percentage of diabetes (5.8%, p=0.68). We saw statistically significant differences in the average use of epidural analgesia in Flanders vs our population (69.3% vs 82.7%, p=0.01) and in the number of planned deliveries (25.4% vs 47.4%, p=0.01.

Postpartum/Postnatal period

More than 83% of all patients decided to (indirect) breastfeed after birth. Fifteen percent decided to start with formula feeding. When questioned, maternal or neonatal COVID-19 infection was never given as a reason for choosing between breastfeeding or bottle feeding at birth. Rates of breastfeeding at birth did not differ between the COVID-19 positive group and the COVID-19 negative group (p=0.81).

Sixteen percent of all babies were admitted to the NICU or medium care neonatal ward. Respiratory distress (43.0%) and prematurity (33.4%) were the most common reasons for admission. There was no statistically significant difference in admissions to the NICU between the COVID-19 positive and negative group (p=0.13). There were no statistical differences in admissions between our population and reference values of 2019 in Flanders (p=0.72) (23).

Twelve babies (5.1%) received a COVID-19 PCR test. Eight of them received the test when they were admitted to the NICU or medium care neonatal ward. They all had COVID-19 positive mothers. None of them tested positive. Four neonates were screened pre-operative or on readmission because of infection or hyperbilirubinemia. One of these four neonates tested positive. The mother of this neonate tested positive one week earlier. There was no difference in abnormalities at physical examination. Neonatal complications were rare, no differences were documented between the two groups.

Questionnaires at discharge & six weeks postpartum

The survey on day 0-3 was completed by 165 women (70% of initial population), 160 women completed the survey at 6 weeks. One patient was excluded from the survey because of stillbirth. Only 32% (n=12) and 43% (n=16) of patients with a current or previous COVID-19 infection completed the survey on day 0-3 and 6 weeks, respectively. This difference is statistically significant (p<0.05) (Figure 1). Questionnaires were not always fully completed by patients, causing some answers to be missing for some patients. Nearly all women were married or living together (98%). Higher education was completed by 86%. Almost half of the women (48%) had completed university studies. Close to 30% of our study population (45/165) worked in the healthcare sector. More than 20% of them had direct contact with COVID-19 patients. They worked, in average, until 28 weeks of pregnancy.

At discharge, 80.4% of all women were breastfeeding. Six women indicated the pandemic to be of influence for their decision, in favor of breastfeeding. At 6 weeks, almost 75% were still breastfeeding. None of them indicated the pandemic to be of influence to stop breastfeeding. At discharge more than 75% of all patients had a midwife service at home, 12% had maternity care. More than half of the women (52%) reported that the COVID-19 pandemic had played a negative role in the level of support they received at home (familial or professional).

From the 165 women who completed the survey at discharge, 12 patients had a proven COVID-19 infection during pregnancy. Another 20 patients indicated that they possibly experienced a COVID-19 infection during pregnancy (cough, cold, fever, difficulty breathing). There was no statistical difference between the COVID-19 positive (proven and/or suspected) group and the negative group in maternal educational level, occupancy in healthcare, postnatal support or rates of breastfeeding (Table 2).

A total of 14.5% (n=23) of all women experienced isolation or quarantine because of COVID-19 virus infection during pregnancy. Women in COVID-19 positive pregnancies were significantly more likely to have been quarantined or isolated.

The GAD-7 was higher than 10 in 13.5% of all women, and higher than 13 in 8.6% of all cases. There was no statistical difference between the COVID-19 positive group and COVID-19 negative group in the mean result or cut-off points of 10 or 13. The EPDS was 13 or higher in 11% of the women who completed the survey at birth. No statistical differences were observed between the COVID-19 positive group and COVID-19 negative group in EPDS scores.

Table 2: Questionnaires outcomes

	COVID-19 negative pregnancies	COVID-19 positive pregnancies	P-value*
Social situation			
Married or living together	147/150 (98.0%)	12/12 (100%)	1.00
Maternal Education Level			
Secondary School	17/149 (11.4%)	3/12 (25.0%)	0.17
College	74/149 (49.7%)	4/12 (33.3%)	0.37
Healthcare worker	44/153 (28.8%)	2/12 (16.0%)	0.51
Breastfeeding			
At discharge	118/149 (79.2%)	10/11 (90.9%)	0.69
6 weeks	102/143 (71.3%)	14/16 (87.5%)	0.24
Postpartum Care			
Midwife	113/149 (75.8%)	10/12 (83.3%)	0.73
Maternity care	20/149 (13.4%)	0/12 (0%)	0.36
Isolation/Quarantine	13/145 (9.0%)	7/11 (63.6%)	0.001
GAD-7	4.7±4.8[1]	4.1±4.5[1]	0.69
>10	20/148 (13.5%)	1/11 (9.1%)	1.00
General	12/148 (8.1%)	1/11 (9.1%)	1.00
EDPS	6.1±4.7[1]	8.7±6.2[1]	0.09
>13	16/142 (11.3%)	1/10 (10%)	1.00

[1] *Mean ± SD*

* *obtained by t-test for continuous and chi-square or Fisher's exact test for categorical variables*

GAD-7: Generalized Anxiety Disorder-7

EDPS: Edinburg Postpartum Depression Scale

Discussion

No significant differences in pregnancy or neonatal outcome between COVID-19 positive pregnancies and negative pregnancies were documented. However, we did see higher GAD-7 and EPDS scores in our study population, than before the COVID-19 pandemic (24). Generalized anxiety disorder (GAD) and postpartum depression have different consequences for mother and child. Studies describe decreased quality of life, disrupted mother-child attachment, and emotional and developmental problems in the child. Moreover, GAD would also have a negative effect on birth weight and increased risk of prematurity (25-29). Prevalence of GAD in pregnancy and postpartum varies in reported studies. Prevalence of GAD during pregnancy varies between 8.5% and 10.5%. In the postpartum period there appears to be more variance in the reported prevalence (4.4% to 10.8%) (26,27). Our percentages are at least at the upper end of this interval (8.6% and 13.5% depending on the chosen cut-off point of the GAD-7). Eleven percent of our study population scored higher than the EDPS cut-off point of 13 at birth. This is significantly higher and more than double, compared to a study performed before the COVID-19 pandemic conducted in 2013 at the same hospital (University Hospital Leuven, Belgium) in pregnant women (EPDS >13 in 4.5%, p<0.05) (24).

Almost one-fifth (18.8%) of all women of our study, were placed in isolation or quarantine during pregnancy or in the 6 weeks post-partum. More than half of mothers indicated that the COVID-19 pandemic had an impact on the level of support provided at home after birth. So, it seems likely that the uncertainty of the COVID-19 pandemic, the potential impact on mother and neonate, the isolation and lack of social contact, impaired mental well-being of all pregnant women and mothers. Two other studies conducted in Europe during the pandemic using GAD-7, reported even higher rates of moderate anxiety (GAD-7 >10), 34.9% and 24.8%, respectively (30,31). A cross-sectional, web-based study conducted in several Western European countries during the pandemic, in pregnant and lactating women, showed GAD-7 (>10) and EDPS (>13) scores similar to our study (in 11% and 15% of pregnant women, respectively) (32). We did not specifically question why women felt more anxious. The importance of prenatal questioning and management of anxiety and depression symptoms, is therefore emphasized. This can impact the mother-infant bonding which can have lifelong consequences for the baby (cfr. first 1000 days of life) (14). Hygiene measures during the pandemic were necessary, but they possibly had an impact on the mental well-being of pregnant women and mothers. It may be interesting to conduct a risk-benefit analysis of the measures introduced during the pandemic, so that this can be factored into decisions in the (hopefully distant) future.

We observed a trend of more urgent deliveries in COVID-19 positive pregnancies. Pregnancy and neonatal outcome data were similar compared to reference values available from 2019 in Flanders (SPE) (23). More epidural analgesia was used as average in our population, but large dispersion was seen between hospitals in Flanders (12.1%-86.5%). The higher percentage of planned deliveries than the average in our population reflects the reality of a tertiary university hospital with its specific pathologies, but was higher than the spread in Flemish hospitals in 2019 (12.4%-36.7%). We cannot exclude that patients with planned deliveries were more easily included in our study due to the study protocol. A large proportion of our pregnant women were caregivers (30%). In comparison, fifteen percent of the general active population in Belgium works in the healthcare sector. It seems reassuring that they were not more likely to be COVID-19 positive. Finally, the COVID-19 pandemic does not appear to have had a negative effect on breastfeeding choice and adherence in our population. Percentages are similar to those of the years before the COVID-19 pandemic in our hospital. Most women reported that the epidemic did not affect this choice. Moreover, the few women who did get influenced by the COVID-19 pandemic, all chose breastfeeding.

Limitations of our study were firstly the limited size of our COVID-19 positive group. As a result, we may not have been able to confirm significant differences that were found in previous studies (e.g., NICU admissions), or have enough power to be sure these differences were really not present (11). Other pregnancy, delivery or neonatal complications were rare, so possible differences were difficult to demonstrate with the current sample of our population. For these data, we were also partially dependent on the accuracy and completeness of the medical record, which resulted in missing date for some patients. We could not include as many patients as we had initially envisaged. There was no record of how many patients were asked to join the study and how many did not want to participate. It is thus unclear whether informed consent wasn't systematically asked or whether many patients didn't want to participate. Selection bias can thus not be ruled out. COVID-19 positive women answered significantly less to the questionnaires at birth and after 6 weeks. This possibly also weakened the difference between the two groups. One might wonder why these women responded less frequently. Perhaps women, whose conditions were more difficult, were less likely to answer, and a form of selection bias has developed as a result (nonresponse bias). COVID-19 positive mothers were also less likely to be Caucasian. Perhaps there were language and cultural barriers for completing the questionnaires. Our study took place during a period when there was still limited PCR testing capacity. A proportion of women reported possible COVID-19 infection without PCR confirmation. It is

unclear if this had an impact on our results. The impact of the COVID-19 pandemic hit socioeconomically disadvantaged communities harder (17). Our study population was very highly educated (almost half of all women had college degrees) and there were almost no single mothers. This is a good representation of our hospital's patient population, but not the general population. It is possible that our population was less affected by the measures taken in the pandemic and the true impact of the COVID-19 pandemic on pregnant women is even greater. The study was performed during the first and second waves of COVID-19 in Belgium, including the summer months of 2020 where there were very few corona infections and measures were much less stringent. How this affected the results is unclear. No sub analysis by period occurred. On the other hand, our study happened during a period where there was still very much uncertainty and conflicting reports about COVID-19 during pregnancy, possibly causing more stress and anxiety then later during the pandemic.

Conclusion

We conducted a prospective observational study during the first and second waves of the COVID-19 pandemic in a tertiary centre. We looked at the possible association between, on the one hand, COVID-19 infection during pregnancy and social measures during the pandemic and, on the other, maternal anxiety and depression, as well as breastfeeding and maternal and neonatal outcomes. We found no statistical differences between COVID-19 positive and negative pregnancies for clinical maternal, neonatal, or breastfeeding outcomes. However, higher levels of generalized anxiety and depressive symptoms were observed in our population compared to the period before the pandemic. This study emphasizes the importance of monitoring mental health in pregnancy and postpartum. It would be interesting to see if now, after the pandemic, anxiety and depression scores are back to pre-pandemic levels.

Conflict of interest

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

REFERENCES

1. European Centre for Disease Prevention and Control. Weekly Covid-19 country overview [Internet]. Stockholm, Sweden: ECDC; 2023 [cited 2023 April 5]. Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases .
2. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Am J Obstet Gynecol. 2020;222(5):415–26.
3. Chen, H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-815.
4. Zhu, H, Wang L, Fang C, Peng S, Zhang L, Chang G,et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60.
5. Schwartz, DA, An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020;144(7):799-805.
6. Dashraath, P, Wong JLJ Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus Disease 2019 (COVID-19) Pandemic and Pregnancy. Am J Obstet Gynecol. 2020;222(6):521-531.
7. Fenizia C, Biasin M, Cetin I, Vergani P, Mileto D, Spinillo A, et al. Nat Commun. 2020;11(1):5128.
8. Martinez-Portilla RJ. Vertical transmission of coronavirus disease 2019. Am J Obstet Gynecol. 2021;224(3):328–9.
9. Facchetti F, Bugatti M, Drera E, Tripodo C, Sartori E, Cancila V, et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of Placenta. EBioMedicine. 2020;59:102951.
10. Yu, N, Li W, Kang Q, Xiong Z, Wang S, Lin X,et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis. 2020;20(5):559-564.
11. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320.
12. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022 ;226(1) :68-89.e3.
13. Mayopoulus G, Ein-Dor T, Li K, Chan S, Dekel S. COVID-19 positivity associated with traumatic stress response to childbirth and no visitors and infant separation in the hospital. Sci Rep. 2021;11(1):13535.
14. Moore T, Arefadib N, Deery A. Keyes M, West, S. The First Thousand Days: An Evidence Paper – Summary [Internet]. Parkville, Victoria, Australia: Centre for Community Child Health, Murdoch Children's Research Institute; 2017 [cited 2023 April 5]. Available from: https://apo.org.au/sites/default/files/resource-files/2017-09/apo-nid112701.pdf.
15. Verweij EJ, M'hamdi HI, Steegers EAP, Reiss IKM, Schoenmakers S. Collateral damage of the Covid-19 pandemic: a Dutch perinatal perspective. BMJ. 2020;369:m2326.
16. Lucas D, Bamber J. Pandemics and maternal health: the indirect effects of COVID-19. Anaesthesia 2021;76:69-75
17. Mishra V, Seyedzenouzi G, Almohtadi A, Chowdhury T, Khashkhusha A, Axiaq A, et al. Health Inequalities During COVID-19 and Their Effects on Morbidity and Mortality. J Healthc Leadersh. 2021;13:19-26.
18. Korukcu O, Ozkaya M, Boran OF, Bakacak M. Factors associated with antenatal depression during the COVID-19 (SARS-CoV2) pandemic: A cross -sectional study in a cohort of Turkish pregnant women. Perspect Psychiatr Care. 2021;58(1):61-70.
19. Pacheco F, Sobral M, Guiomar R, de la Torre-Luque A, Caparros-Gonzales R, Ganho-Avila A. Breastfeeding during COVID-19: A Narrative Review of the Psychological Impact on Mothers. Behav. Sci. 2021 ;11(3) :34.
20. Latorre G, Martinelli D, Guida P, Masi E, De Benedictis R, Maggio L. Impact of COVID-19 pandemic lockdown on exclusive breastfeeding in non-infected mothers. Int Breastfeed J. 2021;16(1):36.
21. JChing C, Zambrano P, Nguyen TT, Tharaney M, Zafimanjaka MG, Mathisen R. Old Tricks, New Opportunities: How Companies Violate the International Code of Marketing of Breast-Milk Substitutes and Undermine Maternal and Child Health during the COVID-19 Pandemic. Int J Environ Res Public Health. 2021;18(5):2381.
22. Taylor A, Atkins R, Kumar R, Adams D, Glover V. A new Mother-to-Infant Bonding Scale: links with early maternal mood. Arch Womens Ment Health. 2005;8(1):45-51.
23. R. Devlieger, R. Goemaes, M. Laubach. Perinatale Activiteiten in Vlaanderen 2019 [Internet]. Brussel:Studiecentrum voor Perinatale Epidemiologie (SPE); 2020 [cited 2023 April 5]. Available from: https://www.zorg-en-gezondheid.be/sites/default/files/2022-04/SPE_Perinatale%20activiteiten%20in%20Vlaanderen%202019_FINAL.pdf
24. Hompes T, Izzi B,Gellens E, Morreels M, Fieuws S, Pexters A, et al. Investigating the influence of maternal cortisol and emotional state during pregnancy on the DNA methylation status of the glucocorticoid receptor gene (NR3C1) promoter region in cord blood. J Psychiatr Res. 2013;47(7):880-91.
25. Tietz,A., Zietlow AL, Reck C. Maternal bonding in mothers with postpartum anxiety disorder: the crucial role of subclinical depressive symptoms and maternal avoidance behaviour. Arch Womens Ment Health. 2014;17(5):433–42.
26. Simpson W, Glazer M, Michalski N, Steiner M, Frey BN. Comparative efficacy of the generalized anxiety disorder 7-item scale and the Edinburgh Postnatal Depression Scale as screening tools for generalized anxiety disorder in pregnancy and the postpartum period. Can J Psychiatry. 2014;59(8):434-440.
27. Misri S, Abizadeh J, Sanders S, Swift E. Perinatal Generalized Anxiety Disorder: Assessment and Treatment. J Womens Health (Larchmt). 2015;24(9):762-770.
28. Dubber S, Reck C, Müller M, Gawlik S. Postpartum bonding: the role of perinatal depression, anxiety and maternal-fetal bonding during pregnancy. Arch Womens Ment Health. 2015;18(2):187-195.
29. Brummelte S, Galea LA. Postpartum depression: Etiology, treatment and consequences for maternal care. Horm Behav. 2016;77:153-66.
30. Rathbone AL, Prescott J, Cross D. Pregnancy in a pandemic: generalised anxiety disorder and health anxiety prevalence. BJM. 2021;29(8) :440-446.
31. Micha G, Hyphantis T, Staikou C, Valsamidis D, Arnaoutoglou E, Tzimas P, et al. Prevalence of postpartum depression and antenatal anxiety symptoms during COVID-19 pandemic: An observational prospective cohort study in Greece. European Journal of Midwifery. 2022;6:23.
32. Ceulemans M, Foulon V, Ngo E, Panchaud A, Winterfeld U, Pomar L, et al. Mental health status of pregnant and breastfeeding women during the COVID-19 pandemic – A multinational cross-sectional study. Acta Obstet Gynecol Scand. 2021;100(7):1219–1229.

Feasibility study of a low-cost bubble CPAP system in a neonatal medium care unit in Belgium

Sophie Vanbinst [a,b], Emmi Van Damme [b], Anke Raaijmakers [b,c]

[a] University of Antwerp, Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium
[b] ZNA Jan Palfijn, Department of Paediatrics, Antwerp, Belgium
[c] University of Leuven, Department of Development and Regeneration, Leuven, Belgium

anke.raaijmakers@zna.be

Keywords

Respiratory distress syndrome ; RDS ; respiratory support ; premature birth ; CPAP.

Abstract

Objectives: We aimed to evaluate the implementation and use of a high quality innovative bubble continuous positive airway pressure (bCPAP) System into a neonatal unit in Belgium.

Methods: A prospective observational study of neonates who met criteria for non-invasive respiratory support was conducted. All medical and nursing staff completed an on-line Thinkific course, followed by a live demonstration and practice of device application. Clinical indicator and device settings were recorded for every neonate. Staff surveys were administered after the training, after treatment of a neonate with a Vayu bCPAP System, and eight months after device introduction.

Results: Seven neonates were treated with Vayu bCPAP Systems. Their mean birth weight was 3170g with a median duration of treatment with bCPAP of 19 hours (IQR 2h–6d). Four term neonates had transient tachypnea of the newborn (TTN, n=4). One preterm and one term baby suffered from respiratory distress syndrome (RDS, n=2) and one baby had meconium aspiration syndrome (MAS, n=1). Six of the seven neonates improved their respiratory status and were weaned off the bCPAP System. One neonate needed more extensive ventilatory support and was transferred to a higher level neonatal intensive care unit (NICU). Staff surveys demonstrated that the devices were easy to use and satisfaction rates were high.

Conclusion: It was feasible to use Vayu bCPAP Systems to provide neonates with non-invasive respiratory support in our neonatal unit. Since implementation of this device there is less hesitancy among the medical staff to start babies on CPAP.

Introduction

Complications of prematurity including respiratory distress syndrome (RDS) are among the leading causes of morbidity and mortality during the neonatal period globally (1). To improve outcomes of infants with respiratory distress, WHO recommends use of continuous positive airway pressure (CPAP) as it has been shown effective in reducing morbidity and mortality among premature neonates (2). Early initiation of CPAP on neonates with RDS is associated with a reduced risk of respiratory failure requiring mechanical ventilation (3, 4).

RDS is the leading cause of death in preterm neonates and affects about one percent of newborns worldwide (5). Several advances have been made in the treatment of RDS including use of antenatal steroids, surfactant replacement therapy and CPAP. CPAP is a non-invasive respiratory support system that provides a continuous level of positive pressure to the airways, thereby distending the lungs, preventing alveolar collapse and improving ventilation.

Bubble CPAP (bCPAP) is a relatively low-cost method of assisting ventilation in neonates with respiratory distress. It has been shown an effective method at delivering nasal CPAP to preterm infants with RDS as well as in cases of meconium aspiration, pneumoniae, and apnea of prematurity, among other acute respiratory conditions (4). Most conventional CPAP systems require compressed air and advanced bioengineering support to ensure that the devices accurately deliver the required pressures, flow rates, and fractions of inspired oxygen (FiO2). Specialized training of nurses in CPAP is also necessary.

Over the past few years, Vayu Global Health Innovations has developed a ground-breaking bubble CPAP device (Vayu bCPAP System) that provides inspired concentrations of oxygen, flow rates, and pressures comparable to gold standard CPAP devices, yet does not require compressed air, electricity or highly skilled bioengineering support (6). Prior in vitro studies showed that the bCPAP system provides accurate control of CPAP pressures, oxygen concentration and humidification comparable with commercial CPAP devices. Delivered pressure (4-10 cm H2O) and oxygen concentrations (30-100%) were evaluated within 0.5 cm H2O and 4%, respectively, across all device settings in a breathing lung model (ASL 500 Test Lung). Tidal volume and flow remained consistent across all CPAP and oxygen concentrations settings. The bCPAP System sources humidity both from the humidity present in entrained ambient air and from a passive bubble humidifier. Relative humidity levels were tested by using a 3-dimensional heated lung model and a hygrometer. A relative humidity of > 80% was observed with the bubble humidifier which meets standard levels and is comparable with commercial devices (7). The Vayu bCPAP device was designed to meet the urgent need to make CPAP available, affordable, and easy to use in hospitals worldwide; both in low-income countries where resources are scarce as well as in hospitals in developed countries where the need for CPAP may be infrequent.

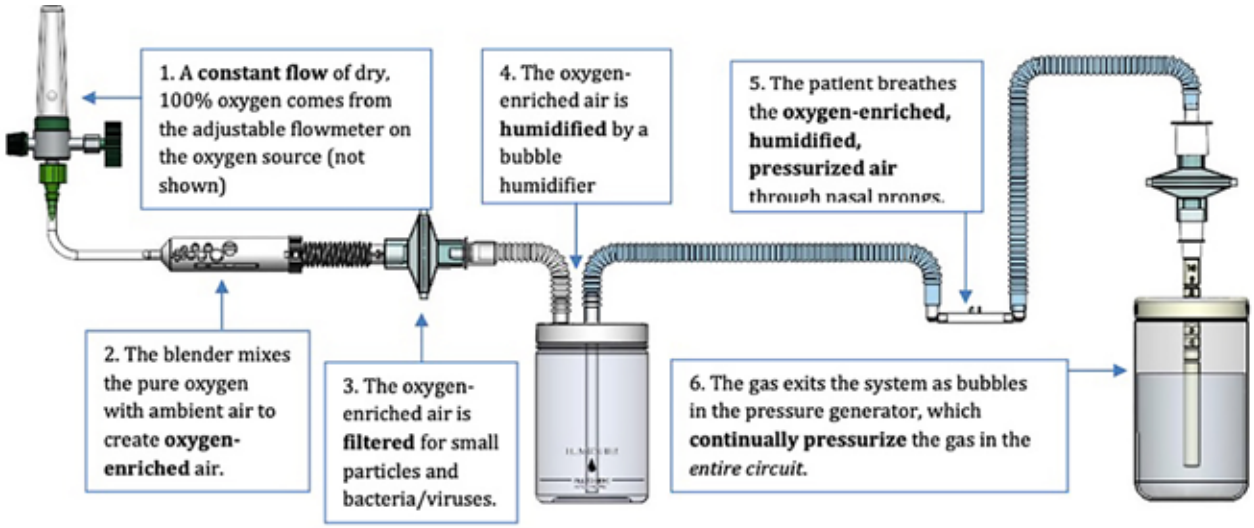
We hypothesized that given its unique properties, the Vayu bCPAP System would be easy to use, increase compliance of hospital staff with CPAP, and protect neonates from deteriorating further. We aimed to assess the feasibility and usability of the Vayu bCPAP System for respiratory support among neonates.

Methods

Setting

This prospective observational study took place in the (medium-care) neonatal unit at ZNA Hospitals Jan Palfijn General Hospital. The delivery suite accommodates approximately 1000 deliveries per year. The neonatal unit consists of 12 medium care beds where non-invasive respiratory support is available for neonates >33 weeks of gestation. In cases of

Figure 1: Description of the system.



prematurity less than 33 weeks' gestation or respiratory failure requiring invasive ventilation, transfer to a higher neonatal intensive care unit (NICU) is initiated. There are three higher level NICU's available within 15 km of our center. Prior to implementation of Vayu bCPAP Systems our unit could not care for more than one neonate on CPAP (Medin, ICC Medical, Germany) at a time.

The Vayu bCPAP System

The Vayu bCPAP System (Figure 1) centers around an innovative air/oxygen blender. The blender is an injected molded piece (polymer) that takes an input of pressurized oxygen and outputs a mixture of ambient air and oxygen (7). The FiO2 of the resulting jet can be adjusted by changing the distance between the nozzle and orifice openings. The FiO2 changes linearly with change in distance. At -25 mm of separation, 30% is achieved. When the nozzle is 25 mm into the orifice opening, the peak FiO2 of 100% is reached. If an FiO2 of 21% is desired the Vayu bCPAP System can be connected to pressurized medical air instead of a continuous oxygen flow. The blender is most efficient in pulling in ambient air at a setting of 40% to maintain bubbling when connected to medical air. The blender can provide 30-100% oxygen. Oxygen was titrated based on saturation monitoring and was set to the lowest possible percentage to maintain saturations > 92%. Furthermore, the mixed gas is filtered for small particles immediately after the blender, with an option to also filter in the exhalation limb. The humidifier filled with sterile water humidifies the oxygen enriched air prior to being delivered to the neonate. The pressure in the system is developed by the neonate's exhalation being delivered into the wand, which is submerged in the pressure generator. The pressure can be adjusted from 4 to 10 cm of water by adjusting the depth of the wand.

Table 1: Characteristics of the included patients.

Characteristics	1	2	3	4	5	6	7
Sex	M	F	M	M	M	M	M
Gestational age	40w+1	41w	40w+1	37w+6	37w+1	37w+4	33w+6
Apgar score (1-5 min)	5-6	8-9	9-9	9-10	9-10	5-6	6-7
Birthweight (g)	3609	4120	3400	3125	2260	3220	2460
Indication	TTN	MAS	TTN	TTN	RDS	TTN	RDS
RSS	5	NA	NA	8	5	8	9
Duration of treatment	5h	5d	2h	25h	7h	19h	6d

* TTN: transient tachypnea of the neonate; MAS: meconium aspirations syndrome; RDS: respiratory distress syndrome; RSS: respiratory severity score, NA: not available.

Table 2: Evaluation of training.

Questions	Participants (n)	Median	Interquartile range
1. How easy or difficult was it to implement the VAYU bCPAP?	26	8	8 – 10
2. How do you compare the ease of use of the VAYU bCPAP systems to other available CPAP devices?	26	9	7 – 10
3. How prepared did you feel using the VAYU bCPAP system after training?	26	9	8 – 10
4. Would you recommend this device to other healthcare providers?	26	9	7 – 10

* Every trainee filled out a questionnaire after the training session.
There were 4 numeric questions who are listed in the table above. The scale of response options went from 0 (very difficult/unprepared/unlikely) to 10 (very easy/prepared/likely).

Intervention

The study was approved by the ethics committee of the hospital network (ZNA hospitals, Antwerp). All nurses and pediatricians were trained through an online course (Thinkific), followed by a one-hour live demonstration and practice session on device application. There were subsequent individual training sessions. An online training course as well as a smart phone Respiratory Severity Score (RSS) calculator were available to all staff (8). Immediately after the initial training a nine-question survey was completed by every participant. There were four numerical questions, one question was yes-or-no and four were open ended. The survey evaluated the quality of training and subjective readiness (Appendix A). The method of cleaning and reprocessing was reviewed in detail with the head of the sterilization department. The breathing tubes, filters and nasal prongs were disposed of after each neonate. Indication for the use of nasal CPAP was determined by the medical staff depending on the degree of respiratory distress and/or apneas associated with TTN (transient tachypnea of the newborn), RDS, MAS (meconium aspiration syndrome), pneumonia,

Appendix A. Questionnaire after training session.

Feasibility/Usability	
How easy or difficult was it to implement the VAYU bCPAP?	Very difficult ---- difficult ---- easy ---- very easy 1 2 3 4 5 6 7 8 9 10
How do you compare the ease of use of the VAYU bCPAP systems to other available bCPAP devices?	More difficult ---- same ease of use ---- Easier 1 2 3 4 5 6 7 8 9 10
Do you believe that the VAYU bCPAP system helps infants? (please circle best answer)	No Unsure Yes
How prepared did you feel using the VAYU bCPAP system after training	Unprepared ---- somewhat prepared ---- Very prepared 1 2 3 4 5 6 7 8 9 10
Describe how the trainings can be improved	
Were there any barriers to the use of VAYU bCPAP systems	
What are the positive attributes of the VAYU bCPAP system (including monitoring, initiating, cleaning…)	
What are the negative attributes of the VAYU bCPAP system(including monitoring, initiating, cleaning…)	
Would you recommend this device to other healthcare providers?	Extremely Unlikely ---- Unsure ---- Extremely Likely 1 2 3 4 5 6 7 8 9 10

sepsis, congenital lung disease or tracheomalacia. In general, an RSS of ≥ 5 was deemed an indication for bCPAP. If the RSS was below 5 but the attending physician found it necessary to place the baby on CPAP, the physician could overrule the score. Exclusion criteria were the same as those for a conventional CPAP system: anatomic anomalies, respiratory failure, pneumothorax, and neurological impairment.

Data and analysis

When a neonate was placed on a Vayu bCPAP device (maximum of two babies at the same time), baseline characteristics including date and time of birth, sex, birth weight, gestational age, respiratory severity score, oxygen saturation, heart rate and respiratory rate were documented. Initial settings of the bCPAP system and any subsequent changes were recorded. During the treatment of a neonate with bCPAP, an evaluation form with three questions were filled out by the nurse taking care of the baby. Eight months after implementation of Vayu bCPAP Systems in our unit an evaluation form directed to those that used Vayu bCPAP Systems was administered. The survey assessed implementation, feasibility, and ease of use.

Results

Between January 1, 2022, and September 30, 2022, seven neonates that showed signs of respiratory distress were placed on Vayu bCPAP Systems (Table 1). Six were male and one female. Three neonates had an RSS of 5, two with 8 and one with 9. The RSS was not recorded in two neonates at the time of CPAP initiation. Six of the seven neonates were term (gestational age beyond 37 weeks) and one was 33 weeks and 6 days. The underlying causes of respiratory distress included transient tachypnea of the newborn (TTN, n=4), RDS (n=2), and meconium aspiration syndrome (MAS, n=1). Three term neonates were treated with Vayu bCPAP Systems for a few hours, one for 19 hours, and another for 25 hours. The neonate with MAS was treated with a Vayu bCPAP System for five days while the premature neonate was treated for six days. Six out of the seven neonates improved with their treatment and were weaned from bCPAP. One of the neonates with RDS was transferred to a higher level NICU because of persistent respiratory distress after seven hours on bCPAP.

Twenty-six health care workers enrolled in the initial training, after which each participant completed the survey. The median of the four numerical questions on this survey was 8 or 9 (Table 2). The yes-or-no question about whether the participant believed the Vayu bCPAP could help infants, was unanimously answered, 'yes'. The ease of installation, ability to provide CPAP without electricity, the compactness, and the possibility to use the Vayu device on transport were seen as favorable attributes. It was also mentioned a few times that bubbling in the pressure generator provided helpful constant feedback on device function, and allowed for rapid discovery of any loss of pressure in the system, such as might arise from tubing disconnections. The nurses described that their understanding of CPAP improved after the training course.

Staff suggestions for device improvements included: add a mechanism to shield the baby from the device noise and include options in length of the breathing tubes. Staff wished to be sure that skin to skin contact with the parents was possible while on bCPAP. Some staff wondered about the need for an orogastric tube instead of a nasogastric tube, which is generally well tolerated by the newborn. Seven staff members responded to the eight month questionnaire. The median score of the two questions about the ease of installation and use of the Vayu device in comparison to a gold standard CPAP device was for both 4 out of 5 (IQR 3–5). The question about the participants' level of support around the implementation of Vayu bCPAP systems in our unit scored a median of 5 out of 5 (IQR 3–5). Generally, the staff felt the Vayu bCPAP System is an asset to our unit.

Discussion

Respiratory distress is common in neonates worldwide and CPAP has been proven to reduce morbidity and mortality. However, until now, commercially available CPAP systems require electricity, compressed air and advanced bioengineering support. In our hospital, we had the opportunity to implement an easy-to-use bCPAP device. Because Vayu bCPAP Systems only need oxygen and sterile water, we hypothesized they could be helpful in our hospital and worldwide, especially where electricity is not reliable. As this system has a lower cost than all other CPAP devices and is less complex, hospitals in developed countries where CPAP is not often used could benefit as well.

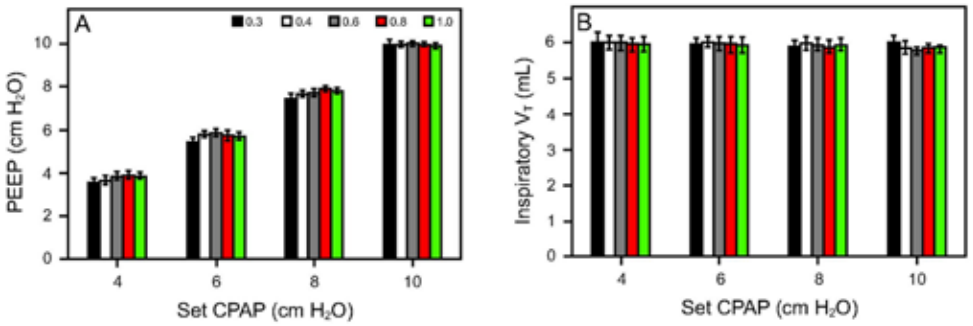
Since we are a neonatal care unit that only admits neonates over 33 weeks of gestation, the number of neonates who need non-invasive respiratory support is relatively small and unpredictable. Even though our observational study had a small study group, our staff agreed on the ease of application and use of this bCPAP device in comparison with our previous conventional CPAP machines. Since there is a need of constant bubbling for the bCPAP to work effectively, it is easy to rapidly identify any connection malfunctions.

The training courses went very smoothly. Since the training course is available online it is convenient to prepare all the nurses and doctors at the same time. Throughout the year of this study the VAYU team was always available for questions and technical support. We recommend retaking the training course at least annually, since the use of CPAP in our hospital is uncommon.

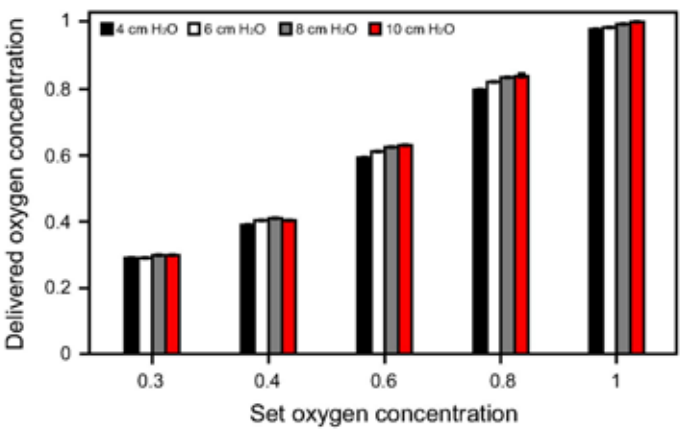
The main disadvantage of the Vayu bCPAP System is the noise produced by the high velocity jet in the blender and the bubbling in the pressure generator. It is known that preterm newborns exposed to elevated ambient noise may be affected adversely (9). We installed our Vayu bCPAP Systems outside of the incubators to protect the neonates from the device's noise. To assess noise and monitor potential improvements, it would be worthwhile to measure dB levels in the neonatal units. Future updates can subsequently focus on further noise reduction.

This study needs to be evaluated within its strengths and limitations. The strengths include the universal training which generated a universal approach to all neonates and the use of a respiratory distress score to indicate the necessity for CPAP. Limitations of the study are the small number of neonates included in the study, however, given the low frequency of CPAP use in units like ours, this was out of our control. We did not compare the former and new CPAP systems as the VAYU bCPAP was FDA approved and implemented as standard care. Further studies could be set up with a parallel control group to compare both devices at the same time to assess the easiness of use and performance. A possible selection bias might have occurred, however, all babies received bCPAP when clinically indicated.

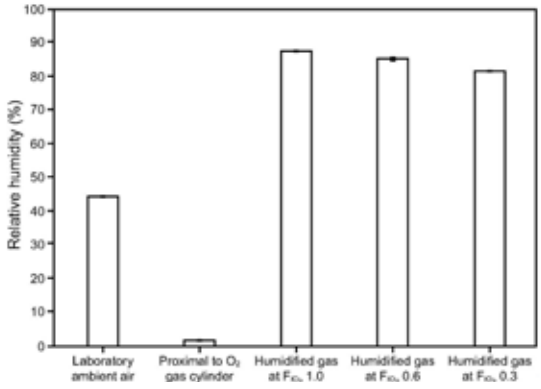
Appendix B. In vitro results on bCPAP device performance (7).



Results for PEEP (A) and tidal volume (B) for all set CPAP levels and oxygen concentration settings. Each bar indicates the mean value of 20 breaths, and the error bars denote SD.



Measured oxygen concentration as a function of a set oxygen concentration to illustrate the deviation from the intended value. Each bar indicates the mean value of 20 breaths and the error bars denote SDs. In each group, the different set CPAPs are denoted by different colors.



The relative humidity at each condition. Each bar indicates the mean of either 1 min of observation or 20 breaths. The error bars denote SDs. The first 2 conditions are reference values to the latter 3 conditions, which are simulated breathing.

Although VAYU Global Health provided the bCPAP devices, they had no influence on the study design and data interpretation. We acknowledge that their support and training might have caused bias in the implementation of the device. However, we decided to treat all babies the same and routine care protocols were adapted.

Additionally, the ratings of the medical staff could be biased as they were collected at the end of the training sessions. The response rate on the eight-month questionnaire was low (7 out of 26 responders); only seven neonates were placed on the Vayu bCPAP, so most staff members responded they could not submit the questionnaire because they didn't attend the installation process.

Altogether our unit agrees on the success and feasibility of implementation of this device. We hope to inform other neonatal units that additional studies and expertise are desired since this system could become an essential and easy-to-use part of their unit.

Conclusions

Implementation of VAYU bCPAP Systems was successful in our neonatal unit. We implemented this device after providing adequate training to our medical staff. The Vayu device is easy-to-use and compact. Noise arising from the blender and the pressure generator could be further optimized. The high quality, portability, low cost, and the lack of reliance on electricity and bioengineering support are considerable benefits for use worldwide. Overall, the staff in our neonatal unit were very satisfied after training and use of the Vayu bCPAP System.

Acknowledgments

The authors gratefully acknowledge the nurses and staff working at Jan Palfijn General Hospital, Antwerp. They thank VAYU Global Health Foundation as well for providing all VAYU bCPAP Systems.

Conflicts of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. WHO. The Global Health Observatory Geneva: World Health Organization; 2022 [cited 2022 Aug 21]. Available from: https://www.who.int/data/gho.
2. WHO recommendations on interventions to improve preterm birth outcomes. Geneva: World Health Organization; 2015 [cited 2022 Aug 21]. Available from: https://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf.
3. Badiee Z, Naseri F, Sadeghnia A. Early versus delayed initiation of nasal continuous positive airway pressure for treatment of respiratory distress syndrome in premature newborns: A randomized clinical trial. Adv Biomed Res. 2013;2:4.
4. Subramaniam P, Ho JJ, Davis PG. Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants. Cochrane Database Syst Rev. 2016(6):Cd001243.
5. Dyer J. Neonatal Respiratory Distress Syndrome: Tackling A Worldwide Problem. P t. 2019;44(1):12-4.
6. Averting Newborn Deaths. Medford, Massachusets, USA: Vayu Global Healt Innovations; [cited 2022 Aug 2021]. Available from: https://vayuinnovations.org/vayu-bcpap/.
7. M LD, Ng EK, A MB, DiBlasi RM, Poli JA, Burke TF. Evaluation of a Bubble CPAP System for Low Resource Settings. Respir Care. 2021;66(10):1572-81.
8. Hedstrom AB, Gove NE, Mayock DE, Batra M. Performance of the Silverman Andersen Respiratory Severity Score in predicting PCO(2) and respiratory support in newborns: a prospective cohort study. J Perinatol. 2018;38(5):505-11.
9. Wachman EM, Lahav A. The effects of noise on preterm infants in the NICU. Arch Dis Child Fetal Neonatal Ed. 2011;96(4):F305-9.

ENTEROL® 250 mg

Saccharomyces boulardii CNCM I-745

10	10,32 €	10	10,32 €	10	10,32 €
20	19,36 €	20	19,36 €	20	19,36 €
50	38,96 €				

BIOCODEX

INFORMATIONS ESSENTIELLES. DENOMINATION DU MEDICAMENT Enterol 250 mg, poudre pour suspension buvable. Enterol 250 mg, gélules. *Saccharomyces boulardii* CNCM I-745 COMPOSITION QUALITATIVE ET QUANTITATIVE Enterol 250 mg, poudre pour suspension buvable : Chaque sachet-dose de poudre pour suspension buvable contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x 10^9 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Enterol 250 mg, gélules : Chaque gélule contient 250 mg de *Saccharomyces boulardii* CNCM I-745 sous forme lyophilisée (soit au minimum 6 x 10^9 cellules reviviscentes au moment de la fabrication et 1 x 10^9 cellules lyophilisées reviviscentes à la date de péremption). Excipient(s) à effet notoire (voir rubrique 4.4 du RCP) : Enterol 250 mg, poudre pour suspension buvable : fructose, lactose monohydraté, sorbitol. Enterol 250 mg, gélules : lactose monohydraté. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable : Poudre pour suspension buvable. Enterol 250 mg, gélules : Gélule. DONNEES CLINIQUES Indications thérapeutiques • Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à *Clostridium difficile* ou rechute de diarrhée à *Clostridium difficile*. • Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. Posologie et mode d'administration Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique. Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. Précautions à prendre avant la manipulation ou l'administration du médicament En raison d'un risque de contamination aéroportée, les sachets ou gélules ne peuvent pas être ouverts dans les chambres des patients. Les professionnels de la santé doivent porter des gants durant la manipulation de probiotiques en vue de leur administration, puis les jeter immédiatement après usage et se laver les mains avec soin (voir rubrique 4.4 du RCP). Durée du traitement : Prévention des récurrences ou rechute de diarrhée à *Clostridium difficile* : 4 semaines. Traitement de la diarrhée en complément à la réhydratation orale chez l'enfant : 1 semaine. Contre-indications • Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. • Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie (voir rubrique 4.4. du RCP). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745. Effets indésirables Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. Affections vasculaires Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales Très rare : dyspnée. Affections gastro-intestinales. Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané. Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration. Très rares : soif. Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration (Belgique : www.notifieruneffetindesirable.be, adr@afmps.be; Luxembourg : www.guichet.lu/pharmacovigilance). TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA - Square Marie Curie 20 - 1070 Bruxelles - Belgique - Tél : 0032(0)23704790. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE Enterol 250 mg, poudre pour suspension buvable : BE269026. Enterol 250 mg, gélules en flacon en verre : BE269035. Enterol 250 mg, gélules en plaquette: BE397896. MODE DE DELIVRANCE Délivrance libre DATE DE MISE A JOUR DU TEXTE Mise à jour : 01/2023. Approbation : 03/2023.

2023_ENT_HCP_007

From purpura to idiopathic purpura fulminans: a guidance in diagnosis and therapy

Liselot De Cloedt [a], Inez Vanholder [b], Coskun Arkaz [c], Cynthia Lafaire [c], Filip Thiessen [c], Thierry Tondu [c], Marijke Traen [d], Elisabeth LIM Duval [e]

[a] AZ Monica, Department of Paediatrics, Deurne and University of Antwerp, Faculty of Medicine and Health Sciences, Wilrijk, Belgium
[b] University of Antwerp, Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium
[c] University of Antwerp, Antwerp University Hospital, Department of Abdominal, Paediatric and Plastic Surgery, Edegem, Belgium
[d] AZ Monica, Department of Paediatrics, Deurne, Belgium
[e] University of Antwerp, Antwerp University Hospital, Paediatric Intensive Care Unit, Edegem, Belgium

els_duval@yahoo.com

Keywords

Varicella zoster virus ; chicken pox ; disseminated intravascular coagulation ; children : idiopathic purpura fulminans.

Abstract

Varicella is a common infection in children. Although benign in most cases, severe complications can occur, of which idiopathic purpura fulminans is one of the most devastating with high morbidity and mortality. It is a haematological emergency characterised clinically by well-demarcated erythematous maculae progressing rapidly to haemorrhagic necrosis. This form of purpura should be suspected in an otherwise healthy child with a history of varicella, no underlying sepsis, and coagulopathy with low protein S or C levels. Mimicking autoantibodies to anticoagulants, mainly against protein S, are thought to be aetiological factors. Therapy is based on the treatment of the underlying disease in combination with plasmapheresis and immunosuppression against the circulating autoantibodies. Depending on the degree of bleeding or hypercoagulability, plasma transfusion or anticoagulation may be considered.

We present a two-year-old girl with rapidly progressive purpura, leading to full-thickness skin necrosis requiring multiple surgeries and skin grafts. As early recognition and treatment is essential to reduce mortality and to prevent severe morbidity, awareness of this syndrome and its clinical evolution is important. We tried to establish a helpful guidance to facilitate diagnosis and treatment of idiopathic purpura fulminans.

Introduction

Varicella or chickenpox, caused by varicella-zoster virus, is a very common infection in children, characterized by vesiculo-papulous rash and fever. Although in most cases self-limiting, some rare but serious complications can occur, varicella-associated idiopathic purpura fulminans being one of them. Purpura fulminans (PF) is well known in paediatrics. It is an acute thrombotic disease that can occur during severe sepsis or in the context of protein C (PC) or S (PS) deficiency. In rare instances, PF can also occur after normally benign infections such as chickenpox or herpes. Autoantibodies to PC or PS, whether combined with diffuse intravascular coagulation (DIC) or not, are presumed to be the cause of this form of PF, called idiopathic PF (IPF) (1-3). Early clinical recognition appears to be difficult in practice and correct therapy also remains to be defined. Nevertheless, early identification and prompt treatment could reduce the mortality and often severe morbidity associated with this condition.

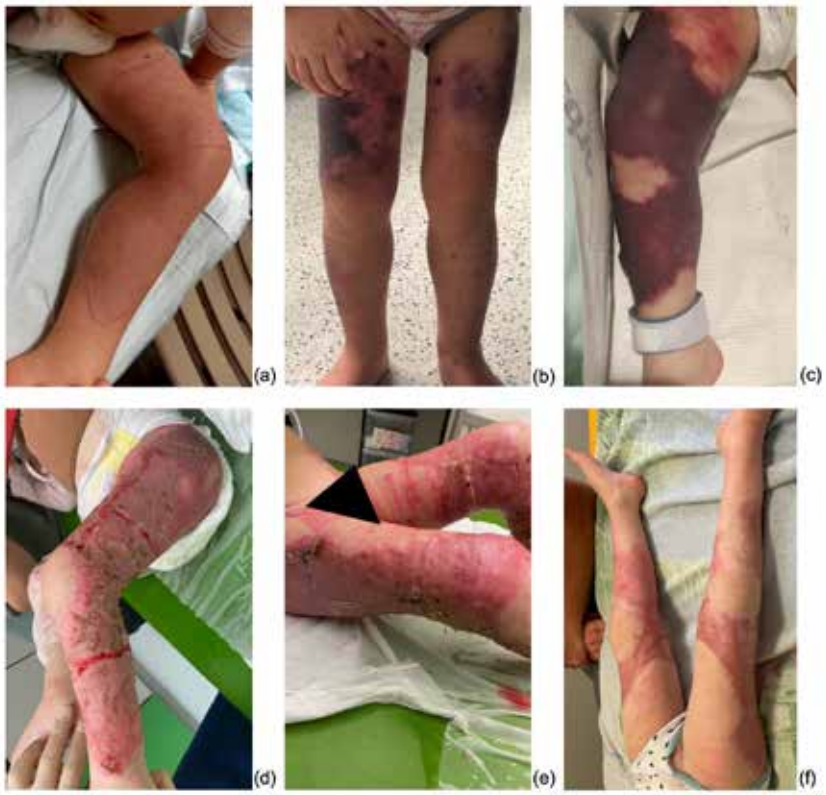
We present a case of a previously healthy two-year-old girl with IPF four days after the onset of a varicella infection. She developed full thickness skin necrosis which needed surgical debridement and skin grafting of both legs. This case demonstrates that the clinical picture might be misleading with delayed therapy as a result. English literature was reviewed to obtain a helpful guidance for the clinician in diagnosing and treating this pathology.

Case report

A two-year-old girl presented at the emergency department with what appeared to be ecchymoses on both legs (Figure 1a). She had developed mild varicella four days ago, with low-grade fever and general malaise, but appeared otherwise well. Further anamnesis revealed that she had been born prematurely at 33 weeks; there were no previous hospitalisations or history of bleeding diathesis. On suspicion of cellulitis, although not typical, she was admitted and started on intravenous antibiotics (penicillin and clindamycin). Laboratory evaluation showed a slightly prolonged activated partial thromboplastin time (APTT) and a slightly elevated C-reactive protein. Leukocytes were normal, as were thrombocytes, PTT, INR and D-dimers.

Within 24 hours, the lesions rapidly progressed to purpura and became painful with oedema of both legs (Figure 1b). Laboratory follow-up revealed evidence of disseminated intravascular coagulation (DIC) with prolonged plasma clotting time (INR of 2,95, normal range 0,8-1,2), thrombocytopenia (46x1000/µL, normal range 166-396x1000/µL), high D-dimers (>80 mcg/mL, normal range <0.65 mcg/mL) and reduced plasma fibrinogen (<30 mg/dL, normal range 170-350 mg/dL). Suspecting ongoing sepsis despite broad-spectrum antibiotics, she was transferred to the paediatric intensive care unit (PICU). Penicillin was changed to ceftriaxone and acyclovir was added. Post-varicella IPF was clinically suspected and treatment with fresh frozen plasma (FFP, 20 ml/kg/d), immunoglobulins (Ig, 0.8 g/kg) and methylprednisolone (2 mg/kg/d) was started and continued for three days. Both PC and PS activity came indeed back low (41% (71-125%) and <3% (70-130%, respectively)), supporting the working hypothesis. Low molecular weight heparin (LMWH) was started subcutaneously aiming at an anti-Factor Xa level between 0.5 and 1 U/ml. Clindamycin was stopped after three days, acyclovir was given for seven days.

Figure 1: Clinical presentation at the emergency department (a) and 24 hours (b) and 48 hours (c) after onset. Lesions after surgical debridement and grafting (d), at discharge (e) and two months later (f).



Despite treatment, the purpura progressed to bullae and necrosis (Figure 1c). In collaboration with the Department of Plastic Surgery the wounds were treated on a daily base under procedural analgesia with ketamine to await further demarcation. On day six, she developed fever and inflammatory parameters increased. The antibiotics were changed to piperacillin-tazobactam, and skin culture revealed a *Moraxella* species. Meanwhile, both platelet count and PC level normalised, but PS level remained very low (< 3%). Lupus anticoagulant was negative and antithrombin activity and active protein C resistance were normal. Despite adequate anti-Factor Xa levels, the child developed a small thrombus at the tip of a central catheter in the right subclavian vein. The line was removed. Anticoagulation therapy was changed to rivaroxaban, a novel oral anticoagulant (NOAC).

After three and a half weeks the injuries were well demarcated. Initial surgical debridement revealed full thickness skin necrosis with areas of fat necrosis; vacuum assisted closure (VAC) was used postoperatively. The patient underwent two additional surgical debridements and VAC modifications to obtain well vascularised tissue for skin grafts (Figure 1d). Due to the large skin defects compared to the body surface, the Meek micrografting technique was used: skin grafts were cut into micrografts and expanded at a ratio of 1:3 to obtain sufficient coverage. One week after successful skin grafting, donor skin was placed over the grafts for temporary covering and protection. The donor skin could be removed one week later (Figure 1e). The girl was discharged after sufficient wound healing and continued to receive ambulatory and rehabilitation care (Figure 1f).

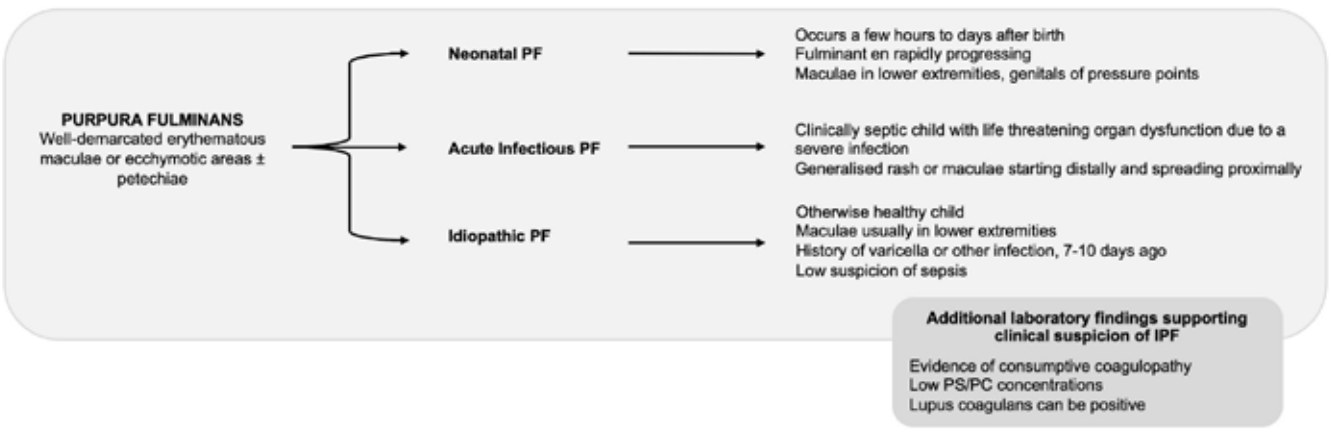
NOAC was continued for 2.5 months, at which time PS levels normalised (78%). One year after the onset of symptoms, she still wears her pressure garments and receives intensive physiotherapy. She can walk and bend her knees independently.

Discussion

Purpura fulminans is characterised by overwhelming endothrombosis in the both dermal and systemic microcirculation, resulting in rapidly progressive haemorrhagic skin necrosis, gangrene and multiple organ failure. Mortality is high, up to 50%, and those who survive often experience long-term morbidity due to contractures, amputation or severe scarring (1–4). Several mechanisms may underlie PF, most involving to the PS and/or PC anticoagulation pathway (Figure 2) (1,3–7).

In *neonatal PF*, there is a congenital deficiency of PC or PS, resulting in severe PF within hours to days after birth. This form of PF is caused by a homozygous or compound heterozygous pathogenic variant in the *PROC* or *PROS* gene and manifests mainly at the level of the lower limbs, male genitals and pressure points such as the heels and buttocks (3,4,6,7). Deficiency of anticoagulant factors can also be acquired, for example in severe sepsis, where systemic activation of coagulation causes consumption of anticoagulants. This *leads to acute infectious PF* with streptococcal disease accounting for the majority of cases. The clinical picture manifests as a septic-appearing child, with organ failure and a skin pattern that typically develops in the distal extremities

Figure 2: Types of purpura fulminans and how to differentiate.



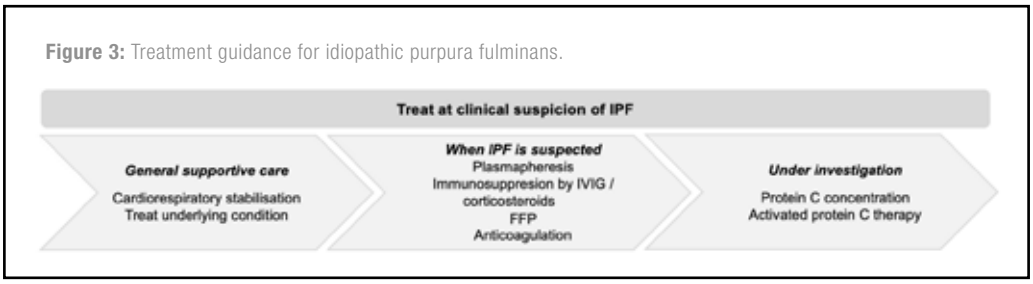


Figure 3: Treatment guidance for idiopathic purpura fulminans.

rapidly progressing proximally or a generalised diffuse rash affecting the whole body surface (3,4,7). Finally, PF can occur post-infectiously as an autoimmune response to otherwise benign childhood diseases such as varicella. This postinfectious PF, also known as *idiopathic PF*, typically occurs seven to ten days after the primary infection (1,5,6). The incidence post-varicella PF is rare, only 0.05 to 0.16%, but it is one of the most devastating complications. The viral infection probably induces the production of IgG-mediated autoantibodies against PS (mainly) or PC or anti-thrombin III (3,7–11). Although the exact mechanism has not been fully elucidated yet, the most likely pathophysiology of IPF appears to be cross-reactivity against the virus and PS via molecular mimicry (9,11,12).

IPF should be suspected clinically by the appearance of well-demarcated erythematous maculae or ecchymosis, with or without petechiae, a few days after a varicella infection. Lesions usually appear first and primarily on the extremities, particularly the thighs and lower legs, while distal lower extremities and upper limbs often appear to be spared (1,3,4,8,9). They rapidly increase in size and intensity and develop into painful blue-black, non-blanchable haemorrhagic necrosis. Bullae may form, culminating in gangrene and full-thickness necrosis within 24 to 48 h. The clinical picture may eventually deteriorate to multi-organ failure due to large-vessel venous thrombosis and systemic microvascular thrombosis (3,5,6). If this clinical picture is observed in an otherwise healthy child, a recent (less than 15 days ago) varicella or other infection is anamnestically reported, and no other signs of sepsis are identified, IPF should be strongly suspected and treatment should be initiated (1,3,6,9).

Although the typical presentation of IPF is a laboratory picture of DIC without a clinically severely ill/septic looking child, there is no simple test to confirm the diagnosis. Laboratory tests often show prolonged plasma clotting times, thrombocytopenia, decreased plasma fibrinogen concentration or increased plasma fibrin degradation products, but these findings are aspecific and can occur in DIC of any cause (3,7,8). As IPF is caused by an autoantibody-mediated decrease in the plasma concentration of PS (or less often PC), concentrations of these antithrombotic agents should be measured. A plasma concentration of PS or PC below 30% makes the diagnosis of IPF likely (3,4,9).

In addition, autoantibodies against anticoagulant proteins such as PS or PC, but also against lupus anticoagulant, anticardiolipin or prothrombin fragment 1+2, may be found during or after varicella infection. The correlation between the levels of these autoantibodies and the incidence of complications of varicella infection, such as IPF, is still under debate. However, the presence of lupus anticoagulant has been frequently reported in IPF (3,10,13,14).

The diagnosis of IPF should be made by careful consideration of clinical and biochemical factors and exclusion of any other underlying factors such as sepsis, but therapy should not be delayed until all biochemical information is available (3,4). Patients with lower platelet counts and lower concentrations of PS or PC can be expected to have a more severe (9,10,13,14).

Early recognition and treatment of IPF and its underlying cause are essential to reduce mortality and to prevent major long-term health sequelae. This was already written down by Fishbein in 1969 (15). However, there is still no consensus on the treatment of IPF, although an aggressive, multi-modality approach is usually advocated to reduce the significant morbidity and mortality (2). Plasmapheresis and Ig-therapy have been suggested as the most effective treatment against the PS inhibitor, with FFP being beneficial in temporarily replacing PS and PC in circulating plasma (2,3,9). Immunosuppressive therapy, including intravenous Ig and prednisolone, should be considered to suppress further production of autoantibodies to PS (2,3,5,8,9). As IPF is predominantly a thrombotic process resulting from a deficiency of antithrombotic factors, most if not all patients are anticoagulated with LMWH at the time of diagnosis (2,3,8). Ongoing anticoagulation may be required if there is large vessel thrombosis (3). Others advocate the use of anticoagulants until the protein S levels return to normal (2,8). However, normal and safe levels of many thrombotic markers in childhood have yet to be determined, specifically in infants and young children. Several other treatment modalities require further investigation before they can be withheld, such as protein C concentrate or activated protein C therapy (4,16). The balance between of clotting and anticoagulant substances is usually restored after about three months. Autoantibodies appear to be transient and disappear completely within a few weeks to months, regardless of the therapy used (1,3, 9–11). The skin lesions that have occurred will often take weeks or even months to heal, depending on the degree of necrosis. Surgical debridement, fasciotomy or amputation may be necessary. Contractures, prolonged hospital stay and cosmetic injuries, among others, can cause developmental, physical and psychosocial limitations in these patients. A multidisciplinary approach with close collaboration between PICU team, paediatric haematologist, surgeons and physiotherapists should be initiated, often followed by prolonged stay in rehabilitation centres (3).

Conclusion

IPF is a serious complication of varicella and is associated with high mortality and morbidity. Early recognition and treatment are essential to improve outcome, but there is still no consensus on how to establish the diagnosis and how to treat efficiently and safely. IPF should be suspected when purpura fulminans occurs several days after varicella infection. However, the initial phase is often clinically confused with purpura fulminans due to sepsis, delaying the appropriate treatment. Awareness of this syndrome, and its clinical progression from macula to purpura, is therefore important.

The pathophysiology of IPF is also not yet fully elucidated. Although molecular mimicry is thought to be at the basis, other immunological pathways also need to be investigated. Many diagnostic and therapeutic options have been described, but a clear guideline is lacking. Although more research is needed, we hope that we have given the paediatrician some helpful guidance on how to recognise and treat IPF.

Conflict of interest

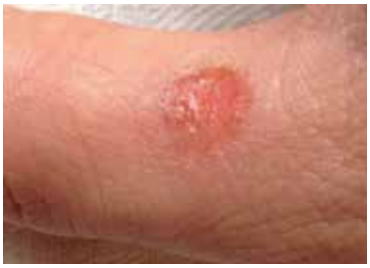
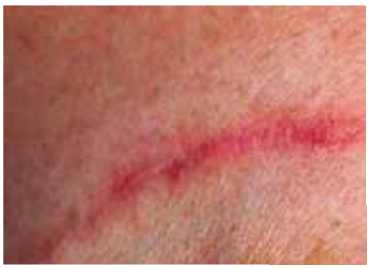
The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

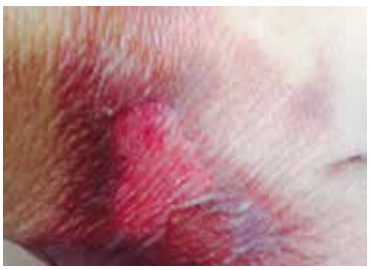
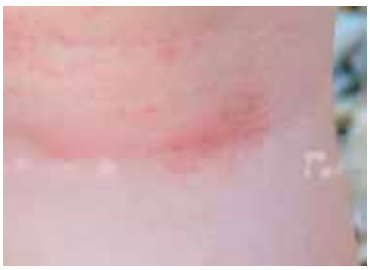
REFERENCES

1. Woods CR, Johnson CA. Varicella purpura fulminans associated with heterozygosity for factor V Leiden and transient protein S deficiency. Pediatrics. 1998, 102(5): 1208–1210.
2. Busuttil DP, Hay CRM, Lewis MA, Wynn RF. Aggressive multiple modality therapy for varicella-associated purpura fulminans. Br Jl Haematol. 2000, 110(4): 1012–1013.
3. Chalmers E, Cooper P, Forman K, Grimley C, Khair K, Minford A, et al. Purpura fulminans: recognition, diagnosis and management. Arch Dis Child. 2011, 96(11): 1066–1071.

4. Colling ME, Bendapudi PK. Purpura Fulminans: Mechanism and Management of Dysregulated Hemostasis. Transfus Med Rev. 2018, 32(2): 69–76.
5. Levin M, Eley BS, Louis J, Cohen H, Young L, Heyderman RS. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. J Pediatr. 1995, 127(3): 355–363.
6. Francis RB. Acquired purpura fulminans. Semin Thromb Hemost. 1990, 16(4): 310–325.
7. Talwar A, Kumar S, Gopal M, Nandini A. Spectrum of purpura fulminans: report of three classical prototypes and review of management strategies. Indian J Dermatol Venereol Leprol. 2012, 78(2): 228.
8. Abdulmalik A, Al-Ateeqi W, Al-Khawari M, Al-Osaimi S. Varicella-associated purpura fulminans: chicken pox is not always benign. Med Princ Pract. 2006, 15(3): 232–234.
9. Theron A, Dautremay O, Boissier E, Zerroukhi A, Baleine J, Moulis L, et al. Idiopathic purpura fulminans associated with anti-protein S antibodies in children: a multicenter case series and systematic review. Blood Adv. 2022, 6(2): 495–502.
10. Josephson C, Nuss R, Jacobson L, Hacker MR, Murphy J, Weinberg A, et al. The varicella-autoantibody syndrome. Ped Res. 2001, 50(3): 345–352.
11. Regnault V, Boehlen F, Ozsahin H, Wahl D, De Groot PG, Lecompte T, et al. Anti-protein S antibodies following a varicella infection: detection, characterization and influence on thrombin generation. J Thromb Haemost. 2005, 3(6): 1243–1249.
12. Januário G, Ramroop S, Shingadia D V., Novelli V. Postinfectious purpura fulminans secondary to varicella-induced protein S deficiency. Pediatr Infect Dis J. 2010, 29(10): 981–983.
13. Manco-Johnson MJ, Nuss R, Key N, Moertel C, Jacobson L, Meech S, et al. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. J Pediatr. 1996, 128(3): 319–323.
14. Z Kurugöl, F Vardar, F Özkinay, K Kavakli, C Özkinay. Lupus anticoagulant and protein S deficiency in otherwise healthy children with acute varicella infection. Acta Paediatr. 2000, 89(10): 1186–1189.
15. Fishbein RH. Purpura fulminans: an analysis of the lesion and its treatment. J Pediatr Surg. 1969, 4(3): 320–329.
16. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014, 2(1): 1–8.

LA ROCHE POSAY
LABORATOIRE DERMATOLOGIQUE

CICAPLAST BALSEM B5+

HERSTELLENDE KALMERENDE BALSEM

MULTI-INDICATIES

Gezicht · Lichaam · Intiemes zones

Baby's · Kinderen · Volwassenen

UNIEKE FORMULE

HERSTELLENDE EFFICIËNTIE

NIEUW [TRIBIOMA]
Herbalanceert het microbioom

[MADECASSOSIDE]
Versnelt het herstel van de epidermis

[KOPER + ZINK + MANGAAN]
Zuiverende bestanddelen

[KARITÉBOTER + GLYCERINE]
Lipidenherstellend en hydraterend

VERZACHTENDE KRACHT

[5% PANTHENOL]
Kalmeert intens het oncomfortabele gevoel

TOLERANTIE en DOELTREFFENDHEID

Bewezen op **20.000 PERSONEN** (1 week tot 97 jaar) op **21 VERSCHILLENDE LETSELS** onder pediatrische en dermatologische controle

BALSEM TEXTUUR
Niet vet. Plakt niet.
ZONDER PARFUM - ZONDER ALCOHOL

40ml - CNK: 4488-649
100ml - CNK: 4488-656

LA ROCHE-POSAY. DERMATOLOGISCHE EFFICIËNTIE.

www.laroche-posay.be

Failure to thrive, from a frequent symptom to a rare diagnosis

Ninon Chelon [a], Francoise Mouchet [b], Aurélie Empain [c], Audrey Van Hecke [d]

[a] Queen Fabiola Children's University Hospital, Université Libre de Bruxelles, Brussels, Belgium
[b] CHU Saint-Pierre, Division of Infectious Diseases, Université Libre de Bruxelles, Brussels, Belgium
[c] Queen Fabiola Children's University Hospital, Department of Nutrition and Metabolism, Université Libre de Bruxelles, Brussels, Belgium
[d] Queen Fabiola Children's University Hospital, Department of Neurology, Université Libre de Bruxelles, Brussels, Belgium

ninon.chelon@ulb.be

Keywords

Niemann-Pick disease type C; failure to thrive; lysosomal storage disease; neurometabolic disorder; infant; case report.

Abstract

Niemann-Pick type C (NPC) disease is a neurometabolic disorder that causes premature death and rapidly progressive neurological disability. It affects 1 in 100,000 live births and has a heterogeneous presentation.
Case: We present a 3-month-old boy with significant failure to thrive that was initially misdiagnosed as acquired CMV infection. He had concomitant RSV bronchitis with acute respiratory failure.
Long follow-up, family history and genetic testing led to the diagnosis of Niemann-Pick type C disease.
Conclusion: Long-term follow-up is essential for the diagnosis of rare diseases.

Introduction

Failure to thrive (FTT) is a common sign in pediatrics. Its combination with developmental delay and organomegaly may indicate rarer underlying conditions. This case illustrates the complexity of establishing a specific diagnosis, the importance of ruling out differential diagnoses, and the importance of long-term follow-up for our patients.

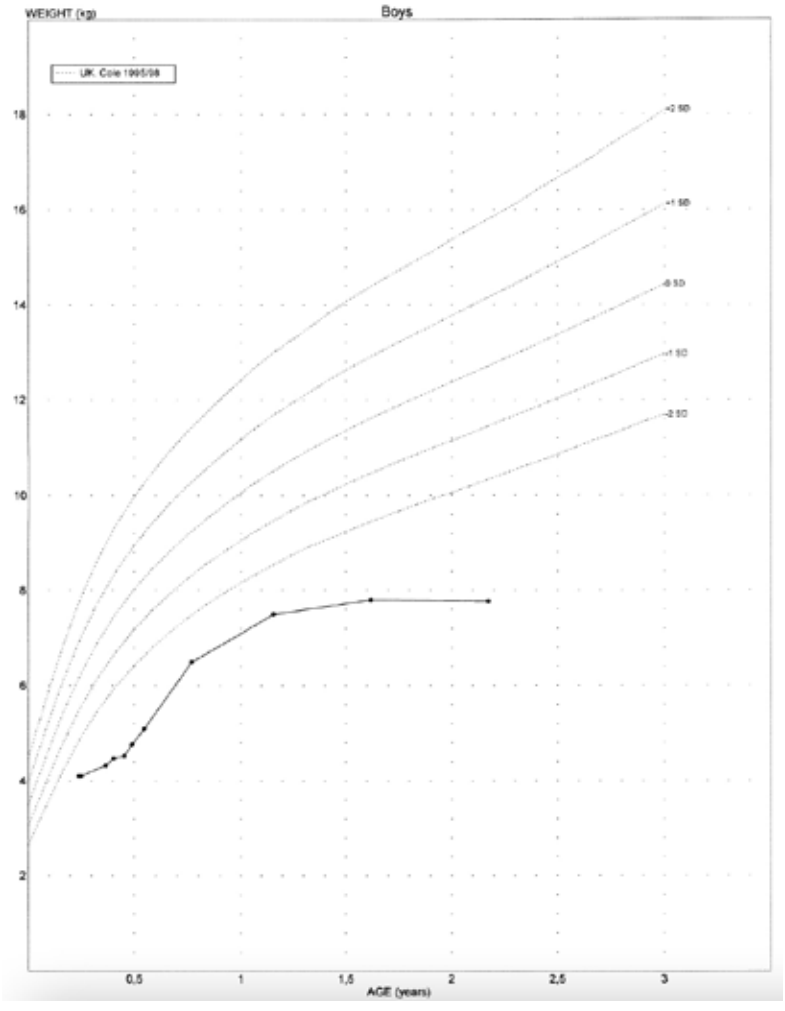
Case report

A three-month-old boy with a history of failure to thrive (FTT) had a lower respiratory tract infection for 3 days. On admission, his biometric measurements (weight, height and head circumference) were below the 3rd percentile on the WHO charts. Physical examination revealed a thin baby with grayish skin coloration. He was mildly dyspneic. Pulmonary auscultation revealed widespread rhonchi, crepitations, and wheezing. The abdomen was distended with massive hepatomegaly and an enlarged spleen, respectively 5 cm and 2 cm below the costal margin. Neurological examination revealed only axial hypotonia.

Initial investigations revealed a normocytic normochromic anemia with a hemoglobin of 9 g/dL [NL 9.5-13.5 g/dL]. Alanine aminotransferase and aspartate aminotransferase were elevated to 1.5 times the upper limit of normal (ULN). Gamma glutamyl transferase level was 3.3 times the ULN, and total bilirubin was 3 times the ULN (mainly indirect).

The international normalized ratio (INR) was within normal limits. A nasal swab was positive for respiratory syncytial virus (RSV). He was admitted to the hospital with a diagnosis of acute bronchiolitis and FTT. Chest radiographs supported the diagnosis of bronchiolitis.

Figure 1: Weight on the WHO curves from birth to the age of 2 years.



Further anamnesis revealed that the pregnancy was unremarkable except for intrauterine growth restriction. The family was from Syria. The parents are consanguineous in the 1st degree and the couple reported the death of a previous child at the age of 4 years due to an unknown neurological disorder with liver involvement.

Further biological investigations revealed a positive IgM serology for cytomegalovirus (CMV) and a positive CMV-PCR in urine. Acquired CMV-acquired infection was confirmed by a negative CMV-PCR in the newborn blood spot test. Because of hepatosplenomegaly, metabolic analyses were performed. No vacuolated lymphocytes were found. Lipid assessment was normal. Enzymatic assays for sphingomyelinase and glucocerebrosidase were normal, excluding acid sphingomyelinase deficiency (ex- Nieman-Pick type A/B diseases) and Gaucher's disease, respectively.

Measurements of Lyso509, chitotriosidase, oxysterols or lysosphingo-myeline-509 were not performed.

Abdominal ultrasonography (US) confirmed the hepatosplenomegaly without any other associated abnormalities. The infant developed respiratory failure requiring continuous positive airway pressure and oxygenation. After 42 days of hospitalization the patient was discharged home with a diagnosis of RSV-bronchiolitis and acquired CMV infection.

After hospitalization his weight and height progressed in harmony under 3rd percentile (Figure 1 and 2).

In the following months, the hepatosplenomegaly did not resolve. Generalized hypotonia persisted and global developmental delay became apparent. Multigene panel sequencing revealed a heterozygous frameshift variant (c.2972_2973delAG) in the NPC 1 gene on chromosome 18, identifying a Niemann-Pick type C disease. At the age of 2, the patient began to lose the ability to sit and slowly regressed. He died prematurely at the age of 2 years and 5 months.

Discussion

Failure to thrive is a common medical condition in pediatrics. Poor caloric intake or social difficulties account for most cases, although an organic condition must be ruled out.

The presentation of FTT in association with hepatosplenomegaly and developmental delay, as well as the history, link it to the spectrum of congenital neuro-metabolic disorders.

The current accessibility of genetics made the final diagnosis of Niemann-Pick type C (NPC).

NPC is a rare autosomal recessive disorder characterized by late-endosomal and lysosomal storage of unesterified cholesterol affecting ~ 1: 100,000 live births (1). It is caused by biallelic mutations in either the NPC1 or NPC2 gene, with NPC1 accounting for about 95% of cases and NPC2 for the remaining 5% (2).

These genes code for ubiquitous proteins (3). Lack of their function leads to the accumulation of lipid species such as sphingosine, cholesterol, sphingomyelin, and glycosphingolipids in late endosomes/lysosomes. Typically, the liver, spleen and brain are affected (4).

The clinical presentation and onset of the disease can vary widely (1). The age at which neurological symptoms appear determines the severity and prognosis of the disease (1). Therefore, the classification of NPC is based on the age of onset of neurological symptoms, which can be categorized as early infantile, late infantile, juvenile, and adolescent/adult (1, 2).

In younger patients, systemic signs typically manifest before neurologic signs (5). In the neonatal period, approximately 40% of cases present with hepatosplenomegaly and prolonged cholestatic jaundice (6). A genotype/phenotype correlation has been observed in the literature, and the patient's phenotype corresponds to the identified mutation (5, 7). Figure 3 summarizes the symptoms based on the patient's age. NPC should be considered as a potential diagnosis when the etiology of any of these symptoms remains unclear, such as prolonged neonatal jaundice, splenomegaly, gelastic cataplexia, and supranuclear gaze palsy (2).

Historically, the diagnosis has been made by skin biopsy and Filipin staining for unesterified cholesterol (8). Biochemical markers such as oxysterols, lyso-SM-509 (specific), and lyso-sphingomyelin can be used as screening tools, but genetic sequencing is necessary to confirm the diagnosis (8).

Due to the variability of symptoms and the age of onset, the diagnosis of NPC is often delayed or missed, suggesting that the true prevalence of the disorder may be higher. Early diagnosis is crucial as it can potentially affect the course of the disease. In fact, early initiation of misglustat therapy can slow disease progression and prolong a higher quality of life (6). Misglustat is a competitive inhibitor of glucosylceramide synthase. However, careful patient selection is necessary, as it can only extend good quality of life and not improve poor quality of life. Furthermore, a confirmed diagnosis allows for genetic counseling for future pregnancies.

Treatment options will continue to evolve in the coming years, making earliest possible diagnosis even more important.

Figure 2: Height on the WHO curves from birth to the age of 2 years.

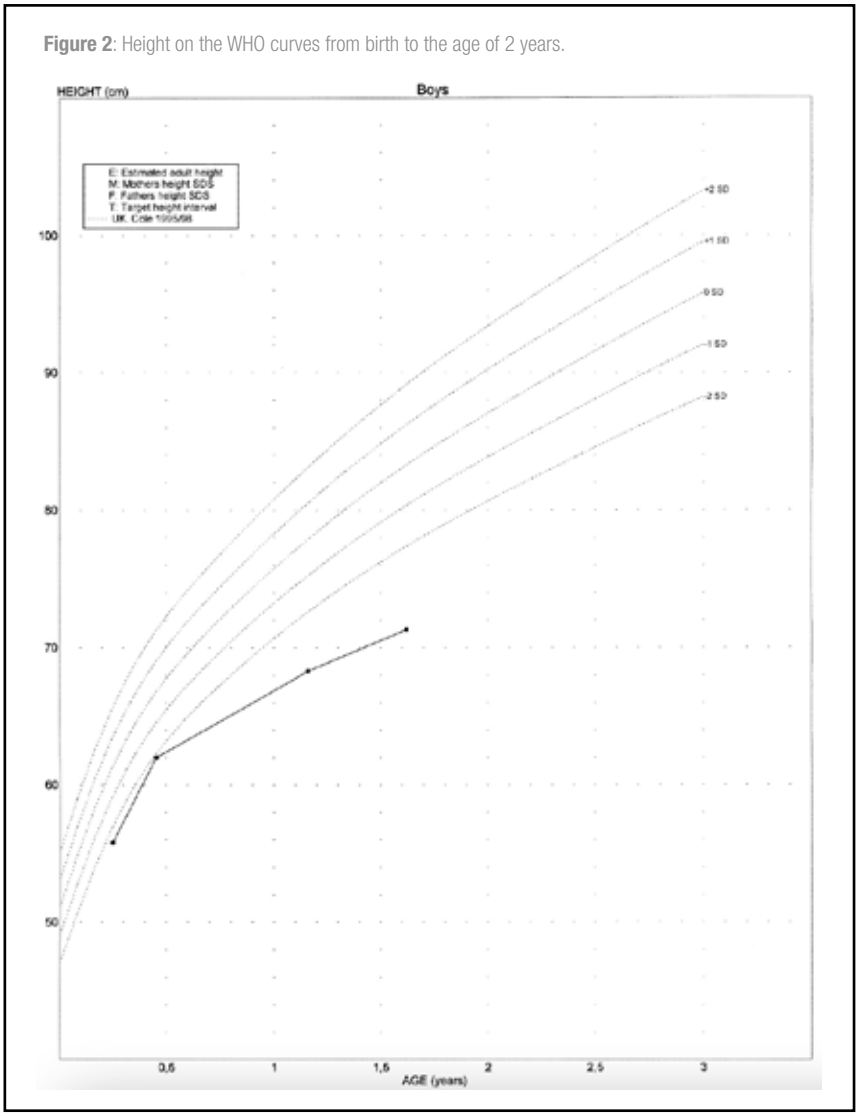
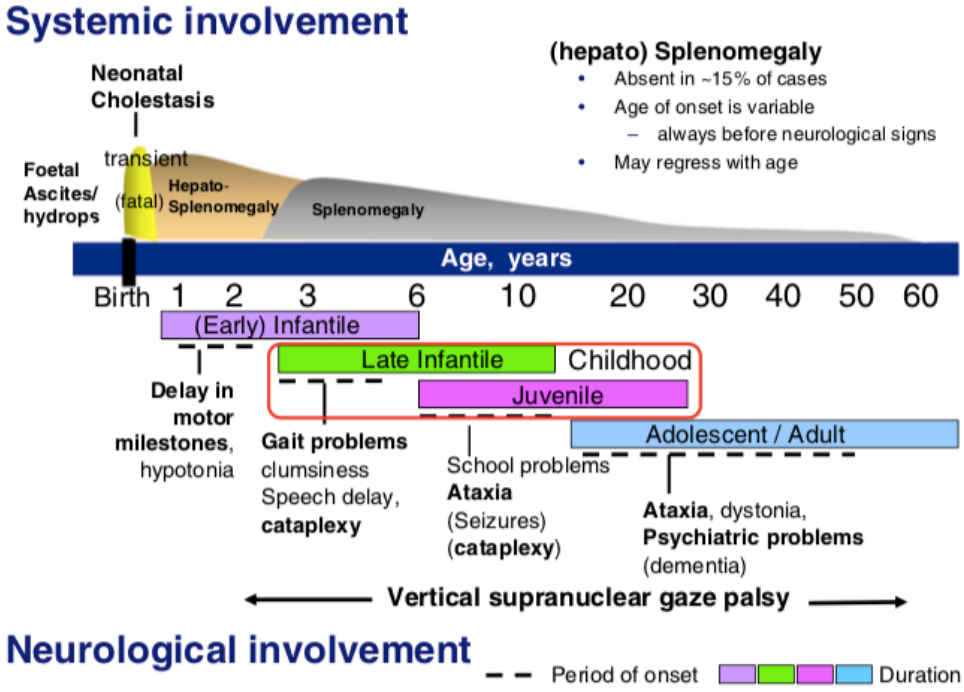


Figure 3: Schematic representation of the clinical aspects of Niemann-Pick C disease. Emphasis is given to the main initial neuro- logical manifestations (published with permission of M.T Vanier and Springer Nature) (9)



Conclusion

This case illustrates the need for long-term follow-up of patients, especially when clinical symptoms persist. Our patient was discharged from the hospital with an incomplete diagnosis and without a good follow-up, his diagnosis could have been missed. We also want to highlight the impact of the genetic testing, which can be useful in such situations.

Finally, neurometabolic diseases are rare and pediatricians should be able to recognize red flag symptoms in order to refer to a multidisciplinary pediatric center.

Conflict of interest

The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

REFERENCES

1. Geberhiwot T, Moro A, Dardis A, Ramaswami U, Sirrs S, Marfa MP, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet J Rare Dis. 2018;13(1):50.
2. La Maladie de Niemann-Pick type C (NP-C). Diagnostic et Signes Cliniques. Paris, France: Société Française de Pédiatrie; 2010 [cited 2023 June 12]. Available from: https://www.sfpediatrie.com/sites/www.sfpediatrie.com/files/documents/BrochureFocus/Focus_2_NiemmannPick.pdf.
3. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16.
4. Carreira AC, Pokorna S, Ventura AE, Walker MW, Futerman AH, Lloyd-Evans E, et al. Biophysical impact of sphingosine and other abnormal lipid accumulation in Niemann-Pick disease type C cell models. Biochim Biophys Acta Mol Cell Biol Lipids. 2021;1866(8):158944.
5. López de Frutos L, Cebolla JJ, de Castro-Orós I, Irún P, Giraldo P. Neonatal cholestasis and Niemann-pick type C disease: A literature review. Clin Res Hepatol Gastroenterol. 2021;45(6):101757.
6. Pineda M, Juríčková K, Karimzadeh P, Kolnikova M, Malinova V, Insua JL, et al. Disease characteristics, prognosis and miglustat treatment effects on disease progression in patients with Niemann-Pick disease Type C: an international, multicenter, retrospective chart review. Orphanet J Rare Dis. 2019;14(1):32.
7. Polese-Bonatto M, Bock H, Farias ACS, Mergener R, Matte MC, Gil MS, et al. Niemann-Pick Disease Type C: Mutation Spectrum and Novel Sequence Variations in the Human NPC1 Gene. Mol Neurobiol. 2019;56(9):6426-35.
8. Sobrido MJ, Bauer P, de Koning T, Klopstock T, Nadjar Y, Patterson MC, et al. Recommendations for patient screening in ultra-rare inherited metabolic diseases: what have we learned from Niemann-Pick disease type C? Orphanet J Rare Dis. 2019;14(1):20.
9. Vanier MT. Complex lipid trafficking in Niemann-Pick disease type C. J Inherit Metab Dis. 2015;38(1):187-99.

Mustela®

Stelatopia + vous

Apaise efficacement les peaux à tendance atopique et l'esprit des parents.

Crème relipidante anti-grattage

99% d'ingrédients d'origine naturelle

COSMETIQUE BIO CHARTE COSMEBIO®

Sans parfum

Apaise instantanément

Anti-récidive

ECOCERT COSMOS ORGANIC

Kinsbourne syndrome as complication of a *Mycoplasma pneumoniae* infection

Linda Adouane [a], Marie Hoyoux [b], Julie Frère [b], Christophe Barrea [c]

[a] University of Liège, Liège University Hospital, Department of Pediatrics, Liege, Belgium
[b] University of Liège, Liège University Hospital, Department of Pediatrics, Division of Infectiology, Liege, Belgium
[c] University of Liège, Liège University Hospital, Department of Pediatrics, Division of Neurology, Liege, Belgium

linda.adouane@hotmail.com

Keywords

Mycoplasma pneumoniae ; Kinsbourne syndrome ; opsomyoclonus-ataxia.

Abstract

Kinsbourne syndrome also known as opsoclonus-myoclonus-ataxia syndrome (OMAS) or more commonly dancing eyes and feet syndrome is a rare neurological disorder. This disorder affects children at an average age of 6 to 36 months. It associates opsomyoclonias and ataxia with behavioral disturbances. The pathophysiology is not well understood but seems to involve a dysimmunitary process; its etiology is often either paraneoplasic or parainfectious. Spontaneous resolution without immunomodulatory treatment has been described.

We describe here the case of a young five-year-old patient with Kinsbourne syndrome associated with *Mycoplasma pneumoniae* infection.

Case presentations

A five-year-old boy with no medical history was admitted to the emergency department with acute respiratory distress in a context of a week-long febrile upper respiratory tract infection. He was diagnosed with a left-sided bronchopneumonia complicated by a large pleural effusion (Figure 1A). The child was admitted to the intensive care unit where a pleural drain was placed and local fibrinolysis with urokinase was administered. The drain was removed after 9 days,. Non-purulent pleural fluid was drained and bacteriologic analyses were performed. *Mycoplasma pneumoniae* infection was confirmed in both initial blood samples and pleural fluid, first by serology and then by PCR. There was a significant clinical improvement after initial antibiotic therapy with amoxicillin/clavulanic acid (100 mg/kg/d) and clarithromycin (15 mg/kg/d) for 5 days followed by moxifloxacin (10 mg/kg/d) for 15 days (Figure 1B, 1C). On the 10th day of treatment, he presented with rapid, irregular and multidirectional eye movements consistent with opsoclonus, orthostatic ataxia, and myoclonus of the extremities, upper limbs and face. All of these new neurological symptoms disappeared at rest but were exacerbated during attention-grabbing tasks and activities. He also suffered from sudden behavioral changes and sleep disturbances (low frustration tolerance, frequent nocturnal awakenings). An extensive work-up was performed to exclude a neoplastic phenomenon such as neuroblastoma, but all investigations were negative (Table I).

It was thought that this opsoclonus-myoclonus-ataxia syndrome was provoked by the *Mycoplasma pneumoniae* infection, leading to the diagnosis of a rare entity: post-infectious Kinsbourne syndrome. The boy had a slow but favorable evolution with spontaneous resolution and complete disappearance of symptoms within 6 weeks after the initial presentation of the *Mycoplasma pneumoniae*.

Discussion

Mycoplasma pneumoniae is commonly responsible for upper and lower respiratory tract infections, and may be associated with extrapulmonary manifestations (e.g. meningoencephalitis, arthritis, hepatitis, myocarditis, pericarditis…) . Neurological manifestations occur in 0.1% of infections (1) . The diagnosis of a *Mycoplasma pneumoniae* infection is challenging due to the tedious culture conditions and the persistence of IgM antibodies long after acute infection. Culture remains the gold standard for confirming the diagnosis but due to its inherent difficulties, simpler tests have been developed. Among these, PCR (on blood or respiratory fluid) has a higher sensitivity than serology during the first two weeks of the disease, as antibodies tend to appear only one to two weeks after the onset of the infection. During this same period, the serologic response to detect an infection is positive in 23% to 56% using IgM detection versus 96% to 100% using PCR (2). Beyond this period, blood PCR detection remains positive in some patients, for up to 7 weeks after disease onset, with a transition to a clinically asymptomatic carrier state. The bacterial load gradually decreases over time. The rise in IgG levels is still used to confirm the infection, but is not helpful in acute clinical management as their titer usually rise in the convalescent phase after more than 40

Figure 1: Paraclinical work-up done in our patient and its results. Overview of the different differential diagnoses.

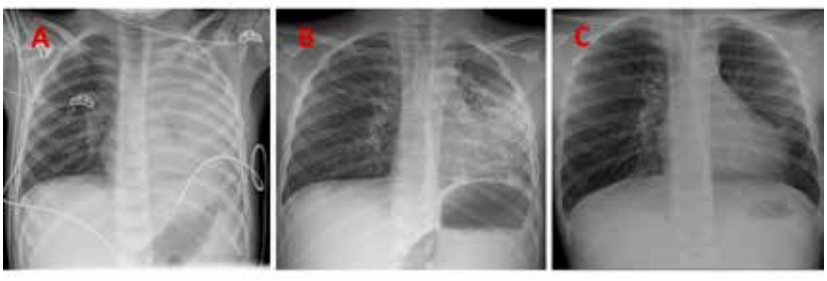


Figure 1: Radiological evolution after initiation of antibiotic therapy.

(A) Chest radiography at Day 0 showing a major left pleural effusion; (B) Day 9 of treatment: reappearance of partial left lung ventilation, persistent mediastinal shift to the left; (C) Day 86: persistence of a minimal residual lingular infiltrate without pleural reaction.

Investigation	Etiology	Results
Thyroid hormone assay	Hyperthyroidism	Normal.
Thyroid ultrasound	Secondary hyperthyroidism	No lesion or nodule. Normal appearance.
Abdominal ultrasound	Neuroblastoma, Hepatoblastoma Expansive tumor phenomenon	Normal.
Chest X-ray	Neuroblastoma. Expansive tumor phenomenon	Slight persistent pleural reaction on the left. No mass. No adenopathy.
Lumbar puncture	Meningitis	Cytology, culture, and multiplex PCR negative.
Blood determination of neuron-specific enolase (NSE)	Neuroblastoma Other tumor of neuroectodermal or neuroendocrine origin.	Normal.
Urinary determination of catecholamines	Neuroblastoma	Normal.
Ophthalmologic examination	Oculomotricity disorder	Normal examination except for opsoclonus.
Electroencephalogram (EEG)	Convulsions	Normal.
Cerebral MRI	Intracranial expansive, infectious or inflammatory process.	Normal.

days post infection (2). Newer diagnostic tests such as Elispot have been proposed but to date it is still difficult to confirm the diagnosis. Therefore, the combination of PCR with serological detection of IgM is the most sensitive method to confirm *Mycoplasma pneumoniae* infection taking into account the specificity and sensitivity of both techniques. In our case, we had less reason to doubt the diagnosis because there was strong evidence for ongoing *Mycoplasma pneumoniae* infection as PCR was positive in both blood and pleural effusion.

Treatment consists of antibiotic therapy with a macrolide which, in addition to its antimicrobial activity, has anti-inflammatory and immunomodulatory properties (3). Antibiotics remain the mainstay of treatment for *Mycoplasma pneumoniae* infection, with or without associated extrapulmonary manifestations. Treatment of neurological manifestations may vary whether these are secondary to active infection (need to prescribe an antibiotic with good brain penetration) or as post-infectious (consider combination with immunosuppressive therapy).

Among these manifestations, Kinsbourne syndrome, also known as opsoclonus-myoclonus-ataxia syndrome (OMAS) or more commonly as "dancing eyes and feet syndrome", is a rare neurological disorder that affects adults and children, with a peak incidence in the pediatric population most often between the ages of 6 and 36 months (1,3,4). It usually associates opsoclonus, myoclonus, truncal and appendicular ataxia with walking difficulties. Behavioral changes such as irritability, attention and sleep disturbances have also been described (4,5). The clinical picture varies from one patient to patient and the expression of the different neurological symptoms can be heterogeneous. Opsoclonus may be intermittent and may appear many weeks after ataxia. Behavioral disturbances can appear several weeks before the onset of typical neurological signs (1). The diversity of the clinical expression makes the diagnosis of OMAS difficult to make in some patients. The etiology of Kinsbourne syndrome is paraneoplastic or parainfectious (1,4,6).

In children, the neoplastic / paraneoplastic etiology must be ruled out first. It is therefore essential to exclude malignant phenomena, in particular neuroblastoma (or another neural crest tumor) which may present with the syndrome of opsomyoclonus and ataxia (5). Central imaging is mandatory. Several other infectious pathogens (EBV, CMV, HCV, HSV, Rotavirus, Coxsackie, Influenza, Salmonella...), have recently been newly associated with the onset of OMAS and are considered to be the primo movens. Emamikhah et al. have recently described cases secondary to COVID-19 (7). Rare cases in the literature mention and describe *Mycoplasma pneumoniae*, a pathogen well known in pediatrics, as an infectious agent responsible for the genesis of OMAS (6). The infectious workup remains essential in patients in whom a neoplastic/paraneoplastic etiology has been excluded as OMAS secondary to medication has not yet been described (6).

The pathophysiology of OMAS is not fully understood, but autoantibodies have previously been detected in some patients and appear to involve an immune process with dysregulation of humoral and cellular systems (6,8). Antineuronal nuclear autoantibodies type 2 (ANNA2) have been described in particular in paraneoplastic conditions (anti-Ri, anti-Yu, anti-Ho) (5,9). To date, no diagnostic biomarker has been identified despite the progress made in the understanding and genesis of this syndrome. Krasenbrink et al. support the idea of a genetic predisposition in OMAS, regardless of the etiology, without having identified or incriminated a specific gene (10). Their study showed that the prevalence of autoimmune diseases and autoantibodies is higher in parents of children with OMAS compared to the control group of parents of children of the same age and sex (3,10).

Kinsbourne syndrome is therefore considered an autoimmune disease whose etiology may be paraneoplastic or postinfectious, may involve several infectious agents, and may have other etiologies yet to be discovered.

In addition to treatment of the underlying cause, which often, but not systematically, leads to an improvement or even resolution of the symptoms, there is also a supportive component to the treatment for which there is no consensus or guidelines (8). Corticosteroids, adrenocorticotropic hormone (ACTH) and immunoglobulins are the most commonly used immunomodulatory agents in pediatrics as first-line therapy. In certain refractory situations, plasmapheresis may be considered. Immunosuppressive treatments, such as cyclophosphamide, cyclosporine A or azathioprine have been used as a last resort, regardless of etiology, because they block the antibody production that may be involved in the process (4,8,10).

Our patient received no treatment and spontaneously improved with nearly complete recovery in less than 6 weeks. Treatment with corticosteroids was considered but not started because of the spontaneous progressive improvement. This is one of the only case reports demonstrating a favorable evolution without any specific treatment.

The prognosis may depend on the etiology and the time of onset of treatment. Idiopathic and parainfectious forms generally have a good prognosis and may resolve spontaneously without treatment. Relative learning difficulties, mild motor, cognitive and behavioral sequelae may persist and may affect the child's future development. Only a few cases have been reported to define their prevalence/incidence and the long-term evolution.

Conclusion

Mycoplasma pneumoniae, a pathogen regularly encountered in respiratory tract infections, can be responsible for numerous extrapulmonary

manifestations. Among these is Kinsbourne syndrome or opso-myoclonus-ataxia syndrome, first described in 1962, an autoimmune disease whose etiology may be paraneoplastic or infectious. Autoimmunity is thought to be at the basis of this syndrome. Only a few cases have been reported in the literature. This case report illustrates the diversity of the clinical picture of an infection with this particular pathogen.

In Kinsbourne syndrome, it is essential to exclude an underlying malignant process at first and to identify the etiologic cause early on in order to target the therapy and determine the prognosis. If a post-infectious etiology is suspected, the diagnosis of *Mycoplasma pneumoniae* remains difficult, due to the lack of specificity/sensitivity of PCR and serology and both tests need to be combined. Corticosteroids and adrenocorticotropic hormone (ACTH) remain the first-line treatment, although there is no consensus or therapeutic guidelines. It should be noted that spontaneous recovery can be achieved without immunomodulatory treatment, as in our case.

Conflict of interest

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

REFERENCES

1. Hero B, Schleiermacher G. Update on pediatric opsoclonus myoclonus syndrome. Neuropediatrics. 2013;44(6):324-9.
2. Nilsson AC, Björkman P, Persson K. Polymerase chain reaction is superior to serology for the diagnosis of acute Mycoplasma pneumoniae infection and reveals a high rate of persistent infection. BMC Microbiol. 2008;8:93.
3. Huber BM, Strozzi S, Steinlin M, Aebi C, Fluri S. Mycoplasma pneumoniae associated opsoclonus-myoclonus syndrome in three cases. Eur J Pediatr. 2010;169(4):441-5.
4. Huddar A, Bindu PS, Nagappa M, Bharath RD, Sinha S, Mathuranath PS, et al. Pediatric opsoclonus-myoclonus-ataxia syndrome: Experience from a tertiary care university hospital. Neurol India. 2018;66(5):1332-7.
5. Blaes F, Dharmalingam B. Childhood opsoclonus-myoclonus syndrome: diagnosis and treatment. Expert Rev Neurother. 2016;16(6):641-8.
6. Gorman MP. Update on diagnosis, treatment, and prognosis in opsoclonus-myoclonus-ataxia syndrome. Curr Opin Pediatr. 2010;22(6):745-50.
7. Emamikhah M, Babadi M, Mehrabani M, Jalili M, Pouranian M, Daraie P, et al. Opsoclonus-myoclonus syndrome, a post-infectious neurologic complication of COVID-19: case series and review of literature. J Neurovirol. 2021;27(1):26-34.
8. Garg RK, Rizvi I, Malhotra HS, Kumar N. Opsoclonus myoclonus syndrome in children: Paraneoplastic versus parainfectious. Neurol India. 2018;66(5):1295-8.
9. Klaas JP, Ahlskog JE, Pittock SJ, Matsumoto JY, Aksamit AJ, Bartleson JD, et al. Adult-Onset Opsoclonus-Myoclonus Syndrome. Arch Neurol. 2012;69(12):1598.
10. Krasenbrink I, Fühlhuber V, Juhasz-Boess I, Stolz E, Hahn A, Kaps M, et al. Increased prevalence of autoimmune disorders and autoantibodies in parents of children with opsoclonus-myoclonus syndrome (OMS). Neuropediatrics. 2007;38(3):114-6.

Catch-up growth in infants and young children with faltering growth

Statement and expert opinion to guide general clinicians

QR code to the full publication

THE ISSUE : What is Known?

Faltering growth (FG) in infants and young children (<2 years of age) is a common problem for general clinicians to see in clinical practice, especially in low-income settings.

FG is associated with a range of adverse outcomes and there may be benefits in promoting catch-up growth where this is indicated.

Healthcare professionals may be deterred from adequately addressing the problem, due to the misconception that addressing faltering growth may promote accelerated growth.

CONSEQUENCES OF FALTERING GROWTH

High-income

Disease related FG: Short term consequences

Studies on mixed populations of hospitalized children have shown that malnutrition is associated with an increase in infectious complications and an increased length of stay.

Disease related FG: Long term consequences

In the longer term malnourished children also have increased rates of impaired cognitive function and behavioral problems, including impaired communication skills and attention-deficit hyperactivity disorders.

Non-disease related FG: Short term consequences

The consequences of faltering growth may include an impact on schooling and cognitive achievements, short stature, and socioeconomic outcomes.

Middle-income

Faltering growth in low and middle-income countries commonly occurs together with numerous health and social outcomes, including poor brain development and delayed cognitive performance; delayed attainment of milestones; greater susceptibility to some infections; higher overall and disease-specific mortality in childhood; lower physical work capacity in adulthood; poorer earnings; and diminished human capital.

Low-income

MANAGEMENT

Nutritional management of disease-related and non-disease-related faltering growth

Nutritional management of disease- and non-disease-related faltering growth requires a **balanced ratio of energy and protein in addition to micronutrients for optimal catch-up**.

Breastfeeding should be supported in both disease- and non-disease-related faltering growth by ensuring assessing technique and supply and only **where appropriate** infant milk fortification, cup feeding or **supplementary formula should be considered**.

In formula fed infants **ready to use energy dense therapeutic feeds with proven efficacy** should be used, where available; if these are not available suitable locally available powdered feeds can be used, applying WHO hygiene safety for mixing.

Modular additions of only fat and carbohydrates to feed and food **should be avoided**, as this reduces the protein to energy ratio.

Nutritional management for both medical and non-medical faltering growth should include **either/both the fortification of accepted foods and advice on foods that are naturally energy dense** and locally available.

The nutritional management plan should include a target for **appropriate catch-up growth that is monitored** at an interval that is deemed appropriate by the healthcare professional, the available healthcare service and the severity of the faltering growth.

Cooke R, et al. J Pediatr Gastroenterol Nutr. 2023; 77(1):7-15.

Important: Breastfeeding is the ideal nutrition for infants.

NUTRICIA

INFATRINI

KLINISCH BEWEZEN[2,15-17]

Onze referentie bij inhaalgroei

Van 0 tot 18 maanden of tot 9 kg

- Voldoet aan de **WHO aanbevelingen** voor inhaalgroei: min. 8,9-11,5 En% eiwit[1]
- Onze unieke **prebiotische mix scGOS/lcFOS** ter ondersteuning van de darmmicrobiota[5]
- **Volledige medische voeding voor zuigelingen** (10 En% eiwitten)
- **Positieve stikstofbalans** vanaf dag 1[15]
- **Volwaardige wei/caseïne-eiwitverhouding 60:40** vergemakkelijkt de maaglediging en vermindert braken en kokhalsreflexen[6-9]
- **LCPs (DHA en ARA)** die de gezichtsscherpte en cognitieve ontwikkeling ondersteunen[3,4]
- **Lage osmolariteit voor een betere tolerantie**[8] wat het risico op gastro-oesofagale reflux[11] en/of osmotische diarree verlaagt[12]
- **Nucleotiden** die het immuunsysteem stimuleren[10]
- **Kant-en-klaar,** wat het risico op bacteriële contaminatie en bereidingsfouten vermindert[13,14*]
- 40% **meer micronutriënten** per 100 ml dan een energieverrijkte zuigelingenvoeding. Dus minder volume nodig om in de behoefte voor zuigelingen te voorzien[2]
- Geschikte formule voor **vochtbeperkingen**
- Verkrijgbaar als **drink- en sondevoeding**

NUTRICIA

Neem contact op met onze diëtisten van de Nutricia Careline:
0800 99 486 • medical.nutrition@nutricia.be • www.nutricia.be
V.U. : Danone Belux N.V. – Werkhuizenkaai 160 – 1000 Brussel

Scan de QR-code voor meer informatie over Infatrini

*voor Infatrini 125 ml, 500 ml

Belangrijk: Borstvoeding is de ideale voeding voor zuigelingen. Infatrini is een voeding voor medisch gebruik. Dieetvoeding bij ziektegerelateerde ondervoeding, groeiachterstand, verhoogde energiebehoefte en/of vochtbeperking. Uitsluitend te gebruiken onder medisch toezicht, na alle voedingsopties te hebben overwogen, met inbegrip van borstvoeding. Informatie uitsluitend voor het (para-) medisch korps.

Referenties: 1. WHO Protein and amino acid requirements in human nutrition: Report of a joint FAO/WHO/UNU expert consultation (technical report series 935). 2007. **2.** Clarke S.E. et al. J Hum Nutr Diet 2007; 20, pp. 329–339 **3.** Birch EE et al. Am J Clin Nut 2010;91:848-59. **4.** Birch EE et al. Early Hum Devel **5.** Moro G et al. J Pediatr Gastroenterol Nutr 2002; 34: 291-295 **6.** Fried MD et al. J Pediatr 1992; 120(4): 569–572. **7.** Billeaud C et al. Eur J Clin Nutr 1990; 44(8):577–583. **8.** Brun AC et al. Abstract accepted at 30th ESPEN. Florence, Italy. 13–16 September 2008. **9.** Graham-Parker C et al. JPEN J Parenter Enteral Nutr 2001; 25(Suppl 14):Abstract 0051 **10.** Carver JD, et al. Pediatrics. 1991;88(2):359–63 **11.** Sutphen JL & Dillard VL. Gastroenterology 1989;97(3):601-604 **12.** Kukuruzovic RH & Brewster DR. J Paediatr Child Health 2002;38(6):571-7 **13.** Clarke SE et al. J. Hum. Nutr. Diet. 2007; 20 (4): 329-339. **14.** Mathus-vliegen EMH et al. JPEN J Parenter Enteral Nutr. 2006;30(6):519-25. **15.** Van Waardenburg DA et al. Clin Nutr. 2009;28(3):249-55 **16.** Evans S, et al. J Hum Nutr Diet 2006; 19: 191-7 **17.** De Betue CT, et al. Arch Dis Child 2011; 96: 817-22

Idiopathic infantile hypercalcemia in a child presenting with failure to thrive: a case report

Trees Kempen [a], Kristien Evens [b]

[a] KU Leuven, Faculty of Medicine, Leuven, Belgium
[b] Sint-Andriesziekenhuis, department of Pediatrics, Tielt, Belgium

trees.kempen@telenet.be

Keywords

Idiopathic infantile hypercalcemia ; CYP24A1 ; failure-to-thrive ; case report.

Abstract

Idiopathic infantile hypercalcemia is caused by loss-of-function mutations in the *CYP24A1* gene, which encodes an enzyme that degrades vitamin D. The disease is characterized by nonspecific symptoms. In this case study, the infant merely presents with failure to thrive and dehydration, giving rise to a broad differential diagnosis. Ultrasound revealed bilateral nephrocalcinosis. Genetic research showed two compound mutations in the *CYP24A1* gene. Following a diet low in calcium and vitamin D and starting calcium-lowering therapy, led to adequate weight gain and normalized calcium levels. The case highlights the importance of determining full serum electrolytes in children with failure to thrive.

Introduction

The fat-soluble vitamin D plays a substantial role in calcium- and phosphate homeostasis (1). For this purpose, supplementation of 400-600 international units (IU) per day (depending on skin color) is routinely recommended in all newborns up to the age of 6 years (2). The degradation of active vitamin D or calcitriol is catalyzed by CYP24A1, a member of the cytochrome P450 family. Loss-of-function mutations in this enzyme cause a disease called 'idiopathic infantile hypercalcemia (IIH) type 1', which presents with nonspecific symptoms such as hypotonia, polyuria, dehydration and feeding difficulties due to hypercalcemia (1). Once diagnosed, calcium-lowering therapy should be initiated and vitamin D supplementation discontinued immediately. Caution should be taken in asymptomatic carriers, as in this case, external factors like excessive calcium or vitamin D intake may still cause late sequalae (3). We describe a case of an infant with IIH merely presenting with failure to thrive (FTT) and dehydration.

Case report

A 5-month-old girl presented to the emergency department because of poor feeding that had worsened over the past week. During this week she had fever that resolved spontaneously. According to the parents, there was no associated vomiting or diarrhea and urine production was still adequate.

There were no peculiarities in her past history. She was born at term with a normal birth weight. The infant was still exclusively breastfed at the time of presentation. Both parents were of Romanian origin, there was no consanguinity and all siblings were in good health. The infant was not receiving any medications in addition to the recommended daily dose of 400 IU of vitamin D per day.

Physical examination showed a lean and listless infant with mild signs of dehydration. There were no symptoms of infection and no syndromic stigmata. She had lost 160 grams over the past 6 weeks and the growth chart indicated that her weight had decreased 2.5 standard deviations over the previous two months.

Initial blood results revealed mild leucocytosis with normal C-reactive protein (CRP) level, acidosis, hyponatremia and hyperkaliemia. The nasopharyngeal aspirate was positive for Influenza A. Intravenous (IV) rehydration was started. On admission to the hospital, subsequent blood tests showed elevated levels of both total calcium (4,07 mmol/L, reference range 1,95-2,80 mmol/L) and free calcium (2,04 mmol/L, reference range 1,15-1,27 mmol/L). Phosphate levels were normal. Parathyroid hormone (PTH) was suppressed with a value of <6 ng/L (reference range 15-65 ng/L). 25-hydroxy vitamin D3 was markedly raised (> 100 ng/mL, reference range 10-44,8 ng/mL) with also high levels of 1,25-dihydroxy vitamin D3 (198,7 pg/mL, reference range 19-95 pg/mL). Urinalysis showed hypercalciuria with a calcium/creatinine ratio of 3,380 mg/mg (reference range <0,6 mg/mg). Renal ultrasound showed nephrocalcinosis.

The parents denied any excessive use of vitamin D supplements. No evidence of malignancy, granulomatous disease or congenital disorders was found. Genetic analysis revealed two compound heterozygous mutations in the CYP24A1 gene: c443T>C, p. (Leu148Pro) in exon 2 and c.1186C>T, p. (Arg396Trp) in exon 9.

Intravenous hyperhydration and formula low in calcium and vitamin D were started, and supplemental vitamin D was discontinued. A daily low dose of fluconazole, which can reduce the formation of 1,25-dihydroxy vitamin D3, was started. In addition, two doses of bisphosphonates were given to lower calcium levels more rapidly. Calcium and PTH levels returned to normal within three months. Feeding difficulties resolved, solid foods could be introduced, and adequate weight gain was achieved.

Discussion

Idiopathic infantile hypercalcemia was first described in the early 1950s when formula milk, heavily fortified with vitamin D, caused symptoms such as failure to thrive, vomiting, dehydration or even death in children with intrinsic hypersensitivity to vitamin D. However, it was not until 2011 that Schlingmann et al. described mutations in the CYP24A1 gene that explained this hypersensitivity (1). Later, pathogenic variants in the SLC34A1 gene, which encodes a sodium-phosphate IIa cotransporter, were found to be another molecular basis for IIH (type 2) by causing renal phosphate wasting, leading to an inappropriate increase in 1,25-dihydroxy vitamin D3 synthesis (3,4). In the presented case, both genetic mutations were investigated, although normal serum phosphate levels suggested the diagnosis of IIH type 1. The two compound loss-of-function mutations in this patient were previously described in De Paolis et al. as causing IIH type 1 (3).

The CYP24A1 enzyme catalyzes the breakdown of 1,25-dihydroxy vitamin D3 (active form) and its precursor 25-hydroxy vitamin D3 into metabolites that can be excreted (1). Low calcium levels stimulate the production of PTH which in turn downregulates CYP24A1. This process leads to an increase in concentration of active vitamin D and thus to an increase in calcium levels through intestinal absorption and renal reabsorption. In IIH type 1, loss-of-function mutations in the CYP24A1 gene prevent the breakdown of active vitamin, causing calcium levels to rise to pathological levels (3).

IIH often manifests early, usually at 3 to 7 months of age (5). Affected children may present with a variety of symptoms, including vomiting, polyuria, dehydration, anorexia, constipation and weight loss. Lethargy and muscular hypotonia may also occur (3,5,6). Sometimes, the disease can be accompanied by seizures, pancreatitis or psychiatric symptoms (6). Our patient presented with failure to thrive, which is described in about three quarters of the cases reported in literature (7). If the initial symptoms go undetected, other problems such as kidney stones, renal failure, osteoporosis or calcium deposition in the cornea or joints may develop. Patients who are carrier of a mutation may also show these latent symptoms, mainly when vitamin D is taken in excess (3,5).

Typical laboratory findings are hypercalcemia, hypercalciuria and supressed PTH levels (3). 1,25-dihydroxy vitamin D3 is usually slightly elevated but tends to normalize due to downregulation by PTH (5). Another diagnostic clue is an elevated ratio of serum 25-hydroxy vitamin D3 to its catabolite 24,25-dihydroxy vitamin D3 (5,8). In some patients, abdominal ultrasound may reveal nephrocalcinosis (1).

Failure to thrive can be caused by a wide range of conditions. The finding of PTH-independent hypercalcemia with normal to high calcitriol levels suggests the possible diagnosis. In children, congenital causes, such as IIH types 1 and 2, are more common than acquired etiologies. Early onset of the condition, consanguinity, a family history of hypercalcemia or a history of multiple or recurrent kidney stones, should raise the suspicion of a genetic disorder (3). Some congenital syndromes associated with hypercalcemia, such as William syndrome, Down syndrome, and Jansen disease, can be identified by dysmorphic features (6,8). PTH-independent hypercalcemia may also be seen in some rare inborn errors of metabolism such as blue diaper syndrome, hypophosphatasia, congenital lactase deficiency or disaccharide intolerance (6). Among the acquired disorders, (accidental) intoxication with vitamin D, vitamin A or some drugs should be considered first (6). Extrarenal overproduction of vitamin D occurs in granulomatous disorders or malignancies such as lymphoma or ovarian dysgerminoma. In neonates, subcutaneous fat necrosis is a rare and reversible cause of hypercalcemia, caused by the formation of a granulomatous infiltrate in the necrotic area (6,8).

Children diagnosed with IIH require prompt treatment. Hyperhydration with or without loop diuretics will stimulate calcium excretion and rapidly reduce calcium levels. A diet low in calcium and vitamin D has to be prescribed (3,8). In the next phase of treatment, a more prolonged reduction of calcium levels should be achieved. Several options have been explored, including the use of corticosteroids, especially for hypercalcemia due to granulomatous disease, or the use of calcitonin, although its effect is short-lived (3,6). A 2- to 3-day course of bisphosphonates can be given to inhibit osteoclast activity and thereby lowering calcium levels. This course can be repeated every 6 to 8 weeks (3,6). In addition, azole antifungals are known to be general inhibitors of the cytochrome P450 complex. Consequently, they also interfere with the function of the 25-hydroxylase and 1-alpha-hydroxylase enzymes, thereby reducing the production of vitamin D. Ketoconazole is a more potent inhibitor with a higher risk of hepatic and renal toxicity than the more readily available fluconazole (3,5,9). Rifampicin is an inducer of the CYP3A4 enzyme, which could act as different approach to break down vitamin D (6). It is important that these medications are gradually reduced as calcium levels normalize (5).

In the literature little is known about the natural course and prognosis of IIH. According to some studies hypercalcemia resolves spontaneously in most children at the age of one to three years. In a small number of patients, suboptimal calcium levels persist into adulthood (5,6). Long-term adverse outcomes have been reported, including mild to moderate intellectual disability, anxiety and hyperactivity (5). The implications on bone development also remain unclear, as both low, normal and high bone mineral density have been described (8). In the presented case, the patient showed a rapid catch-up growth after initiation of diet and calcium-lowering therapy. Treatment with fluconazole could be weaned after approximately three months.

Conclusion

When a child presents with failure to thrive, hypercalcemia needs to be excluded by performing a complete serum electrolyte panel during the diagnostic evaluation. A genetic cause of hypercalcemia should be considered in the presence of early onset of disease or conspicuous family or medical history. In these cases, IIH should be considered in the differential diagnosis. High-dose vitamin D supplementation should be used with caution, as it may endanger children with *CYP24A1* mutations. Finally, more research is needed on the natural course and the long-term impact of IIH.

Conflict of interest

All authors declare that they have no conflict of interest in relation to the realization of this case report.

REFERENCES

1. Schlingmann KP, Kaufmann M, Weber S, Irwin A, Goos C, John U, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia.. N Engl J Med. 2011;365(5):668-74.
2. De Ronne N, De Schepper J. Vitamine D suppletie bij de zuigeling en het jonge kind: Aanbevelingen kind en gezin en voedingscel vlaamse vereniging voor kindergeneeskunde. Farm Tijdschr voor Belgie. 2013;3:12–21.
3. De Paolis E, Scaglione GL, De Bonis M, Minucci A, Capoluongo E. CYP24A1 and SLC34A1 genetic defects associated with idiopathic infantile hypercalcemia: From genotype to phenotype. Clin Chem Lab Med. 2019;57(11):1650–67.
4. Schlingmann KP, Ruminska J, Kaufmann M, Dursun I, Patti M, Kranz B, et al. Autosomal-recessive mutations in SLC34A1 encoDing sodium-phosphate cotransporter 2a cause idiopathic infantile hypercalcemia. J Am Soc Nephrol. 2016;27(2):604–14.
5. Marks BE, Doyle DA. Idiopathic infantile hypercalcemia: Case report and review of the literature. J Pediatr Endocrinol Metab. 2016;29(2):127–32.
6. Stokes VJ, Nielsen MF, Hannan FM, Thakker R V. Hypercalcemic Disorders in Children. J Bone Miner Res. 2017;32(11):2157–70.
7. Madsen JOB, Sauer S, Beck B, Johannesen J. CYP24A1 mutation in a girl infant with idiopathic infantile hypercalcemia. JJ Clin Res Pediatr Endocrinol. 2018;10(1):83–6.
8. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: Mechanisms, diagnosis, and treatment. Endocr Rev. 2016;37(5):521–47.
9. Sayers J, Hynes AM, Srivastava S, Dowen F, Quinton R, Datta HK, et al. Successful treatment of hypercalcaemia associated with a CYP24A1 mutation with fluconazole. Clin Kidney J. 2015;8(4):453–5.

Prix public **€ 86,52**

Si vous ne recommandez pas la vaccination contre le MenB à vos patients,

qui le fera ?

81% des parents considèrent leur médecin comme la source principale d'information concernant la vaccination de leurs enfants (n=800)[2]

BEXSERO
Vaccin méningococcique groupe B
(ADNr, composant, adsorbé)

BEXSERO est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B.[1]

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT : Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001 ; EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine recombinante NadA de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Protéine de fusion recombinante fHbp de Neisseria meningitidis groupe B[1, 2, 3] : 50 microgrammes • Vésicules de membrane externe (OMV) de Neisseria meningitidis groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'E. coli par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **FORME PHARMACEUTIQUE :** Suspension injectable. Suspension liquide blanche opalescente. **DONNÉES CLINIQUES : Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par Neisseria meningitidis de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a]. **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c] - Primovaccination : Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b, c]. **Age lors de la première dose :** Nourrissons de 6 à 11 mois. **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année de vie avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 12 à 23 mois. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose : Enfants de 2 à 10 ans. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose : Adolescents (à partir de 11 ans) et adultes*. Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. - [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 mois. - [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. - [d] Voir rubrique 5.1 du RCP complet. - * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et Haemophilus influenzae de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000). Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée. Peu fréquent : convulsions (y compris convulsions fébriles). Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). Peu fréquent : eczéma. Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l.,Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 26/04/2023 (v15). **MODE DE DELIVRANCE :** Sur prescription médicale.

Références : 1. SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

PM-BE-BEX-ADVR-230002 - Août 2023 | ER: GlaxoSmithKline Pharmaceuticals s.a./n.v. Site Apollo Avenue Pascal, 2-4-6 1300 Wavre Belgium

GSK

Severe persistent hypocalcemia occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency

Justine Lombard [a], Dominique Biarent [b], Delphine Michez [a]

[a] EpiCURA Hospital, Department of pediatrics, Hornu, Belgium
[b] Université Libre de Bruxelles, Hôpital Universitaire des Enfants, Pediatric Intensive Care & Emergency Department, Brussels, Belgium

justine.lombard@ulb.be

Keywords

Hypocalcemia ; vitamin D ; vitamin D deficiency ; treatment ; child.

Abstract

This article describes two cases of severe persistent hypocalcemia occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency. We compared these cases with hungry bone syndrome (HBS) occurring after parathyroidectomy. Studies of hypocalcemia due to vitamin D deficiency suggest a potential risk of hungry bone (HB)-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation. This article highlights the pitfalls of hypocalcemia management. Hypocalcemia should be actively treated with calcium boluses and continuous infusion to avoid the possibility of HB-like syndrome.

Introduction

The incidence of vitamin D deficiency is increasing in developed countries (1–4). Complications from vitamin D deficiency and hypocalcemia include rickets, seizures, cardiomyopathy, and has a significant impact on morbidity and mortality in children (1–5).

We present two cases of children with symptomatic hypocalcemia, and an unexpected severe worsening after initiation of calcium and vitamin D treatment, resembling hungry bone syndrome (HBS).

The aim of our presentation is to compare our 2 cases with HBS, which has been described mainly after parathyroid or thyroid removal surgery (5,6).

Studies on hypocalcemia due to vitamin D deficiency, suggest a potential risk of hungry bone (HB)-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation (7,8).

Case presentations

Case 1

A 6-month-old male was admitted to the emergency department after a third episode of brief seizures without accompanying fever.

This full-term healthy child, born from to an inbred family from Pakistan, was breastfed and received fruit and vegetable supplements. He received all scheduled vaccines but no vitamin supplementation. His growth was normal. The mother and the child had dark skin and wore traditional clothing. There was no family history of epilepsy. The mother wasn't taking any medications or vitamins.

On admission, physical and neurological examinations were normal. Plasma biology (Table 1) revealed anemia, vitamin B12 and iron deficiency, and severe hypocalcemia (Ca 1.4 mmol/L [N 2.25-2.75 mmol/L]).

Cerebrospinal fluid analysis, brain CT scan, and electroencephalogram were normal. He was treated with intravenous (IV) calcium gluconate (24 mg/kg/day of elemental Ca) and oral cholecalciferol 800 units/day.

After a few days of treatment, the hypocalcemia worsened (Ca 1.27 mmol/L), and new episodes of seizures occurred.

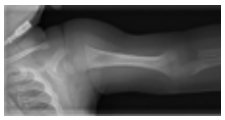
Diagnostic tests showed a high parathyroid hormone (PTH) level, severe vitamin D deficiency, normal phosphorus, elevated alkaline phosphatase (ALP), but no urinary calcium loss (urinary Ca/creatinine : 0,44 mmol/mol creatinine [0,034-0,690 mmol/mol creatinine]).

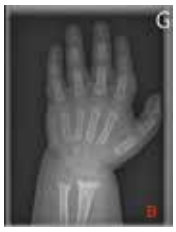
Radiographic findings were typical of rickets (Figure 1) and also showed cardiomegaly. Echocardiography showed mild cardiac dysfunction with dilated left ventricle, but without clinical impact.

Table 1: value at admission and etiological assessment.

	Value	Unit	Standards
Hemoglobin	10,7	g/dL	10,5-13,5
White cells	11 030	/mm^3	6000-17500
C-reactive protein	7,82	mg/L	<0,5
Calcium	1,4	mmol/L	2,25-2,75
Ionized calcium	0,65	mmol/L	1,12-1,32
Magnesium	0,78	mmol/L	0,63-1,05
Phosphorus	1,7	mmol/L	1,15-2,15
Parathyroid hormone	94,9	ng/L	<49
25-OH-vitamin D	<0,5	mcg/L	30-80
Iron	36	mcg/dL	40-100
Albumin	43,4	g/l	38-54
Alkaline phosphatase	864	UI/L	<449

Figure 1:
A and B : Left arm and wrist of case 1 : poorly demarcated, widened and frayed distal ends of radius and ulna, characteristic of rickets. Same symptoms on the ankle.





Calcium administration was increased to 210 mg/kg/day of oral elemental calcium, and 36 mg/kg/day of intravenous (IV) elemental calcium. Vitamin D administration was increased to 3000 units per day and alfacalcidol was added to the treatment.

On day 3 (D3) the child was transferred to the Paediatric Intensive Care Unit (PICU) due to lack of improvement in calcemia. Notably, after admission to the PICU, the patient developed hypophosphatemia (0.88 mmol/L [1,15 - 2,15 mmol/L]).

In the PICU, the patient received an IV bolus of calcium chloride followed by continuous intravenous infusion of calcium chloride from D3 to D6 (maximum 60 mg/kg/day of elemental calcium). Normocalcemia was achieved on D5. Intravenous calcium administration was continued until D6. Oral calcium carbonate, vitamin D and iron therapy were started.

The exact amount of calcium administered is shown in Table 2.

The mother was vitamin D and iron deficient and was supplemented.

Case 2

A 19-day-old male infant was admitted to the emergency department with cough, nasal congestion and breathing difficulties. The child was afebrile. The mother reported that the infant had clonic movements of the upper limbs for the past two days. He was born at full term but had intrauterine growth restriction (birth weight below the third percentile on Fenton curves). He was born to Syrian healthy parents with dark skin.

Plasma biology on admission revealed hypocalcemia (1.58 mmol/L) and hypovitaminosis D (5.3 mcg/L [N 30-80 mcg/L]). PTH was low (39 ng/L [N <49 mg/L]), ALP was normal and phosphorus was high. There was no urinary calcium loss (Ca/creatinine 0.682 mmol/mol creatinine). Nasopharyngeal microbiology showed a respiratory syncytial virus. The cerebrospinal fluid analysis after lumbar puncture was normal. The child was initially treated with empiric antibiotic therapy and a bolus of 100 mg/kg of Ca gluconate (9.3 mg/kg of elemental Ca). The child also received respiratory support with continuous positive airway pressure (CPAP).

Table 2: Amount of calcium administered.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Case 1									
Per os	Cholecalciferol 800 units	Cholecalciferol 800 units Calcium carbonate 50mg/kg of EC	Cholecalciferol 800 units Alfacalcidol 0,25 mcg Calcium carbonate 105mg/kg of EC	Cholecalciferol 3000 units Alfacalcidol 0,3mcg Calcium carbonate 210 mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 210 mg/kg of EC	Cholecalciferol D 3000 units Calcium carbonate 210mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 210mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 160mg/kg of EC	Cholecalciferol 3000 units Calcium carbonate 160mg/kg of EC
IVC	Calcium gluconate 24mg/kg of EC	Calcium gluconate 24mg/kg of EC		Calcium chloride 60mg/kg of EC	Calcium chloride 60mg/kg of EC	Calcium chloride 30mg/kg of EC	Calcium chloride 6mg/kg of EC		
IVD			Calcium gluconate 36mg/kg of EC	Calcium chloride 0,2 ml/kg (5,5 mg/kg of EC)					
Case 2									
Per os		Cholecalciferol 1000 units Calcium gluconate 50mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,3 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1000 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 50 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC	Cholecalciferol 1500 units Alfacalcidol 0,4 mcg Calcium gluconate 75 mg/kg of EC
IVC		Calcium gluconate 50mg/Kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 50mg/kg of EC	Calcium gluconate 55mg/kg of EC	Calcium gluconate 25mg/kg of EC	Calcium gluconate 25mg/kg of EC	
IVD	Calcium gluconate 9,3 mg/kg of EC	Calcium gluconate 18,6 mg/kg of EC		Calcium chloride 5 bolus 0,1ml/kg (9,1 mg/kg of EC)	Calcium chloride 1 bolus 0,1ml/kg (1,8 mg/kg of EC)				

On D1, the hypocalcemia worsened (Ca 1.33 mmol /L); an IV bolus of 48 mg/kg of elemental calcium was administered and the child was transferred to the PICU.

PTH concentration (48.5 ng/L) and ALP increased. The child received continuous intravenous calcium gluconate (50 mg/kg/day of elemental calcium) and vitamin D supplementation (alfacalcidol and cholecalciferol). Calcemia did not improve and on D3, the child presented with new episodes of clonic movements and a cardiogenic shock with left heart dysfunction requiring the administration of 5 boluses of calcium chloride (9.1mg/kg of elemental calcium), ventilatory support and inotropic drugs. The amount of intravenous calcium gluconate was adjusted to the blood calcium level (maximum 55 mg/kg/day of elemental calcium), as was the amount of oral calcium (maximum 75 mg/kg/day of elemental calcium).

Normocalcemia was achieved on D6. On D 8, calcium supplementation was changed to enteral only.

Genetic investigation was normal, excluding DiGeorge's syndrome, and the child fully recovered one month after this acute episode and did no longer required calcium supplementation.

The exact amount of calcium administered is shown in Table 2.

The mother was also vitamin D deficient (25-OH-vit D <5 mcg/L, PTH 190 ng/L).

Discussion

The two children presented with hypocalcemia of different etiologies.

The first child presented hypocalcemia with elevated PTH, suggesting vitamin D deficiency. He had several risk factors for vitamin D deficiency: breastfeeding, poor dietary diversification, lack of synthetic vitamin D intake, skin color (2,3,9).

The second child had hypocalcemia with low PTH. In neonates, late onset neonatal hypocalcemia is frequently associated with paradoxically normal or low PTH (1,10). This may be explained by a delayed maturation of the parathyroid axis in the neonatal period (7,11,12). The source of calcium then depends on calcium absorption from the gastrointestinal tract. In vitamin D deficiency, calcium absorption cannot meet bone metabolic requirements. The typical biological findings in this situation are low calcium, normal or high phosphorus, and paradoxically normal or a low PTH as seen in our patient (11,13,14,15,16). In this case, the hypocalcemia is also exacerbated by the intrauterine growth restriction, which reduces calcium intake during the third trimester. Maternal hyperparathyroidism secondary to vitamin D deficiency is also thought to play an inhibitory role in hypoparathyroidism in children (10). This suggests a late-onset neonatal hypocalcemia exacerbated by vitamin D deficiency.

These two cases of symptomatic hypocalcemia with prolonged time to successful resolution, but more importantly, worsening plasma calcium concentrations after initiation of calcium and vitamin D administration, suggest a possible HB-like syndrome. Studies on the treatment of hypocalcemia due to vitamin D deficiency suggest a potential risk of HB-like syndrome if calcium treatment is inadequate at the start of vitamin D supplementation (7,8).

In case 1, we hypothesize that intravenous calcium initiates a flux of calcium from the blood to the bones, stopping the process of calcium resorption from the bones as with rickets ("hungry bone-like"). The first patient presented had several risk factors for HBS described in adults studies: elevated ALP and PTH, and bone lesions from rickets (4,6).

In the second case, there is a physiologically high bone turnover due to the young age, worsened by vitamin D deficiency. We suspect that this high bone turnover is the cause of the worsening of calcemia at the start of treatment, with a shift of calcium from the blood to the growing bone ("hungry bone-like"). There were no signs of rickets or bone injury on the chest x-ray and we did not expect bone abnormalities because there was no elevated PTH and the duration of the calcium deprivation was short. In fact, in neonates, hypocalcemia may be symptomatic before bone changes occur due to the physiological period of high metabolic bone demand (4, 14, 15, 17).

HBS is an uncommon cause of hypocalcemia in children (6). This syndrome is mainly described as a postoperative complication of parathyroidectomy but also during treatment of hyperthyroidism or osteoblastic metastases of prostate or breast cancer (18,19). In all these conditions, there is a phenomenon of high metabolic bone turnover. HBS is characterized by a flow of calcium from the blood to the bones, due to a change from an osteoclastic to an osteoblastic process in the bone, leading to hypocalcemia lasting more than four days despite calcium supplementation (6). It is often associated with hypomagnesemia, hypophosphatemia and hyperkalemia (5,6). In the case of parathyroidectomy, a high bone turnover due to high PTH leads to bone injury. The decrease in PTH after surgery results in a shift from osteoclastic to osteoblastic process and a possible HBS.

There is no clear consensus on the treatment of HBS (20).

Lima Ferreira et al. propose a postoperative management protocol for parathyroidectomy to better manage hypocalcemia by identifying risk factors for HBS, and defining the amount of calcium and calcitriol needed based on blood calcium levels. They demonstrate that implementation of this protocol improves detection of HBS and reduces the duration of hypocalcemia (8).

The amount of calcium required for HBS is highly variable (6-12g/day in adult studies) (20).

Treatment of HB-like syndrome would consist of high-dose calcium and vitamin D administration. In the case of symptomatic hypocalcemia, calcium should be started with a bolus of 1-2 mg elemental calcium/kg followed by a continuous intravenous infusion of 1-3 mg elemental calcium/kg/hour (5). Oral treatment should be started as soon as possible to avoid the side effects of intravenous calcium administration (local irritation, tissue necrosis). Serum calcium levels should be monitored several times a day (every 4-6 hours) to adjust the treatment dose (16). Electrocardiographic monitoring is recommended because rapid changes in serum calcium may induce arrhythmias. The active forms of vitamin D are preferred (calcitriol/alfacalcidol). In our cases, optimization of treatment by increasing the doses of IV calcium and vitamin D administered has made it possible to treat the persistent hypocalcemia.

For the treatment of nutritional rickets, it is recommended to give at least 2000 IU/day of oral vitamin D for 3 months, and the intake of calcium should be 500 mg/day (dietary or supplements) (9). Magnesium treatment must also be initiated, as low magnesium levels exacerbate hypocalcemia (5,6,11,20).

Rickets, dilated cardiomyopathy and convulsions associated with hypocalcemia due to vitamin D deficiency are reversible after normalization of blood levels of vitamin D and calcium (2,3). If a child presents with hypocalcemia associated with dietary vitamin D deficiency, chest x-ray, bone x-ray if rickets is suspected (ankles and wrists, where growth plate enlargement may be seen as they are areas of rapid growth), and cardiac ultrasound should be considered (2, 3, 9).

Conclusion

We describe two cases of persistent hypocalcemia, occurring despite vitamin D and calcium supplementation in children with symptomatic vitamin D deficiency. This may be the consequence of a hungry bone-like syndrome in children whose growth is dependent on bone formation.

The term HBS should be reserved for situations in which a hypercatabolic state is converted to an anabolic process, which is not the case in vitamin D deficiency. Hungry bone-like syndrome could occur during vitamin D and calcium supplementation for hypocalcemia with vitamin D deficiency, especially if the patient has a significant bone turnover. For symptomatic hypocalcemia, calcium should be administered as a bolus and continuous intravenous infusion. If the calcemia falls after calcium administration, it suggests a HB-like syndrome and intravenous calcium bolus and vitamin D supplementation should be used to intensify treatment.

Complications of vitamin D deficiency are completely preventable with a good prevention strategy. It is the role of the pediatrician to educate

parents, monitor at-risk children and ensure that any child presenting with hypocalcemia receives appropriate diagnostic testing to elucidate the cause of hypocalcemia and detect potential complications.

Conflict of interest

The authors have no conflicts of interest in relation to the subject matter of this manuscript.

REFERENCES

1. Basatemur E, Sutcliffe A. Incidence of Hypocalcemic Seizures Due to Vitamin D Deficiency in Children in the United Kingdom and Ireland. J Clin Endocrinol Metab. 2015,100(1):E91–95.
2. Uday S, Fratzl-Zelman N, Roschger P, Klaushofer K, Chikermane A, Saraff V, et al. Cardiac, bone and growth plate manifestations in hypocalcemic infants: revealing the hidden body of the vitamin D deficiency iceberg. BMC Pediatr. 2018,18(1):183.
3. Uday S, Högler W. Nutritional Rickets and Osteomalacia in the Twenty-first Century: Revised Concepts, Public Health, and Prevention Strategies. Curr Osteoporos Rep. 2017,15(4):293–302.
4. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. Pediatrics. 2008;122(2):398 417.
5. Anwar F, Abraham J, Nakshabandi A, Lee E. Treatment of hypocalcemia in hungry bone syndrome: A case report. Int J Surg Case Rep. 2018,51:335–339.
6. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. Eur J Endocrinol. 2013,168(3):R45–53.
7. Kelly A, Levine MA. Hypocalcemia in the Critically Ill patient. J Intensive Care Med. 2013,28(3):166–177.
8. Ferreira JL, de Brito Marques F, Freire L, Soares V, Guerreiro L, Silva S, et al. Intensive calcium monitoring improves outcomes on hungry bone syndrome in hyperparathyroidism. Endocrine Regulations. 2021;55(1):30 41.
9. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016,101(2):394–415.
10. Mayia S, Sullivan I, Alllgrove J, Yates R, Malone M, Brain C, et al. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart. 2008; 94:581-584.
11. Thomas T.C, Smith J.M, White P.C, Adhikari S. Transient neonatal hypocalcemia : presentation and outcomes. Paediatrics. 2012,129(6): 1461-1467.
12. Chou P-C, Lin L-C, Hsu J-H, Yang R-C, Jong Y-J, Dai Z-K, et al. Life-threatening Dilated Cardiomyopathy Induced by Late-onset Neonatal Hypocalcemia. Pedneo. 2016, 57(6):535-538.
13. Hatun S, Ozkan B, Orbak Z, Doneray H, Cizmecioglu F, Toprak D, et al. Vitamin D Deficiency in early Infancy. The Journal of Nutrition. 2005;135(2):279 82.
14. Thandrayen K, Pettifor JM. Maternal Vitamin D Status: Implications for the Development of Infantile Nutritional Rickets. Endocrinology and Metabolism Clinics of North America. 2010;39(2):303 20.
15. Seymen-Karabulut G, Günlemez A, Gökalp AS, Hatun Ş, Kaya Narter F, Mutlu M, et al. Vitamin D Deficiency Prevalence in Late Neonatal Hypocalcemia: A Multicenter Study. Jcrpe. 2021;13(4):384 90.
16. Hsu SC, Levine MA. Perinatal calcium metabolism: physiology and pathophysiology. Seminars in Neonatology. 2004;9(1):23 36.
17. Ashraf A, Mick G, Atchison J, Petrey B, Abdullatif H, McCormick K. Prevalence of Hypovitaminosis D in Early Infantile Hypocalcemia. Journal of Pediatric Endocrinology and Metabolism. 2006;19(8).
18. Garla VV, Salim S, Kovvuru KR, Subauste A. Hungry bone syndrome secondary to prostate cancer successfully treated with radium therapy. BMJ Case Reports. 2018;bcr-2018-225039.
19. Bergkamp FJM, van Berkel AM. Unexpected prolonged extreme hypocalcaemia and an inadequate PTH response in a patient with metastatic breast carcinoma. 2003;61(11).
20. Sakr MF. Chapter 11 Hungry Bone Syndrome. In : Sakr MF. Parathyroid Gland Disorders: Controversies and Debates. Springer; 2022. Available on: https://link.springer.com/10.1007/978-3-031-07418-9.

Vitamine D voor kinderen:
er bestaat iets gemakkelijker dan druppels tellen

VISTA-D3™

SMELTTABLETJES

MADE IN BELGIUM

5 VERSCHILLENDE DOSERINGEN (ie)

- **400 – 600 – 800 – 1000 – 2000 –** (**3000** voor volwassenen)
- **NAUWKEURIGE DOSERING:** geen risico dat de moeder te veel of te weinig geeft

PRAKTISCHE TOEDIENING

- **KLEINE SMELTTABLETJES:** diameter 7 mm
- **MICRODRUPPELS OLIE MET VIT.D BINNEN HET TABLETJE:** goede absorptie zonder olie in de mond
- **KINDEREN:** zuigen of knabbelen
- **KINDEREN MET MALABSORPTIE:** laten smelten onder de tong
- **BABY'S:** oplossen in een lepeltje water of in de zuigfles

ZEER GOED AANVAARD

- **FRISSE, NEUTRALE SMAAK**
- **ZONDER:** lactose, gluten, suiker, synthetische zoetstoffen, kleurstoffen

MINDER DAN 5€ PER MAAND

- **VISTA-D3 400:** 120 smelttabletten
- **VISTA-D3 600:** 120 smelttabletten
- **VISTA-D3 800:** 120 smelttabletten
- **VISTA-D3 1000:** 180 smelttabletten
- **VISTA-D3 2000:** 180 smelttabletten
- **VISTA-D3 3000:** 180 smelttabletten

VISTA-D3, met vista voor uw patientjes

STALEN AANVRAGEN ?
Email uw keuze en postadres naar office@vistalife.be

VISTA®

Acute encephalopathy in a neonate associated with infection by SARS-CoV-2

Margarita Tretjakova, Patricia Leroy, Christophe Barrea

University Hospital of Liège, Department of Paediatric Neurology, Liège, Belgium

margo.tretjakova@gmail.com

Keywords

Epilepsy ; punctuate white matter lesions ; SARS-CoV-2 ; meningo-encephalitis ; neonatal seizures.

Abstract

We present the case of a 5-day-old patient who was admitted to the emergency department with initially unilateral and then generalised seizures and lethargy. Cerebral MRI had shown diffusion-restricted symmetrical fronto-parietal lesions consistent with viral encephalitis due to SARS-COV-2. The control MRI showed signs of necrosis with the appearance of cavitation, predominantly on the left side. Neurological follow-up was performed at 1, 3 and 6 months of age and showed no significant neurodevelopmental delay.

Introduction

Our lives have been significantly affected by the SARS-COV-2 (known as COVID-19) pandemic since early 2020. This virus can cause a variety of disease symptoms ranging from asymptomatic carriers to a multisystem inflammatory syndrome in different age groups. Children appear to be less affected by this virus, often showing milder or no symptoms. However, an increasing number of cases have been reported in the literature describing severe disease, particularly neurological, such as lethargy, irritability, hypotonia, apnoea and seizures in young toddlers (1). We present a case of a neonate affected by COVID-19 with seizures due to encephalopathic white matter lesions.

Case report

The patient was a female born at 39 weeks by caesarean section for breech presentation. There were no other complications. The pregnancy was uneventful, except for controlled maternal hyperthyroidism. The Apgar scores were 9 and 10 at 1 and 5 minutes of life, respectively, and her birth measurements were within the normal range for her gestational age.

The patient was admitted to the emergency department because of abnormal movements and lethargy. In the emergency department, she had two further episodes of clonic movements, which started on the left side and then became generalised. There was no association with fever.

Initial blood tests were normal: normoglycaemia, mild leukopenia with 4340 WBC per microlitre, no other abnormalities in the haemogram, negative C-reactive protein, normal electrolytes, liver, and renal function, and basic coagulation tests showing no abnormalities. Empirical treatment with intravenous cefotaxime, amoxicillin, and acyclovir was started to cover the possibility of neonatal sepsis or herpes simplex virus encephalitis. After negative results of blood, urine and CSF cultures, antibiotics and antiviral treatment were discontinued. The seizures were initially controlled with intravenous phenobarbital and midazolam and then successfully managed with levetiracetam. She had no further convulsions.

On the day of admission, a CT-scan of the brain showed no abnormalities. However, a brain magnetic resonance imaging (MRI) scan showed symmetrical fronto-parietal signal abnormalities and restricted diffusion, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of the corpus callosum, and postero-lateral regions of the thalami (Figure 1). These findings were consistent with neonatal encephalopathy.

A complete metabolic analysis, including blood, urine, and CSF amino acid levels, organic acid levels, and acylcarnitine profile, was performed to rule out a metabolic cause. All the results were normal. In addition, rapid exome sequencing revealed no significant pathological genetic mutations.

Analysis of cerebrospinal fluid (CSF) collected on days 1 and 3 showed normal cytology and normal glucose and protein levels (885 mg/L). A nasal swab tested positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (rt-PCR). No other virus was found in her nasal swab, and we were able to rule out rhinovirus, enterovirus, influenza A&B, parainfluenza 1, 2, 3, 4, coronavirus (non-covid-19), cytomegalovirus (CMV). CMV was also tested by PCR on urine and CSF with negative results.

The patient's father had recently tested positive for SARS-COV-2 following mild respiratory symptoms. Her mother was asymptomatic, but her nasal swab tested positive for SARS-COV-2. The PCR SARS-COV-2 test on the CSF was negative. To exclude other viral causes, we tested the CSF for various neurotropic viruses such as herpes simplex virus types 1&2, enteroviruses, varicella-zoster virus, parechovirus, human herpesvirus 6 and CMV, all of which were negative. The patient had no respiratory symptoms related to her SARS-COV-2 infection, and two chest radiographs taken during her hospitalisation showed no specific abnormalities. Based on these findings, our presumptive diagnosis was viral encephalopathy probably due to SARS-COV-2, as this was the only virus detected.

Follow-up brain MRIs at 10 days (Figure 2) and 6 weeks (Figure 3) showed more defined lesions, reduced inflammation, and the appearance of cavitary zones. Spectroscopic analysis confirmed neuronal loss, supporting providing further evidence of a specific necrotizing encephalitis, with SARS-COV-2 being the only etiological factor detected.

Neurological follow-up at 1, 3, and 6 months of age showed no significant neurodevelopmental delay.

Discussion

There are many causes of neonatal encephalopathy, often related to acute brain injury during the perinatal period (2). The lesions described in this case did not correspond to the classic haemorrhagic or ischaemic lesions. Other aetiologies such as genetic or metabolic syndromes were ruled excluded by laboratory investigations. After excluding all other causes, including metabolic, genetic, haemorrhagic, thrombotic, and other bacterial and viral infections, it was concluded that the encephalopathy was due to SARS-COV-2 infection, which is now known to cause early neurological damage

Figure 1: Day 0. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. Diffusion-weighted image shows a symmetrical restricted diffusion (hyperintensity of b-1000 and decrease of apparent diffusion coefficient) in the fronto-parietal regions, predominantly on the fronto-polar cortex, precentral and central gyrus, anterior and posterior commissures of corpus callosum, and the postero-lateral regions of thalami. It is associated with discreet flair hyperintensity in the same region. Also a discreet bilateral contrast enhancement in fronto-parietal leptomeninges is present.

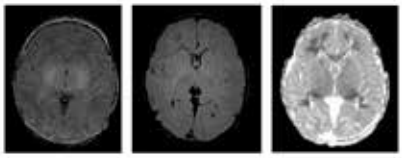


Figure 2: Day 10. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. The first image shows hyperintense lesions in the white matter, especially in the frontal and the parietal regions. The frontal white matter shows signs of necrosis. Diffusion - restricted lesions are found in the corpus callosum.

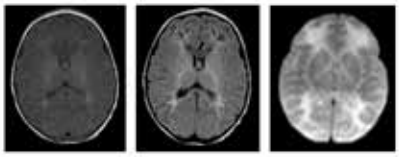
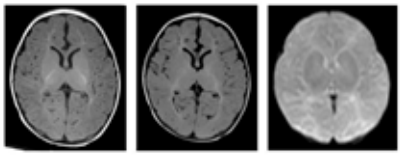


Figure 3: Week 6. From left to right: cerebral MRI in T1, FLAIR, and diffusion-weighted image. This MRI shows the regression of the diffusion restricted lesions, followed by the appearance of white matter lesions in the frontal cortex with the appearance of cavitation, predominantly on the left side.



in neonates (1). We emphasise on the fact that this diagnosis remains presumptive, as it is a diagnosis of exclusion.

Similar neurological lesions have been described in other viral encephalopathies, often associated with rotaviruses or enteroviruses (3, 4). Three similar cases associated with SARS-COV-2 infection have been (5-7). All cases had white matter lesions with restricted diffusion particularly in the corpus callosum and periventricular white matter. Our case, as well as a case described by Fragoso in 2022, showed cytotoxic white matter lesions transitioning into cavities. None of the described cases presented with respiratory symptoms. Of these cases, only one patient was treated with corticoids, in contrast to our patient (5).

The exact mechanism of these neurological lesions remains unclear. In none of these cases was SARS-COV-2 directly detected in the CSF. According to the International Encephalitis Consortium, the CSF pleocytosis is supportive, but not a necessary criterion for encephalitis, particularly in young infants. The major diagnostic criterion is an altered mental status lasting more than 24 hours without an alternative cause as evidence of neurological dysfunction. In addition, at least two additional minor criteria must be present, namely: fever ≥38°C within 72 hours, seizures, new focal neurological findings, CSF pleocytosis (≥5 white blood cells/μL), neuroimaging with brain parenchymal changes, or an electroencephalogram consistent with encephalitis (8). Young infants are more prone to have infectious encephalitis without pleocytosis, for example with enterovirus or parechovirus infections (8). Some authors suggest that central nervous system lesions may result from the virus accessing the central nervous system (CNS) directly or via an excessive cytokine release mechanism (1). The cytokine storm syndrome typically manifests as persistent fever, cytopenia, a high erythrocyte sedimentation rate, increased fibrinogen, and hyperferritinemia (5). However, our patient did not have any of these abnormalities. Studies conducted by Lindan have shown that the most commonly observed neuroimaging manifestation in children, not only neonates, is similar in appearance to ADEM (acute disseminated encephalomyelitis), with patchy or confluent areas of T2 hyperintensity in the grey and white matter, with or without reduced diffusion or enhancement (9).

We would like to emphasize that neurological symptoms due to SARS-CoV-2 represent a non-negligible proportion of affected neonates. A review of the literature on SARS-CoV-2 in neonates (both term and preterm) by Moraes et al in 2022 analysed data from a total of 87 neonates (1). Of these, 23% were asymptomatic. Those with symptoms usually had respiratory symptoms (57.5%) such as respiratory distress, tachypnoea, cough, and coryza. A total of 26.4% had fever. Neurological symptoms were observed in 26.4% of neonates, with lethargy being the most common (9.2%). Gastrointestinal symptoms such as vomiting, feeding intolerance and abdominal distension were seen in 21.8% of patients.

The long-term prognosis of affected children remains uncertain. The neurodevelopment of our patient seems to be completely normal at the age of 3 and 6 months of age, but it should be noted that the prefrontal regions become functional much later. Some other authors conducted a case-control study of newborns diagnosed with SARS-CoV-2 in Wuhan, China (10). A total of five newborns with SARS-CoV-2 were included. Despite a significant difference in the Hammersmith neonatal neurological examination score between infected and non-infected groups at the time of initial evaluation, there was no significant difference in neurobehaviour at 9 months of age. Larger studies with longer follow-up are needed to fully understand the impact of early-onset SARS-CoV-2 encephalitis.

Conclusion

Although our diagnosis is by exclusion and remains presumptive, it is important to consider SARS-CoV-2 infection in neonates presenting with atypical symptoms such as seizures, even in the absenceof respiratory distress. Imaging findings were also non-specific, although they are characteristic of viral encephalitis. Therefore, paediatricians should be aware of these possibilities and test for SARS-CoV-2 in patients with seizures and no other systemic involvement.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES

1. de Moraes FM, de Souza J, Alves LP, de Siqueira MFR, Dos Santos APA, de Carvalho Berardo MM, et al. SARS-CoV-2 Infection and Possible Neonatal Neurological Outcomes: A Literature Review. Viruses. 2022;14(5).
2. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):185-91.
3. Kim M, Hwang JY, Lee YJ, Kim YW, Byun SY, Lee YJ, et al. Clinical and Imaging Findings of Neonatal Seizures Presenting as Diffuse Cerebral White Matter Abnormality on Diffusion-Weighted Imaging without any Structural or Metabolic Etiology. Taehan Yongsang Uihakhoe Chi. 2020;81(6):1412-23.
4. Yeom JS, Park JS, Kim YS, Kim RB, Choi DS, Chung JY, et al. Neonatal seizures and white matter injury: Role of rotavirus infection and probiotics. Brain Dev. 2019;41(1):19-28.
5. Fragoso DC, Marx C, Dutra BG, da Silva CJ, da Silva PM, Martins Maia Junior AC, et al. COVID-19 as a Cause of Acute Neonatal Encephalitis and Cerebral Cytotoxic Edema. Pediatr Infect Dis J. 2021;40(7):e270-e1.
6. Yildiz H, Yarci E, Bozdemir SE, Ozdinc Kizilay N, Mengi S, Beskardesler N, et al. COVID-19-Associated Cerebral White Matter Injury in a Newborn Infant With Afebrile Seizure. Pediatr Infect Dis J. 2021;40(7):e268-e9.
7. Martin PJ, Felker M, Radhakrishnan R. MR Imaging Findings in a Neonate With COVID -19-Associated Encephalitis. Pediatr Neurol. 2021;119:48-9.
8. Messacar K, Fischer M, Dominguez SR, Tyler KL, Abzug MJ. Encephalitis in US Children. Infect Dis Clin North Am. 2018;32(1):145-62.
9. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health. 2021;5(3):167-77.
10. Yan K, Xiao FF, Jiang YW, Xiao TT, Zhang DJ, Yuan WH, et al. Effects of SARS-CoV-2 infection on neuroimaging and neurobehavior in neonates. World J Pediatr. 2021;17(2):171-9.

INFATRINI

CLINIQUEMENT PROUVÉ[2,15-17]

Notre référence pour le retard de croissance

De 0 à 18 mois ou jusqu'à un poids de 9 kg

- **Conforme aux recommandations de l'OMS** pour le rattrapage de croissance: min. 8,9-11,5 %En de protéines.[1]
- **Notre mélange de prébiotiques** unique **scGOS/lcFOS** qui soutient le microbiote intestinal[5]
- **Nutrition médicale complète pour les nourrissons** (10 %En de protéines)
- Bilan **azoté positif** dès le J1[15]
- **Ratio de protéines complètes de lactosérum et de caséine 60:40** ce qui facilite la vidange gastrique, réduit les vomissements et les réflexes nauséeux[6-9]
- **LCPs (DHA et ARA)** qui soutiennent l'acuité visuelle et le développement cognitif[3,4]
- **Faible osmolarité pour une meilleure tolérance**[8] ce qui réduit le risque de reflux gastro-oesophagien[11] et/ou diarrhée osmotique[12]
- **Nucléotides** qui stimulent le système immunitaire[10]
- **Formule prête à l'emploi**, ce qui diminue le risque de contamination ou d'erreurs de préparation[13, 14*]
- 40 % **de micronutriments** en plus par 100 ml qu'une préparation pour nourrissons enrichie en énergie, pour répondre aux besoins des nourrissons avec un plus petit volume[2]
- Formule qui convient **en cas de restriction de volume**
- Disponible en **alimentation orale et par sonde**

NUTRICIA

Prenez contact avec nos diététiciens de La Careline de Nutricia:
0800 99 486 • medical.nutrition@nutricia.be • www.nutricia.be
E.R. : Danone Belux S.A. Quai des Usines 160, 1000 Bruxelles

Scannez le QR code pour plus d'informations sur Infatrini

*** pour Infatrini 125 ml, 500 ml**

Important : L'allaitement maternel est l'alimentation idéale pour les nourrissons. Infatrini est une denrée alimentaire destinée à des fins médicales spéciales pour les besoins nutritionnels des nourrissons dénutris, à risque de dénutrition ou en cas de retard de croissance. A utiliser sous contrôle médical après avoir envisagé toutes les options possibles notamment l'allaitement maternel. Informations uniquement pour le corps (para)médical.

Références : 1. WHO Protein and amino acid requirements in human nutrition: Report of a joint FAO/WHO/UNU expert consultation (technical report series 935). 2007. **2.** Clarke S.E. et al. J Hum Nutr Diet 2007; 20, pp. 329–339 **3.** Birch EE et al. Am J Clin Nut 2010;91:848-59. **4.** Birch EE et al. Early Hum Devel **5.** Moro G et al. J Pediatr Gastroenterol Nutr 2002; 34: 291-295 **6.** Fried MD et al. J Pediatr 1992; 120(4): 569–572. **7.** Billeaud C et al. Eur J Clin Nutr 1990; 44(8):577–583. **8.** Brun AC et al. Abstract accepted at 30th ESPEN. Florence, Italy. 13–16 September 2008. **9.** Graham-Parker C et al. JPEN J Parenter Enteral Nutr 2001; 25(Suppl 14):Abstract 0051 **10.** Carver JD, et al. Pediatrics. 1991;88(2):359–63 **11.** Sutphen JL & Dillard VL. Gastroenterology 1989;97(3):601-604 **12.** Kukuruzovic RH & Brewster DR. J Paediatr Child Health 2002;38(6):571-7 **13.** Clarke SE et al. J. Hum. Nutr. Diet. 2007; 20 (4): 329-339. **14.** Mathus-vliegen EMH et al. JPEN J Parenter Enteral Nutr. 2006;30(6):519-25. **15.** Van Waardenburg DA et al. Clin Nutr. 2009;28(3):249-55 **16.** Evans S, et al. J Hum Nutr Diet 2006; 19: 191-7 **17.** De Betue CT, et al. Arch Dis Child 2011; 96: 817-22

Failure to thrive and hypergammaglobulinemia in a 13-year-old girl with Castleman Disease, a case report

Helene Van Parys [a], David Tuerlinckx [a], Christophe Chantrain [b], Joan Somja [c], Dominique Beckers [a]

[a] Department of Pediatrics, CHU UCL Namur, Yvoir and Namur, Belgium
[b] Department of Pediatrics, CHC Mont Legia, Liège, Belgium., Belgium
[c] Department of Anatomy and Cellular Pathology, CHU Liège, Belgium , Belgium

helenevanparys@gmail.com

Keywords

Failure to thrive – Castleman Disease – Hypergammaglobulinemia - Lymphoproliferation.

Abstract

Castleman Disease is a rare, lymphoproliferative, non-malignant disorder with two subtypes, unicentric or multicentric, depending on the number of lymph node regions affected. Clinical symptoms may be extremely variable often making the diagnosis difficult or leading to delayed diagnosis. We describe a case of failure to thrive associated with late puberty, and severe hypergammaglobulinemia. Through this case report, we aim to recall the clinical features of this rare disorder and to insist on the importance of a broad differential diagnosis in the presence of failure to thrive especially with abnormal biochemical features.

Introduction

Failure to thrive (FTT) and late puberty are most frequently associated with endocrinopathies, syndromes, anorexia nervosa, inflammatory bowel disease or other chronic conditions. However, as we demonstrate in our case, Castleman Disease (CD), a rare and non-malignant lymphoproliferative disorder with very heterogeneous clinical phenotypes, should also be considered in the differential diagnosis. We describe the case of FTT associated with hypergammaglobulinemia and an inflammatory suprarenal mass.

Case report

We report the case of a 13-year-old girl who presented with FTT associated with late puberty (Figure 1). She has no past medical history and both her parents are healthy. Her birth weight and height were 2740 g and 49 cm, respectively. She has a healthy twin sister who is taller than her (BMI 17,2 kg/m^2, -1 SD). The patient's target height is 170 cm (0,6 SD).

Figure 1:
Body Mass Index curve (Flanders, 2004), red arrow indicates the time of surgery.

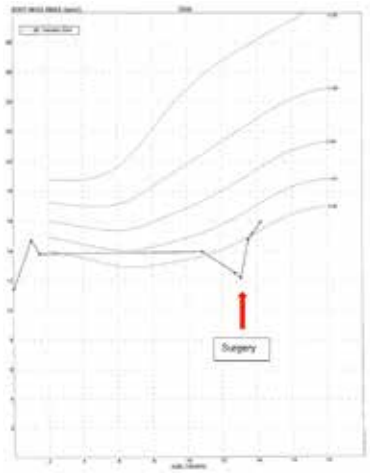
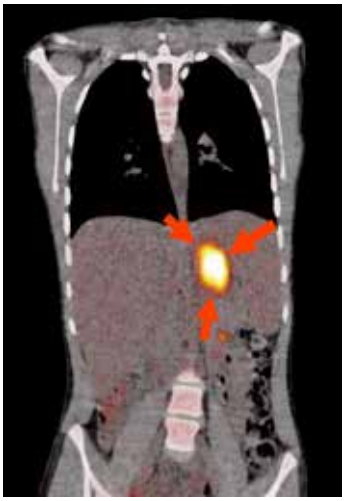


Figure 2:
PET-CT shows a hypermetabolic lesion in the left suprarenal fossa.



In addition to FTT and late puberty, the main symptoms were fatigue, a subfebrile state and a lack of appetite leading to often unfinished meals but frequent snacking. The possibility of anorexia nervosa was excluded based on the absence of food restrictions or the fear of gaining weight. She did not report any digestive symptoms but recalled a blood spot on the toilet paper.

On clinical examination, she was in good condition but lean and pale with a height of 148,8 cm (-1,5 SD); a weight of 27,1 kg (-3,6 SD); BMI of 12,2 kg/m^2 (-4,0 SD) and Tanner stage A1P1M1. She had no dysmorphic features and her vital signs were completely normal.

Complementary investigations revealed an anemia of chronic disease (Hb 7,7 g/dl [N 12-16], hematocrit 27.2% [N 36-46], MCV 63.1 µm3 [N 78-100], reticulocytosis 46.1x103/µl), elevated C-Reactive Protein (CRP 164.4 mg/L [N <5 mg/L]), elevated sedimentation rate (120 mm/h, [N 0-11 mm/h]) normal white blood cell count (7.72x103/µl), elevated platelets (432x103/µl) and normal levels of liver enzymes. Endocrine assessment was normal for prolactin, TSH and free T4, and FSH, LH, estradiol and IGF-1 in the prepubertal range.

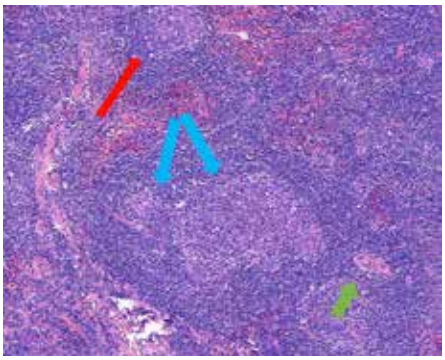
Fecal calprotectin, IgA transglutaminase, anti-Neutrophil cytoplasmic antibodies (ANCA), antisaccharomyces cerevisiae antibodies (ASCA), abdominal ultrasound, gastric endoscopy and colonoscopy were normal.

The following additional workup was performed: tuberculin intradermal test, chest x-ray, lymphocyte typing, and antinuclear factor, all of which were normal. However, a severe hypergammaglobulinemia (total IgG 26,17 g/L [N 5,8-14,5 g/L]) was found.

PET-CT showed a hypermetabolic lesion in the left suprarenal fossa (Figure 2). Transgastric biopsy was performed through echo-

endoscopy. Histologic sections (Figure 3) of the lymph node showed a mainly preserved architecture with hyperplastic lymphoid follicles of various sizes. Some showed slightly atrophic germinal centers surrounded by enlarged mantle cuffs sometimes arranged in concentric rings. Increased vascularity with penetration of radially-oriented hyalinized blood vessels in the germinal centers was also focally observed. Immunohistochemical staining was unremarkable and negative for human herpesvirus-8 disease. The Ebstein-Barr encoding region was negative. There was no evidence of Immunoglobulin heavy chain clonality on molecular analysis. The IgG4/IgG ratio was not elevated and there was no significant amount of IgG4 plasma cells. Folliculolysis and pictures reminiscent of progressive germinal center transformation were also observed. Overall, the histopathologic findings were consistent with a reactive germinal center with Castleman-like modifications.

Figure 3:
Biopsy sample of a suprarenal lymph node, magnification x5, stained with hematoxylin and eosin, shows twinning of the germinal centers (blue arrows), atrophic germinal center with concentric distribution of the mantle cuff (red arrow) and slightly hyalinized vessels penetrating the mantle zone (green arrow).



The suprarenal mass (5,5 cm x 4,5 cm x 3 cm) was surgically resected and the proposed diagnosis of unicentric Castleman Disease was confirmed histologically.. Subsequently, rapid remission ensued with restored appetite, weight gain, and onset of puberty observed. Likewise, biochemical parameters improved rapidly, including normalization of the gamma globulin levels. One year later, there were no signs of recurrence.

Discussion

This case illustrates the need for a stepwise but comprehensive biochemical and imaging workup in the setting of failure to thrive.

We first ruled out the most common diagnoses and then investigated rarer causes. Anorexia nervosa, endocrinopathy and chronic infectious disease were quickly ruled out based on the patient's behavior, endocrine and microbiologic analyses and gastroenterologic workup.

Severe hypergammaglobulinemia (>25g/l) orientated our diagnostic approach. In the largest cohort study of 442 pediatric patients with hypergammaglobulinemia (>20 g/L), Lo et al. reported that 95% of patients had identifiable disorders with nearly half of the patients affected by autoimmune diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease, as well as infectious diseases (EBV, CMV, HIV) and less commonly malignant, drug-related, and other diseases including CD (1).The authors observed that, higher IgG levels, lower white blood cell count, lower hemoglobin levels, lower C-reactive protein levels, as well as female gender were independent risk factors for autoimmune diseases.

Our patient presented with hypergammaglobulinemia and only the low hemoglobin level and the female gender were also in favor of autoimmune / autoinflammatory disease, but extensive workup ruled out such diseases. There was no evidence of chronic infectious disease. Biopsy samples of the suprarenal mass led to the exclusion of malignancy but confirmed reactional lymphoid hyperplasia with Castleman-like modifications.

First described by Benjamin Castleman in 1958, CD is divided into two subtypes depending on the number of affected lymph nodes. Unicentric Castleman Disease (UCD) involves one or more lymph nodes in a single region of the body with similar histopathologic features. UCD is a slowly progressive disease with no specific clinical manifestations (2). Multicentric Castleman Disease (MCD) involves multiple affected lymph node areas, with similar histopathologic characteristics. Patients with MCD present with systemic symptoms and generalized lymphadenopathy, hepatosplenomegaly, cytopenia and organ failure due to inflammatory cytokine secretion (3). In their 2015 study, Munshi et al. estimated the annual incidence of CD in the United States to be between 6500 and 7700 new cases, of which 75% were with UCD, which had a better outcome than patients with MCD (4).

The etiology of CD is unclear. Typical histopathologic aspects of affected lymph nodes are reactive changes, which could be observed with abnormal antigenic stimulation or in a low-grade neoplastic process (5). In the MCD subtype, half of the cases are associated with HHV8 infection, and the other half are HHV8-negative, termed idiopathic MCD (iMCD) (3). Immunological mechanisms such as elevated IL-6 levels are thought to mediate the lymphoproliferative mechanisms. The expression of a viral analog of IL-6 (vIL-6) by HHV-8 may play a role in the downstream mediation of plasmacytosis in the setting of HHV-8 infection (6). Nabel et al. suspected that UCD and or HHV8 negative MCD could be caused by other viruses, but they failed to establish a clear association with any other virus (7). Pediatric CD has similar clinical features compared to adult patients, but the disease mechanism may be different because most adult cases occur in a context of immunodeficiency associated with HIV and/or HHV-8 infection. In children, CD appears to be caused by a primary dysregulation of the immune system (8). In their 2018 retrospective cohort study, Sopfe et al, reported that 75% of their pediatric patients presented with UCD (9). As in our patient, children often present with systemic manifestations such as weight loss, chronic fatigue, fever, and abnormal laboratory results such as elevated erythrocyte sedimentation rate and CRP, microcytic anemia, thrombocytosis and hypergammaglobulinemia (9).

Diagnosis of CD is based on histopathologic findings and is classified into one of two subtypes - hyaline-vascular or mixed/plasmacytic subtype. The histologic differential diagnosis should include malignancies (Hodgkin lymphoma, Non-Hodgkin lymphoma, sarcoma), inflammatory diseases (SLE, systemic-onset juvenile idiopathic arthritis, Sjögren syndrome) or infectious diseases (EBV, CMV, HIV) (5).

The best treatment for UCD is surgery. If complete, surgical resection is usually curative. If surgery is incomplete, radiotherapy or embolization are complementary treatment options. In some cases of limited accessibility, simple clinical surveillance may be considered. Outcomes are excellent with no impact on life expectancy (9).

Although not curative, the management of MCD aims to limit complications due to inflammation and to improve patients' quality of life. In the past, corticosteroids and chemotherapy were used as first line treatments when surgery was not possible. However, their benefits were limited and adverse effects were considerable (8). Currently, new biologic therapies are available including anti-CD20, anti-IL1, and anti-IL6.The current first-line treatment suggested for pediatric patients with MCD is the use of tocilizumab, an anti-IL-6 receptor monoclonal antibody, but recommendations regarding treatment duration and adverse effects are still expected (8, 10).

Conclusion

Castleman Disease is a rare and clinically heterogeneous disorder frequently associated with FTT in children, systemic manifestations, and hypergammaglobulinemia. The diagnostic workup should include autoimmune/autoinflammatory diseases, infectious diseases, malignancies or lymphoproliferative disorders such as CD.

The prognosis of UCD, the most common form of CD in children, is generally excellent after surgical excision with rapid resolution of symptoms. The inflammatory symptoms associated with MCD are alleviated with new biologic therapies that help to improve patients' quality of life.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES

1. Lo MS, Zurakowski D, Son MB, Sundel RP. Hypergammaglobulinemia in the pediatric population as a marker for underlying autoimmune disease: a retrospective cohort study. Pediatr Rheumatol Online J. 2013;11(1):42.
2. Wang S, Chen S, Xu J, Cai S. Clinicopathological characteristics of unicentric retroperitoneal Castleman's disease: a study of 14 cases. World J Surg Oncol. 2016;14(1):3.
3. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of Castleman disease. Cancer Control. 2014;21(4):266-78.
4. Munshi N, Mehra M, van de Velde H, Desai A, Potluri R, Vermeulen J. Use of a claims database to characterize and estimate the incidence rate for Castleman disease. Leuk Lymphoma. 2015;56(5):1252-60.
5. Oksenhendler E. Protocole National de Diagnostic et de Soins (PNDS) Maladie de Castleman 2019 [cited 2023 April 18]:[40 p.]. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2019-11/pnds_castleman_2019.pdf.
6. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. Br J Haematol. 2005;129(1):3-17.
7. Nabel CS, Sameroff S, Shilling D, Alapat D, Ruth JR, Kawano M, et al. Virome capture sequencing does not identify active viral infection in unicentric and idiopathic multicentric Castleman disease. PLoS One. 2019;14(6):e0218660.
8. Borocco C, Ballot-Schmit C, Ackermann O, Aladjidi N, Delaleu J, Giacobbi-Milet V, et al. The French paediatric cohort of Castleman disease: a retrospective report of 23 patients. Orphanet J Rare Dis. 2020;15(1):95.
9. Sopfe J, Endres A, Campbell K, Hayes K, Trout AT, Liang X, et al. Castleman disease in pediatrics: Insights on presentation, treatment, and outcomes from a two-site retrospective cohort study. Pediatr Blood Cancer. 2019;66(5):e27613.
10. Galeotti C, Boucheron A, Guillaume S, Koné-Paut I. Sustained remission of multicentric Castleman disease in children treated with tocilizumab, an anti-interleukin-6 receptor antibody. Mol Cancer Ther. 2012;11(8):1623-6.

Verzacht doeltreffend de huid met neiging tot atopie
geeft rust aan de ouders.

Herlipiderende crème anti-jeuk

99% ingrediënten van natuurlijke oorsprong

COSMETIQUE BIO CHARTE COSMEBIO

Zonder parfum

Verzacht onmiddellijk

Anti-recidief

ECO CERT COSMOS ORGANIC

Sporadic colorectal adenocarcinoma in children: an uncommon diagnosis

Gaëtane Massart [a], Christine Devalck [b], Kalliroy Kotilea [c], Laurine Verset [d], Safiatou Diallo [b]

[a] Université libre de Bruxelles (ULB), Brussels University Hospital, Queen Fabiola Children's University Hospital, Department of Pediatrics, Brussels, Belgium
[b] Université libre de Bruxelles (ULB), Brussels University Hospital, Queen Fabiola Children's University Hospital, Department of Pediatric Oncology, Brussels, Belgium
[c] Université libre de Bruxelles (ULB), Brussels University Hospital, Queen Fabiola Children's University Hospital, Department of Pediatric Gastroenterology, Brussels, Belgium
[d] Université libre de Bruxelles (ULB), Brussels University Hospital, Jules Bordet Institute, Department of Anatomical Pathology, Brussels, Belgium

gaetane.massart@gmail.com

Keywords

Colorectal cancer ; mucinous adenocarcinoma ; children.

Abstract

Colorectal cancer (CRC) is rare in the pediatric population. Low incidence and disease awareness among pediatricians often leads to delayed diagnosis. Compared with adult CRC, pediatric CRC is characterized by an advanced clinical stage at diagnosis and a higher frequency of unfavorable histopathology. We report the case of an 11-year-old boy diagnosed with an adenocarcinoma of the ascending colon without any predisposing factors.

Introduction

In the European Union, colorectal cancer is estimated to account for 12.7% of all new cancer diagnoses and 12.4% of all cancer deaths in 2020. It is the second most common cancer in adults after breast cancer and the second most common cause of cancer death in adults after lung cancer (1). In contrast, CRC is rare in children and adolescents, with an estimated annual incidence of one case per million (2).

Many small series and case reports suggest that children are more likely to present with advanced-stage disease than adults. This phenomenon can be explained by the non-specific symptoms and low awareness of the disease, leading to delayed diagnosis, and by the fact that the tumors found in children are often aggressive with unfavorable histology, suggesting a different pathophysiology.

Clinical case

An 11-year-old boy presented to the emergency department with a 3-month history of abdominal pain and weight loss of 2 kg.

He had been referred 1 month earlier by his general physician for hematochezia. Constipation was diagnosed at that time based on the history and the presence of a small anal fissure scar. A treatment was initiated. On admission, the pain had been increasing for one week and was associated with vomiting, nausea, and fever. He had no medical history except for asthma and no history of travel.

Physical examination revealed a relatively distended abdomen with diffuse rebound and tenderness, right lumbar pain and palpable stool. His vital signs were normal.

Abdominal ultrasound showed a distension of the right colonic frame with suspicion of paralytic ileus. The evaluation was completed with abdominal radiography and a computed tomography, which demonstrated the presence of a right colic flexure-centered mass causing intestinal subocclusion (Figures 1 A and B). Intestinal wall thickening and multiple adenopathies were also seen. A malignant lesion was suspected, yet tumor markers (CEA (carcinoembryonic antigen) and NSE (neuron-specific enolase)) were negative.

Figure 1:
A. An Abdominal X-ray was done at first showing air-fluid levels and a right paravertebral calcification at L2 level.
B. Abdominal computed tomography showed the presence of a right colic flexure centered mass causing intestinal subocclusion.

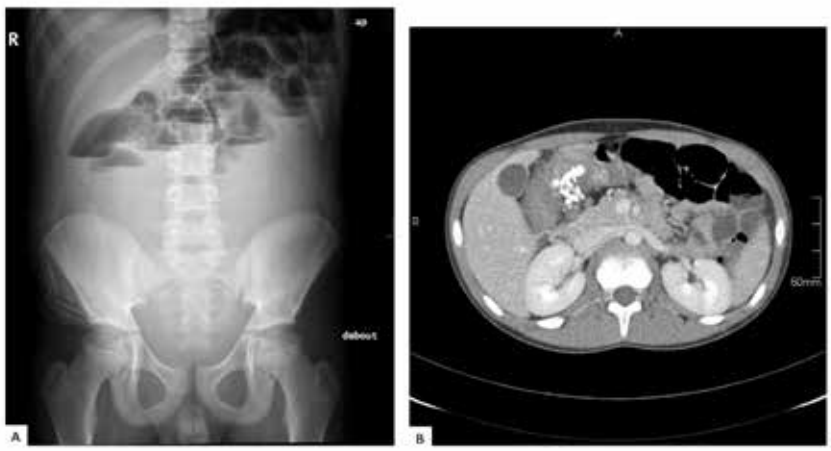


Figure 2:
A and B : Colonoscopy showed an annular, irregular mass with an ulcerated aspect totally obstructing the lumen.

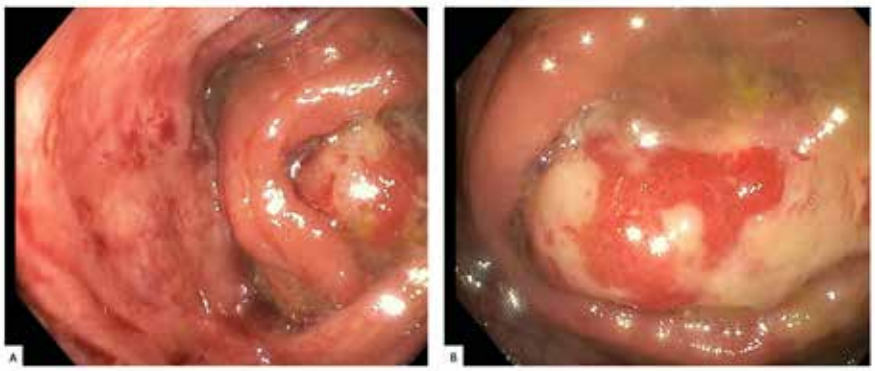
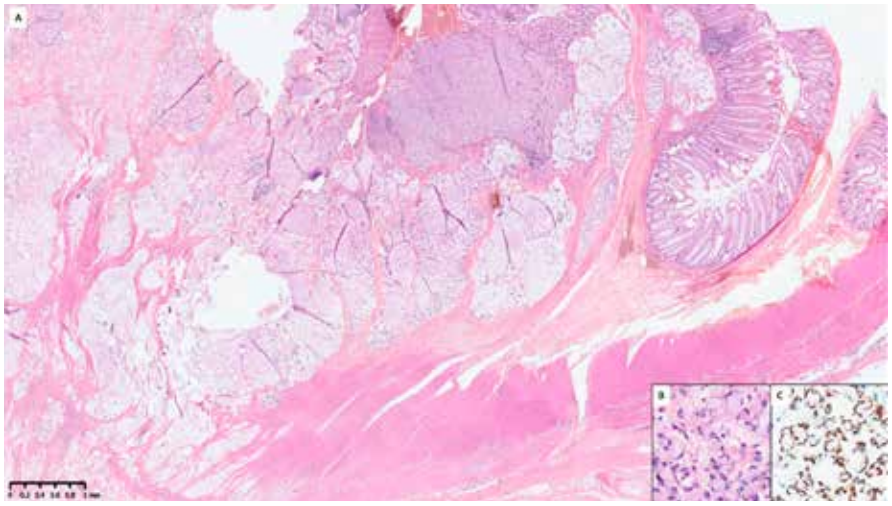


Figure 3:
A. Histopathology of the lesion. H&E staining of the tissue showing tumoral lesions characterized by abundant extracellular mucin with numerous floating signet-ring cells.
B. H&E staining - x40- Isolated tumor cells with an eccentric nucleus and mucus vacuole.
C. x40- Immunohistochemical stains are positive for Anti-CDX2, which is a transcription factor expressed in case of intestinal differentiation.
H&E = hematoxylin and eosin.



A diagnostic laparoscopic surgery with concomitant colonoscopy was scheduled. An annular colon tumor with an ulcerated aspect was found in the right colonic frame, obstructing the lumen (Figures 2 A and B). Pathology of the tumor and lymph node biopsies revealed abundant extracellular mucin with numerous floating signet-ring cells, supporting the diagnosis of mucinous adenocarcinoma (Figure 3 A and B).

A right hemicolectomy was performed. Final pathology results confirmed high-grade mucinous adenocarcinoma extending through the visceral peritoneum. Seven lymph nodes out of the sixty-three removed were metastatic. There was no evidence of metastatic disease to the liver, and the preoperative PET scan was negative. The final staging was pT4aN2bMx according to the 8th edition of the Union for International Cancer Control.

The immunohistochemical profile of the tumor was CK20/CDK2/MUC2 confirming the colic origin, but no evidence of microsatellite instability was found (Figure 3C). Next-generation sequencing of the samples revealed no mutations in the *NRAS*, *KRAS* and *BRAF* genes, but identified a presumed pathogenic point mutation in the tumor suppressor gene *TP53*, a gene associated in about 40 to 50% of sporadic colorectal cancer cases in adults.

A constitutional mutation of TP53 was ruled out.. Further genetic testing for inherited cancer susceptibility syndromes (Hereditary Non-Polyposis Colorectal Cancer, Familial Adenomatous Polyposis (FAP), MUTYH-associated polyposis, Peutz-Jeghers syndrome, Juvenile polyposis syndrome and Cowden syndrome) was also negative.

The patient underwent a FOLFOX chemotherapy regimen consisting of 1 cycle of intravenous 5-fluoruracil and oxaliplatin every 2 weeks. To date, he has completed thirteen cycles of chemotherapy without complication. Follow-up imaging studies have shown no evidence of recurrent disease.

Discussion

While it is one of the most frequent malignancies among adults, colorectal cancer is a rare tumor in the pediatric population, with an incidence of approximately 1 per million. A recently published population-based study using the SEER database (1973-2005) calculated an age-adjusted incidence rate of 0.38 and 802 per million for children/adolescents and adults respectively (2).

Much of the existing literature focuses on young adults or "early-onset" colorectal cancer (< 50 years of age), while fewer series or studies focus on children or adolescents. The largest database study to date was published by Poles et al. in 2015. Using the National Cancer Database, they compared pediatric, early-onset, and older adult patients with a total of 918 pediatric patients (≤ 21 years) (3).

Common presenting signs and symptoms are abdominal pain, vomiting, altered bowel habits, weight loss and hematochezia. However, these are often underestimated because they are nonspecific and can mimic many common functional gastrointestinal disorders in children. In our case, the patient had a history of hematochezia with presence of a small anal fissure scar caused by constipation, itself due to the tumor.

As illustrated by our case, pediatric colorectal cancer is unanimously characterized in the literature by a high occurrence of aggressive histologic subtypes: poorly differentiated, signet-ring or mucinous adenocarcinoma. The cause of this observation has not been elucidated to date. Still, it is suggested that pediatric CRC may have a different pathophysiological process compared to the well-known multistep development described in adult CRC (which usually occurs over approximately 10 years) (4). It has been demonstrated that even in adult CRC, there are significant differences in molecular alterations between mucinous and non-mucinous colorectal adenocarcinoma. Mucinous colorectal adenocarcinoma is characterized by an overexpression of the MUC2 and MUC5AC proteins, high-frequency microsatellite instability and mutations of the *RAS/MAPK* pathway (5).

High-frequency microsatellite instability (MSI) is caused by defects in the mismatch repair system (MMR). It has been found mainly in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) but also in about 15% of sporadic CRC in adults. Few articles suggest a more frequent occurrence of MSI in early-onset sporadic colorectal carcinomas than in late-onset tumors. Furthermore, a different pattern of genetic alterations between both groups has been suggested to cause the altered function of the MMR system. (6-7)

An advanced stage at diagnosis is also a hallmark of pediatric CRC. This is illustrated in the population-based study by Poles et al., in which 62% of

pediatric patients presented with stage 3 and 4 disease at presentation, compared to 49.7% and 37.3% in the early-onset adult and older adult populations respectively (3).

The reason why children present more often at a later stage than adults is still unclear, but the possible explanations include an intrinsically more aggressive behavior of the disease and a delayed diagnosis, itself due to low incidence, non-specific symptoms and lack of awareness by physicians. In their review, Hill et al. compared patients whose time to diagnosis was less than 2 months (20 patients) with those whose diagnosis occurred 2-6 months (12 patients) after symptom onset. This comparison showed that patients with a longer delay to diagnosis tended to have a lower disease stage (p= 0.063) and better overall survival (p=0.014), making it less likely that delayed diagnosis alone explains advanced disease at presentation (8).

CRC most frequently develops sporadically in children. The main known predisposing factors are inflammatory bowel disease and inherited cancer susceptibility syndromes such as FAP and HNPCC, which are inherited autosomal dominant disorders associated with early-onset tumors. However, they seem less frequent in the pediatric population, representing an average of 10% of the cases (9). Several authors, such as Weber et al., have presented evidence suggesting that pediatric patients with predisposing syndromes (mainly HNPCC) have a better prognosis than those with sporadic disease (10).

However, in the case of HNPCC, strict adherence to follow-up guidelines does not seem to explain this observed better prognosis as there are currently no specific recommendations for the follow-up of children. The onset of surveillance colonoscopy is advised to be stratified based on the associated gene, with 25 years being the earliest recommended age.

To date, there are no therapeutic recommendations specific to pediatric CRC, so adult protocols are used. Surgery is considered the keystone of the treatment and should be radical. Complete surgical resection and lymph node dissection are decisive for cure. Saab et al. reported that the common factors among long-term survivors of pediatric CRC were low-stage disease and complete resection.

Depending on the disease stage, surgery may be followed by adjuvant chemotherapy. Oxaliplatin and 5–fluorouracil–based antineoplastic agents are commonly used chemotherapy combinations. For patients with metastatic disease, resection of all metastatic lesions is needed. Therefore, neoadjuvant chemotherapy may be advised (9).

Predictors of poor outcome in addition to disease stage are incomplete resection, mucinous histology, proportion of signet-ring cells > 10 %, and the absence of an in-situ component (2, 8).

Pediatric CRC is also characterized in the literature by a poorer survival rate than in adults. In the population-based study by Sultan et al. using the SEER database, the estimated 5 and 10 years overall survival rates were 40% ± 4,2% and 31% ± 4,4% respectively, in the children/adolescent population. This compares to 60 % ± 0,1% and 54 % ± 0,1% in the adult population. They also observed an improved outcome over time in adults, while no major differences were observed in children and adolescents (2).

Conclusion

Pediatric CRC differs from adult-onset CRC in several aspects. It is characterized by a high occurrence of aggressive histologic subtypes, an advanced clinical stage at diagnosis and, probably due to these aforementioned aspects, a poorer prognosis than adults.

There is evidence that an intrinsically different tumor biology may partially explain these features. In the absence of specific pediatric treatment recommendations, adult protocols are currently used. However, given the possibility of a different pathogenesis, the response to treatment may also be different from adult cancers. This is supported by the fact that even within adult populations, early-onset colorectal cancer is associated with differences in tumor behavior. With this in mind, further studies are needed to adapt the management of pediatric CRC, starting with a better understanding of the physiopathological process.

Due to its rarity and the non-specific nature of the symptoms, it is challenging to provide specific recommendations to general pediatricians regarding suspicion of CRC. Our suggestion is to be vigilant for warning signs and to emphasize the need to re-evaluating the outcomes of any therapeutic intervention.

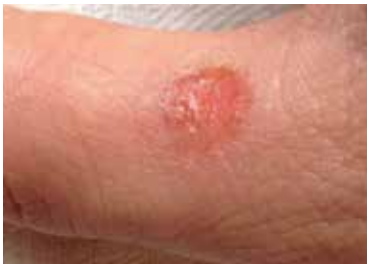
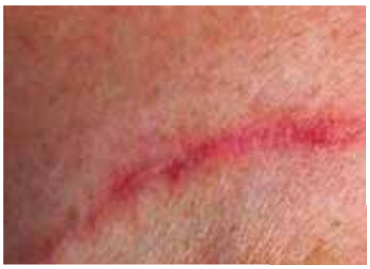
Conflict of interest

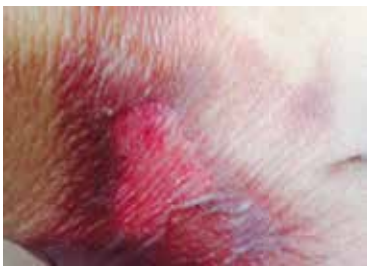
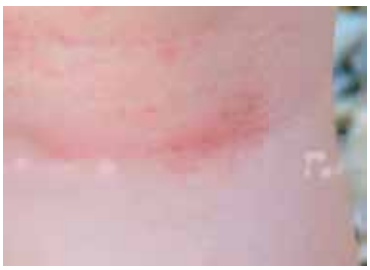
The authors have no conflicts of interest to declare with regard to the topic discussed in this manuscript.

REFERENCES

1. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. nov 2021;157:308-47.
2. Sultan I, Rodriguez-Galindo C, El-Taani H, Pastore G, Casanova M, Gallino G, et al. Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. Cancer. 1 févr 2010;116(3):758-65.
3. Poles GC, Clark DE, Mayo SW, Beierle EA, Goldfarb M, Gow KW, et al. Colorectal carcinoma in pediatric patients: A comparison with adult tumors, treatment and outcomes from the National Cancer Database. J Pediatr Surg. juill 2016;51(7):1061-6.
4. Kim G, Baik SH, Lee KY, Hur H, Min BS, Lyu CJ, et al. Colon carcinoma in childhood: review of the literature with four case reports. Int J Colorectal Dis. févr 2013;28(2):157-64.
5. Luo C, Cen S, Ding G, Wu W. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options. Cancer Commun (Lond). 29 mars 2019;39(1):13.
6. Khan SA, Morris M, Idrees K, Gimbel MI, Rosenberg S, Zeng Z, et al. Colorectal cancer in the very young: a comparative study of tumor markers, pathology and survival in early onset and adult onset patients. J Pediatr Surg. nov 2016;51(11):1812-7.
7. Kim HC, Kim CN, Yu CS, Roh SA, Kim JC. Methylation of the hMLH1 and hMSH2 promoter in early-onset sporadic colorectal carcinomas with microsatellite instability. Int J Colorectal Dis. mai 2003;18(3):196-202.
8. Hill DA, Furman WL, Billups CA, Riedley SE, Cain AM, Rao BN, et al. Colorectal carcinoma in childhood and adolescence: a clinicopathologic review. J Clin Oncol. 20 déc 2007;25(36):5808-14.
9. Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. Paediatr Drugs. 2008;10(3):177-92.
10. Weber ML, Schneider DT, Offenmüller S, Kaatsch P, Einsiedel HG, Benesch M, et al. Pediatric Colorectal Carcinoma is Associated With Excellent Outcome in the Context of Cancer Predisposition Syndromes. Pediatr Blood Cancer. avr 2016;63(4):611-7.

LA ROCHE POSAY
LABORATOIRE DERMATOLOGIQUE

CICAPLAST BAUME B5+

BAUME **RÉPARATEUR APAISANT**
MULTI-INDICATIONS

Visage · Corps · Zones intimes

Nourrissons · Enfants · Adultes

FORMULE UNIQUE

40ml - CNK: 4488-649
100ml - CNK: 4488-656

EFFICACITÉ RÉPARATRICE

NOUVEAU [TRIBIOMA]
Rééquilibre le microbiome

[MADÉCASSOSIDE]
Accélère la réparation épidermique

[CUIVRE + ZINC + MANGANÈSE]
Agents assainissants

[BEURRE DE KARITÉ + GLYCÉRINE]
Relipide et hydrate

FORCE APAISANTE

[5% PANTHÉNOL]
Soulage intensément
les sensations d'inconfort

TOLÉRANCE et EFFICACITÉ

Prouvées sur **20 000 PATIENTS**
(1 semaine à 97 ans)
et **21 LÉSIONS DIFFÉRENTES**
sous contrôle pédiatrique
et dermatologique

TEXTURE BAUME
Non grasse. Non collante.
SANS PARFUM - SANS ALCOOL

LA ROCHE-POSAY. L'EXIGENCE DERMATOLOGIQUE.
www.laroche-posay.be

Birth-related neonatal rib fracture: a case report

Annelies Van den Sande [a], Thomas Gestels [a], Karlijn Van Damme [b], Amanda Trompenaars [b]

[a] University of Antwerp, Antwerp University Hospital, Department of Paediatrics, Edegem, Belgium
[b] University of Antwerp, Antwerp University Hospital, Department of Neonatology, Edegem, Belgium

annelies.vandensande@outlook.be

Keywords

Rib fracture ; birth injury ; neonate ; case report.

Abstract

Rib fractures due to birth trauma are rare, other mechanisms of trauma need to be considered. We report the case of a large for gestational age newborn in the maternity ward with an isolated rib fracture due to birth trauma. Birth was complicated with shoulder dystocia after a vacuum extraction.

Introduction

Bone fractures resulting from birth trauma are not uncommon. Clavicle fractures are the most common with an incidence of up to 3.2% (1). Fractures also occur at other sites, such as the femur, humerus or skull. Rib fractures, however, are rare. Rib fractures are usually localised in multiple ribs and are often accompanied by clavicle fractures (2,3). In this article, we present a case study of a newborn with an isolated rib fracture, aiming to draw attention to this less common form of birth trauma.

Case report

Following an uncomplicated pregnancy a boy was born at a gestational age of 40 weeks and 5 days to a G1P0 mother. During vaginal delivery, vacuum extraction was necessary because of prolonged second stage of delivery. In total three tractions were needed. The delivery was complicated by shoulder dystocia. Suprapubic pressure and McRoberts manoeuvre were needed to lift the shoulder dystocia. APGAR-score was 7 at 1 minute and 9 at 5 minutes after birth. Birth weight was 4,220 gram (93th centile). Physical examination immediately after birth (day 1) showed normal, symmetrical movements and reflexes, and a caput succedaneum. Twelve hours after admission to the maternity ward, the mother heard a cracking sound during movement of the right arm, which reappeared the day after. A second physical examination on the first day was normal. On day 2, however, physical examination revealed a distinct cracking sound when the right arm was moved and a 'crack' could be felt under the right scapula. Range of motion of the arm was normal, apart from abduction of the right shoulder, which was limited to 75°. There were no signs of Erb's or Klumpke's paresis. There was no sign of pain during the clinical examination. A chest radiograph showed no clear fractures of the humerus and scapula, but there was uncertainty regarding a possible fracture at the level of the anterior part of the third and fourth rib. According to the radiology department, a rib fracture following a complicated birth would be expected to occur posteriorly rather than anteriorly. The familial history was negative for underlying diseases causing bone fractures. There were no arguments for non-accidental injury. On day 3, the cracking sound was still heard during spontaneous, painless movements. There was no residual limitation of movement of the right arm and shoulder. The boy was discharged from the hospital. Conservative treatment with physiotherapy was started. At follow-up after one week, the parents reported that their child sometimes cried when changing clothes, but there were no signs of pain when picking him up. The cracking sound diminished, but was still present. Clinical examination withheld a cracking feeling at the right side of the back, but no movement limitations. An anterior-posterior oblique ('3/4') radiograph (Figures 1 and 2) showed a minimally displaced fracture posterolateral to the seventh rib on the right side. As full recovery was expected, no clinical follow-up was scheduled. A telephone follow-up at nine months reported that the 'crack' had disappeared and motor development was normal.

Figure 1: fracture of posterolateral side of the right 7th rib.

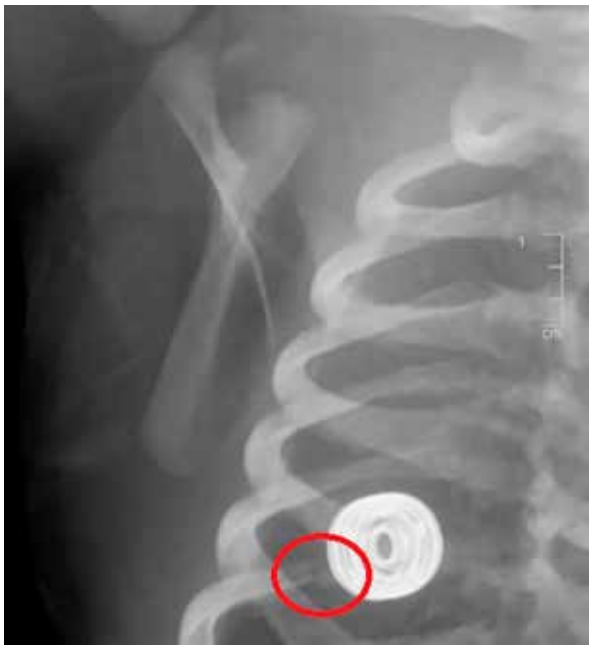
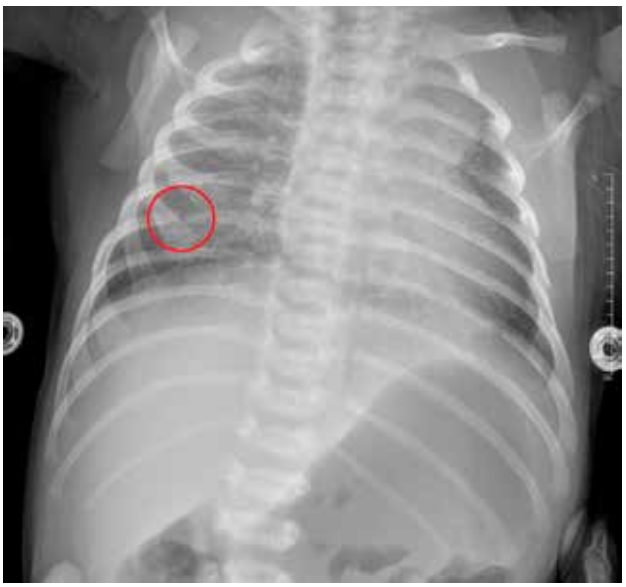


Figure 2: Fracture of posterolateral side of the right 7th rib, anterior-posterior oblique view.



Discussion

The incidence of fractures in the neonatal period varies amongst different studies. A single centre study in the United Kingdom by Rehm et al. mentioned a 0.075% fracture rate amongst all live births (1). In a nationwide Swedish study, conducted by Högberg et al., a 0.29% fracture rate was observed in all newborns (2). Another single centre study, conducted in Wales by Wei et al., reported a fracture rate of 1.6% in the neonatal intensive care department, which included more premature infants having metabolic bone disease (4). The incidence of fractures is possibly underestimated because children might lack symptoms and not every child will get a radiological evaluation.

Up to 95.5% of all neonatal fractures are located in the clavicle, with maternal short stature or obesity, large for gestational age child, instrumental delivery and shoulder dystocia being the main risk factors (2).

Very little literature is available on rib fractures due to birth trauma in the neonatal period. Van Rijn et al. reviewed all 10 published cases of rib fractures caused by birth trauma until 2008 and added 3 new cases. In all cases rib fractures were located in multiple ribs; in 6 cases an associated ipsilateral clavicle fracture was found and 9 out of 13 neonates were large for gestational age with birth weight >4 kg (3). In the study conducted by Rehm et al., one rib fracture was found in a total of 66 fractures in 84,761 live births. (1) In the nationwide Swedish study mentioned above, only 10 out of 5,336 fractures (= 0.002%) found in 1,855,267 live born neonates were rib fractures. In all of the cases rib fractures were associated with an ipsilateral clavicle fracture. Half of them had a birth weight over 4kg, four of them had shoulder dystocia and in four cases vacuum extraction was used. (2) In our case the neonate was large for gestational age (>4kg) and birth was complicated by shoulder dystocia. The rib fracture was not associated with a clavicle fracture and it was localized in only one rib, which is rare considering in all previously published cases, multiple rib fractures were found.

Birth trauma as a cause of rib fractures is very rare, therefore it is always necessary to consider other differential diagnoses. Firstly, non-accidental injury (NAI) has to be excluded. No studies on NAI and rib fractures that includes only neonates are available. Barsness et al. reported a positive predictive value of 95% for rib fractures as an indicator of NAI in children under the age of 3 (5). In two studies in infants by Bulloch et al. and Cadzow and Armstong, respectively 82% and 83% of rib fractures were caused by NAI (6,7). Differentiating birth trauma from non-accidental injury is difficult, since both have similar trauma mechanisms and predispose to a similar type of rib fractures. In some forms of NAI, the abuser applies anterior-posterior compression to the thorax when encircling the thorax with both hands, shaking and gripping the child with consequent anterior displacement of the vertebrae. This pressure results most often in posterior rib fractures, but also lateral fractures. Childbirth also circular exerts pressure on the thorax through the narrow birth canal, combined with rotational forces, leverage over the pubic symphysis and relative fixation of one side of the thorax, resulting in mid-posterior, unilateral rib fracture (3,8). A second differential diagnosis for neonatal rib fractures is cardiopulmonary resuscitation (CPR). CPR results in rib fractures in 0-2% of resuscitations. After changing the technique of CPR from the two-finger technique to the two-thumbs method, some studies reported an increase in rib fractures, while others did not (9). Thirdly, accidental injury can result in neonatal rib fractures as well. In the study by Högberg et al. 7.4% of fractures in neonates were caused by accidental trauma, 92.6% by birth trauma (2). At last, several underlying conditions and diseases can predispose to rib fractures. In premature neonates metabolic bone disease facilitates fractures. Osteogenesis imperfecta (OI), hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH) have also been described as predisposing to neonatal rib fractures (3).

Chest radiograph is the golden standard for diagnosing fractures. Considering the fracture site is mainly posterior, anterior-posterior oblique views are necessary to image rib fractures as they might be missed in normal anterior-posterior views, as was in our case. Ultrasound can be a safe alternative to X-ray in diagnosing fractures. A recent study by Liu indicates 100% sensitivity and specificity of ultrasound for detecting fractures in infants (10).

No specific guideline is available for treatment of rib fractures in neonates. In general a conservative approach is chosen with adequate analgesia and physiotherapy for mobilisation and positioning.

We suggest the following work-up for neonates with rib fractures. First, it is important to conduct a thorough anamnesis to detect risk factors of NAI and to screen for genetic predisposition to underlying conditions such as OI or FHH. Secondly, a full clinical investigation is carried out, searching for other fractures, bruises or signs of associated diseases such as blue sclerae in OI. Severe hyperparathyroidism and OI often result in multiple fractures, although in NAI also multiple fractures can be found (3). Associated clavicle fractures can point to birth trauma. Thirdly, when in doubt of the diagnosis of rib fractures, X-rays with oblique views can be helpful; if necessary additional radiographs can be made to exclude fractures in other sites. Finally, in cases with an aberrant family history, multiple fracture sites, other clinical features and no indications for traumatic birth, a blood test for underlying diseases is indicated, including calcium, phosphorus, alkaline phosphatase, parathormone and vitamin D levels (3). Additional genetic testing can be considered.

In our case, the lack of arguments for NAI, the negative family history and clinical investigation were reassuring. X-rays for the diagnosis of the posterior rib fracture showed no other fracture sites. The birth weight was high (>4kg), vacuum extraction was carried out and birth was complicated with shoulder dystocia, three arguments that increase the risk of birth trauma. Therefore no further work-up was carried out.

Conclusion

Rib fractures in neonates due to birth trauma are rare. Risk factors might be a large for gestational age child, instrumental delivery, shoulder dystocia and associated clavicle fractures. Always consider alternative trauma mechanisms such as non-accidental injury or underlying diseases. The golden standard for diagnosing rib fractures due to birth trauma is chest X-ray, including oblique views since the fracture site is usually posterior.

Conflict of interest

The authors have no conflict of interest to declare.

Informed consent

Written informed consent was obtained from the parents of the patient for publication of this article.

REFERENCES

1. Rehm A, Promod P, Ogilvy-Stuart A. Neonatal birth fractures: a retrospective tertiary maternity hospital review. J Obstet Gynaecol. 2020;40(4):485-90.
2. Hogberg U, Fellman V, Thiblin I, Karlsson R, Wester K. Difficult birth is the main contributor to birth-related fracture and accidents to other neonatal fractures. Acta Paediatr. 2020;109(10):2040-48.
3. van Rijn RR, Bilo RA, Robben SG. Birth-related mid-posterior rib fractures in neonates: a report of three cases (and a possible fourth case) and a review of the literature. Pediatr Radiol. 2009;39(1):30-34.
4. Wei C, Stevens J, Harrison S, Mott A, Warner J. Fractures in a tertiary Neonatal Intensive Care Unit in Wales. Acta Paediatr. 2012;101(6):587-90.
5. Barsness KA, Cha ES, Bensard DD, Calkins CM, Partrick DA, Karrer FM, et al. The positive predictive value of rib fractures as an indicator of nonaccidental trauma in children. J Trauma. 2003;54(6):1107-10.
6. Bulloch B, Schubert CJ, Brophy PD, Johnson N, Reed MH, Shapiro RA. Cause and clinical characteristics of rib fractures in infants. Pediatrics. 2000;105(4):E48.
7. Cadzow SP, Armstrong KL. Rib fractures in infants: red alert! The clinical features, investigations and child protection outcomes. J Paediatr Child Health. 2000;36(4):322-6.
8. Worn MJ, Jones MD. Rib fractures in infancy: establishing the mechanisms of cause from the injuries--a literature review. Med Sci Law. 2007;47(3):200-12.
9. Franke I, Pingen A, Schiffmann H, Vogel M, Vlajnic D, Ganschow R, et al. Cardiopulmonary resuscitation (CPR)-related posterior rib fractures in neonates and infants following recommended changes in CPR techniques. Child Abuse Negl. 2014;38(7):1267-74.
10. Liu J, Zhang L, Qiu RX. Ultrasound Instead of X-Ray to Diagnose Neonatal Fractures: A Feasibility Study Based on a Case Series. Front Pediatr. 2022;10:847776.

ENTEROL® 250 mg

Saccharomyces boulardii CNCM I-745

10	10,32 €	10	10,32 €	10	10,32 €
20	19,36 €	20	19,36 €	20	19,36 €
50	38,96 €				

BIOCODEX Benelux

ESSENTIELE GEGEVENS. NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie. Enterol 250 mg harde capsules. *Saccharomyces boulardii* CNCM I-745. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 10^9 levensvatbare cellen op het ogenblik van de fabricage en 1 x 10^9 gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 10^9 levensvatbare cellen op het ogenblik van de fabricage en 1 x 10^9 gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect (zie rubriek 4.4 van de SKP): Enterol 250 mg poeder voor orale suspensie: fructose, lactosemonohydraat, sorbitol. Enterol 250 mg harde capsules: lactosemonohydraat. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS Therapeutische indicaties • Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door *Clostridium difficile* of hervallen in een diarree veroorzaakt door *Clostridium difficile*. • Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. Dosering en wijze van toediening Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: • Harde capsules: de harde capsules met wat water inslikken. • Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen (zie rubriek 4.4 van de SKP). Duur van de behandeling Preventie van een nieuwe episode of recidief van diarree door *Clostridium difficile*: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties • Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP vermelde hulpstoffen. • Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie (zie rubriek 4.4 van de SKP). • Allergie voor gisten, vooral *Saccharomyces boulardii* CNCM I-745. Bijwerkingen De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥1/1.000, < 1/100), zelden (≥ 1/10.000, < 1/1.000), zeer zelden (< 1/10.000), niet bekend (kan met de beschikbare gegevens niet worden bepaald). Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden: fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745. Frequentie niet bekend: sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden: anafylactische shock Bloedvataandoeningen Zeer zelden: anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden: dyspneu Maagdarmstelselaandoeningen Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden: jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden: dorst Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem (Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg.be). HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Marie Curiesquare 20 - 1070 Brussel - België Tel: 0032(0)23704790. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026. Enterol 250 mg harde capsules in glazen flesje: BE 269035. Enterol 250 mg harde capsules in blisterverpakking: BE 397896. AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 01/2023. Goedkeuring: 03/2023.

2023_ENT_HCP_007

New insight in sepsis capillary leak syndrome: alpha 1 AMPK, from the comprehension of key molecular mechanisms to the exploration of a new therapeutic approach

PhD thesis presented on 4 March 2021 at the UCLouvain, Brussels, Belgium

Marine Angé [a,b]
Promoter: Sandrine Horman [a]
Co-promoter: Diego Castanares-Zapatero [a,c]

[a] Pôle de Recherche Cardiovasculaire (CARD), Institut de Recherche Expérimentale et Clinique (IREC), UCLouvain, Brussels, Belgium
[b] Division of Pediatrics, Cliniques Universitaires Saint Luc, Brussels, Belgium
[c] Division of Intensive Care, Cliniques Universitaires Saint Luc, Brussels, Belgium

marine.ange@hubruxelles.be

Keywords

alpha 1 AMPK ; sepsis ; canagliflozin ; endothelial permeability ; VE-cadherin ; connexin 43 ; heat shock protein 27 ; actin cytoskeleton.

Introduction

Sepsis is a major health concern worldwide, and is defined as a syndrome of dysregulated host response to infection causing life-threatening organ dysfunction.

Despite significant advances in the understanding of the disease, the therapeutic management of septic patients primarily relies on supportive care and mortality rates remain unacceptably high, around 40% (1). Sepsis capillary leak syndrome (SCLS), mainly caused by vascular hyperpermeability, is a critical process in sepsis pathophysiology and has been demonstrated to be an independent prognostic factor of survival (2). Moreover, growing evidence supports that maintenance of vascular barrier integrity improves sepsis outcome (3). However, no therapeutic proposal that targets SCLS has so far reached the clinical trial stage. SCLS is caused by vascular barrier disruption. Under healthy conditions, endothelial cells are sealed to one another by inter-endothelial junctions (IEJs) that effectively control the passage of molecules in a size-selective manner. Vascular endothelial cadherin (VE-Cad), the major component of adherens junctions (AJs), is a protein essentially involved in this regulation (4). Its stability depends on the actin cytoskeleton, whose polymerization is notably regulated by the phosphorylation of heat-shock protein of 27 kDa (HSP27), downstream of the p38 MAP kinase (p38MAPK) (5). Upon sepsis, stress mediators trigger signalling cascades that induce actin cytoskeleton contraction, AJs disruption, and loss of endothelial barrier function (6). This event is characterized by the formation of intercellular gaps, leading to plasma leaking through the endothelium and resulting in widespread oedema, finally compromising microcirculation (7).

The catalytic subunit of AMP-activated protein kinase (AMPK) is primarily expressed under its α1-isoform within the microvascular endothelium; there, it acts as a major regulator of the actin cytoskeleton and IEJs (8).

Canagliflozin, an inhibitor of sodium-glucose co-transporter 2 (SGLT2i), is currently prescribed as oral glucose-lowering agent to patients with diabetes. Independently of modulating glucose transport, clinically relevant canagliflozin concentrations also activate AMPK in different cell types, including human endothelial cells (9).

Interestingly, in addition to increasing renal glucose excretion, strong evidence supports that canagliflozin exerts significant cardiovascular protective effects, whose exact mechanisms are still poorly understood (10). On account of its effect on AMPK activity, we hypothesized that canagliflozin may constitute a new therapeutic option to target SCLS. In this thesis, we aimed (a) to characterize the role of endothelial α1AMPK in endothelial barrier function during sepsis, (b) to identify the molecular mechanisms involved in this regulation (c) to demonstrate the potential (AMPK dependent) protective effect of canagliflozin against SCLS.

Methods

α1AMPK expression and/or activity was modulated in human dermal microvascular endothelial cells (HMECs) using either α1AMPK-targeting small interfering RNA or the direct pharmacological AMPK activator 991, prior to lipopolysaccharide (LPS) treatment. Western blotting was used to analyse the expression and/or phosphorylation of proteins that compose cellular junctions (zonula occludens-1 (ZO-1), vascular endothelial cadherin (VE-Cad), connexin 43 (Cx43)), or that regulate actin cytoskeleton (p38 MAPK; heat shock protein 27 (HSP27)). Functional endothelial permeability was assessed by *in vitro* Transwell assays, and quantification of cellular junctions in the plasma membrane was assessed by immunofluorescence. Actin cytoskeleton remodelling was evaluated through actin fluorescent staining.

A mouse model of specific and conditional endothelial α1AMPK deletion was generated (e-AMPK WT/KO). Canagliflozin was administered by oral gavage, and endotoxemia was induced by intraperitoneal injections of sublethal doses of LPS. Capillary leak was monitored with Evans Blue Dye (EBD) and plasmatic albumin levels.

Results

First, we have demonstrated the pivotal role of α1AMPK in the regulation of endothelial barrier function. *In vitro*, we described that α1AMPK invalidation is associated with increased endothelial permeability, while AMPK activation by 991 leads to endothelial barrier reinforcement against LPS injury. In vivo, EBD detection on myocardial sections showed that specific endothelial α1AMPK deletion is associated with increased vascular leakage in response to endotoxemia, while its pharmacological activation protects against this mechanism in e-AMPK WT, but not KO animals.

Second, we investigated the underlying molecular mechanisms of this protective effect, and demonstrated that α1AMPK deficiency is associated

with reduced expression of CX43, ZO-1, and VE-Cad. The drastic loss of CX43 is likely responsible for the subsequent decreased expression and localization of ZO-1 and VE-Cad in the plasma membrane of endothelial cells. Moreover, α1AMPK activation by 991 protects against LPS-induced endothelial barrier disruption by reinforcing cortical actin cytoskeleton. This is due to a mechanism that involves the phosphorylation of p38 MAPK and HSP27, which is nonetheless independent of the small GTPase Rac1.

Third, we described protectives effects of canagliflozin on endothelial barrier function submitted to sepsis conditions. *In vitro*, we reproduced the protective effects previously described with the pharmacological activator 991. We described that their abrogation appears inconstant in AMPK depleted cells, indicating that AMPK-independent mechanisms seem involved. In vivo, canagliflozin administration drastically reduced LPS-induced myocardial oedema and maintained albumin plasma levels. Endotoxemia-induced myocardial oedema and hypoalbuminemia persisted despite canagliflozin treatment in e-AMPK KO animals, demonstrating that canagliflozin protection involves endothelial α1AMPK. We confirmed that this protection involves both activation of p38MAPK/HSP27 pathway and preservation of VE-Cad integrity.

Finally, we validated these results in human endothelial cells submitted to human plasma collected from volunteers (HV) or septic shock (SS) patients. Immunostainings show that both HV and SS plasma affect VE-Cad architecture, with SS plasma inducing higher VE-Cad disruption. Of major interest, canagliflozin importantly preserved VE-Cad integrity while slightly enhancing its membrane expression in HMECs exposed to both HV and SS plasma.

REFERENCES

1. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016;193(3):259-72.
2. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care. 2015;19(1):251.
3. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascón GA, et al. THE ENDOTHELIUM IN SEPSIS. Shock. 2016;45(3):259-70.
4. Giannotta M, Trani M, Dejana E. VE-cadherin and endothelial adherens junctions: active guardians of vascular integrity. Dev Cell. 2013;26(5):441-54.
5. Guay J, Lambert H, Gingras-Breton G, Lavoie JN, Huot J, Landry J. Regulation of actin filament dynamics by p38 map kinase-mediated phosphorylation of heat shock protein 27. J Cell Sci. 1997;110 (Pt 3):357-68.
6. Lampugnani MG, Dejana E, Giampietro C. Vascular Endothelial (VE)-Cadherin, Endothelial Adherens Junctions, and Vascular Disease. Cold Spring Harb Perspect Biol. 2018;10(10).
7. Lee WL, Slutsky AS. Sepsis and endothelial permeability. N Engl J Med. 2010;363(7):689-91.
8. Angé M, Castanares-Zapatero D, De Poortere J, Dufeys C, Courtoy GE, Bouzin C, et al. α1AMP-Activated Protein Kinase Protects against Lipopolysaccharide-Induced Endothelial Barrier Disruption via Junctional Reinforcement and Activation of the p38 MAPK/HSP27 Pathway. Int J Mol Sci. 2020;21(15).
9. Hawley SA, Ford RJ, Smith BK, Gowans GJ, Mancini SJ, Pitt RD, et al. The Na+/Glucose Cotransporter Inhibitor Canagliflozin Activates AMPK by Inhibiting Mitochondrial Function and Increasing Cellular AMP Levels. Diabetes. 2016;65(9):2784-94.
10. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9.

IMPORTANCE DE L'HYDRATATION DU NOURRISSON DURANT LA PÉRIODE HIVERNALE

Chez les nourrissons et les jeunes enfants, le maintien d'un apport adéquat en liquides est physiologiquement important tout au long de l'année. Cependant, il faut être particulièrement vigilant en hiver, saison durant laquelle le risque de nombreuses infections dont les principaux symptômes sont associés à une déshydratation est accru.[1,2]

La masse corporelle des nouveau-nés est composée d'environ 75% d'eau. Ce pourcentage diminue rapidement au cours de la première année de vie pour atteindre 60%, et reste relativement stable tout au long de l'enfance jusqu'à l'adolescence. La maturation progressive de la fonction rénale vers 2 ans ainsi qu'un rapport surface corporelle/masse corporelle plus élevé, se traduisant par une perte d'eau plus importante à travers la peau, expliquent en partie pourquoi les besoins en eau sont plus élevés chez l'enfant par rapport aux adultes.[1]

L'EFSA (European Food Safety Authority) a défini les apports adéquats en fonction des groupes d'âge (Tableau). Néanmoins, ces besoins peuvent varier d'un nourrisson à l'autre, et l'apport adéquat nécessite parfois un ajustement en fonction du niveau d'activité et des conditions environnementales telles que la chaleur et l'humidité.[3]

Recommandation de l'EFSA sur les apports adéquats en eau chez les nourrissons de 0 à 36 mois.

Groupe d'âge	Apports adéquats
0-6 mois	100-190 ml/kg sous forme de lait
6 à 12 mois	800-1000 ml/jour
1 à 2 ans	1100-1200 ml/jour
2 à 3 ans	1300 ml/jour

Les nourrissons et les jeunes enfants sont particulièrement sensibles aux maladies diarrhéiques et à la déshydratation en raison d'un métabolisme plus élevé, de leur incapacité à communiquer leurs besoins ou à s'hydrater eux-mêmes, d'une transpiration plus importante au cours des premiers mois de la vie, ou de processus pathologiques entraînant une perte de liquide.[4]

Déshydratation chez le nourrisson: attention aux maladies hivernales

Dans la majorité des cas, la déshydratation des nourrissons est la conséquence d'une gastro-entérite, affection fréquente pendant les mois d'hiver, responsable de symptômes favorisant les pertes hydriques: diarrhée, vomissements et fièvre.[4]

Les infections virales, notamment les rotavirus, les norovirus et les entérovirus, sont à l'origine de 75 à 90 % des cas de diarrhée infectieuse. En cas d'infection bactérienne, les principaux agents pathogènes incluent Salmonella, Shigella et Escherichia coli.[4]

Une hydratation adéquate des tissus corporels est essentielle à la santé et à la vie. Une perte de poids corporel, qui correspond à une perte d'eau corporelle, d'environ 1% est normalement compensée dans les 24 heures. En l'absence de compensation et lorsque les pertes d'eau corporelle continuent d'augmenter, des réductions des performances physiques et cognitives, de la thermorégulation et de la fonction cardiovasculaire se produisent. Une perte de 10% ou plus d'eau corporelle peut être fatale.[3]

Recommandations pour la consommation d'eau par les nourrissons

L'eau qui convient généralement à l'alimentation des nourrissons comprend l'eau de source répondant aux normes de sécurité et l'eau en bouteille commerciale (eau de source naturelle ou eau traitée à faible teneur en minéraux).[5] Dans le choix de la source d'eau utilisée soit comme boisson, soit dans la préparation du lait maternisé, il est important de veiller à ce que celle-ci contient un minimum de nitrates, source potentielle d'intoxication.[6] Dans tous les cas de figure, l'eau utilisée pour l'alimentation des nourrissons doit être stérilisée pour les enfants de moins de 4 mois.[5]

En cas de perte d'eau pendant une maladie (fièvre, diarrhée...), il faut continuer à donner du lait maternel ou une préparation pour nour-rissons plutôt que de l'eau, afin d'éviter des déséquilibres électrolytiques. Une thérapie de réhydratation orale peut être nécessaire.[5]

L'eau est essentielle à la vie, elle est également essentielle pour le devenir des nourrissons. En effet, l'acquisition d'habitudes de consommation saines est importante dès la petite enfance car de nombreux comportements alimentaires acquis pendant l'enfance persistent à l'âge adulte. Les enfants qui boivent peu d'eau deviendront des adultes qui en boivent peu, avec des conséquences potentielles sur la santé rénale et métabolique ainsi que sur les troubles cognitifs et de l'humeur.[1]

Références:

1. Bottin J. H. et al., Hydration in Children: What Do We Know and Why Does it Matter? Annals of Nutrition & Metabolism 2019; 74(3): 11–18. **2**. Childhood winter illnesses - Knowing what to do. NHS. **3**. Scientific Opinion on Dietary Reference Values for water. EFSA Journal 2010; 8(3): 1459. **4**.Vega R. M. et Avva U., Pediatric Dehydration [Updated 2022 May 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436022/ **5**. Nutrition Guideline: Healthy Infants and Young Children – Water. Alberta Health Services, November 2013. P 6.1.1-6.1.5. https://www.albertahealthservices.ca/ **6**. Greer F. R. et Shannon M., American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Committee on Environmental Health. Infant methemoglobinemia: the role of dietary nitrate in food and water. Pediatrics 2005; 116(3): 784-786

Working towards an optimal nutritional status in people with Cystic Fibrosis

PhD thesis presented on 25/08/2022 at Ghent University, Ghent, Belgium

Dimitri Declercq [abcd]

Promoters: Stephanie Van Biervliet [ad], Bruno Lapauw [de]

[a] Cystic Fibrosis Reference Centre, Department of Paediatrics, Ghent University Hospital, Ghent, Belgium.
[b] Department of Paediatrics, Centre for children and adolescents with diabetes, Ghent University Hospital, Ghent, Belgium.
[c] Centre for Nutrition and Dietetics, Ghent University Hospital, Ghent, Belgium.
[d] Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium.
[e] Department of Endocrinology, Ghent University Hospital, Ghent, Belgium.

Dimitri.Declercq@uzgent.be

Keywords

Cystic Fibrosis, nutritional status, sodium, sodium status, enteral nutrition, enteral tube feeding, cystic fibrosis related diabetes, continuous glucose monitoring.

Background

Cystic Fibrosis (CF) is an autosomal recessive disease caused by cystic fibrosis transmembrane conductance regulator (CFTR)-gene mutations affecting chloride secretion, sodium reabsorption, and water transport in epithelial cells. This leads to dehydrated mucus secretions impacting multiple organs (1, 2). Exocrine pancreatic insufficiency (EPI) is the earliest CF manifestation and respiratory failure is the primary cause of death. In Europe, the incidence of CF is approximately 1/3500 Caucasian births, with an incidence of 1/2850 births reported in Belgium (3). CF is associated with co-morbidities such as Cystic Fibrosis related Liver Disease, Cystic Fibrosis Related Bone Disease and Cystic Fibrosis Related Diabetes (CFRD) (2).

EPI impacts nutritional status by causing maldigestion and malabsorption of nutrients in the absence of supplemented pancreatic enzymes. There is a well-established association between nutritional status (expressed as BMI) and pulmonary function (expressed as forced expiratory volume in 1 second, FEV1, percent predicted (pp)), which ultimately affects survival. Therefore improving nutritional status is a cornerstone of CF therapy (2).

The ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with CF highlighted the need to increase knowledge on nutritional demand and nutritional status in CF (2). This thesis aimed to answer the following research questions (RQ): (a) "Does enteral nutrition have a long-term effect on the nutritional status of children and adults with CF?", (b) "How can the sodium status in children and adults with CF be evaluated?", and (c) "What's the impact of impaired glucose metabolism on nutritional status and pulmonary function?"

Method

As an introduction to the thesis, a narrative review was conducted, focusing on the reconsideration of nutritional therapy in people with CF (pwCF) (1). The narrative review was limited to evaluating the use of growth charts, body composition, pancreatic enzyme therapy, and protein intake and digestion. A literature search was performed across three databases: PubMed, Scopus, and Web of Science, form June 2014 to June 2017.

To study the impact of enteral tube feeding (ETF) on nutritional status and pulmonary function, data from the Belgian CF Registry (BCFR) was used in a retrospective case – control study design (4). All patients (n=1482) in the BCFR were considered. Children and adults who received ETF between 2000 and 2013 and met the inclusion criteria were included. Statistical analysis was performed on 113 cases receiving ETF and 226 age, sex, pancreatic status and genotype class-matched controls. As the BCFR lacked data on growth velocity, a subsequent retrospective case – control multicentre study (UZ Brussel (UB) and Ghent University Hospital (GUH)) was performed (5). This second study aimed to explore the long-term effect of ETF on nutritional status, growth velocity, and pulmonary function in children with CF, comparing the timing of ETF initiation to current European guidelines (2). Children with CF who started ETF between 2006 and 2016 were included. Data from the patients' medical records 3 years before and five years after the start of ETF were collected. A total of 24/197 patients (UB+GUH) and 18 controls (GUH) were included for analysis, matched for age, sex, and pancreatic function.

A narrative review on sodium status and replacement in pwCF served as an introduction to the third part of the thesis (6). In June 2019, an electronic literature search was conducted in the databases PubMed, Web of Science, and Scopus. The literature search was limited to publications in English, focusing on primary research studies published since 1951. Twelve originals studies were identified and analysed. The narrative review addressed the evidence on the pathophysiology, prevalence, and clinical influence of sodium deficiency in people with CF, the indistinct recommendations for infants, children and adults, and the methods to assess sodium status. Based on the results of this review, a prospective study was performed (7). The aim was to evaluate urinary salt parameters as a surrogate for fractional excretion of sodium (FENa) in a large group of children and adults with CF in order to facilitate future follow-up of the sodium status using a spot urine sample. Between January 2019 and December 2020, urine and blood samples were collected from 222 patients followed at the GUH during an annual follow-up visit. FENa and urinary surrogate parameters for sodium status were calculated. The hypothesis was that the urinary sodium/creatinine ratio corresponding to the FENa ≥ 0.5% would differ across age categories in patients with CF.

In the fourth study, we examined the impact of impaired glucose metabolism on nutritional status and FEV1pp in pwCF who were not previously diagnosed with diabetes (8). Since the insidious nature of CFRD and the lack of clinically relevant continuous glucose monitoring (CGM) indices, we studied diurnal and nocturnal CGM-derived glycaemic patterns. Additionally, CGM-derived indices of glycaemic control were studied in relation to FEV1pp and nutritional status. Patients with an impaired OGTT and/or increased HbA1c were recommended to wear a CGM (Dexcom® G4) for seven days. CGM data of 47 pwCF, followed at the Ghent University Hospital (children, n = 26) was analysed.

All studies were approved by the Ethical Committee of the Ghent University Hospital.

Results

"*Does enteral tube feeding have a long-term effect on the nutritional status of children and adults with CF?*"

To address this RQ the findings from our longitudinal registry study and multicentre study will be discussed (4, 5). Some pwCF are unable to consume an adequate amount of nutrients, affecting weight gain and growth. CF centres use ETF to increase nutrient intake (2). In our longitudinal study, age of ETF initiation varied widely. Approximately 50% of the patients were < 10 years of age, and ± 25% were ≥ 18 years of age. All ETF-patients had lower BMI and height z-scores at the first registration in the BCFR compared to controls. After 3 years, their BMI z-scores recovered to the levels observed approximately 4 years before starting ETF but never reached the recommended threshold. We did not observe significant improvements in height z-scores in children.

In our multicentre study, we found a delay in ETF initiation compared with the guidelines, with 60% of the patients already having a BMI z-score < 1.3 three years before starting ETF (5). This percentage increased to 80% at ETF initiation, with six out of 24 patients already stunted. After starting ETF, growth velocity increased in the first year, but patients remained below their genetic potential for height. We could not recommend an ideal ETF start time, but younger patients showed greater height z-score improvement. Overall, ETF prevented further decline in BMI and FEV1pp over a period of five years but should be commenced in time (4, 5).

"How can the sodium status in children and adults with CF be evaluated?"

PwCF have hypertonic sweat which increases the risk for electrolyte disturbances. Monitoring sodium status in individuals with CF, especially in infants, is imperative. Relying solely on serum sodium as a clinical parameter may delay the diagnosis of deficiency. FENa is cumbersome as it requires simultaneous urine and blood samples. Since sodium requirements and thus supplementation change based on patients' circumstances, repeated measurements are necessary. In our study we observed a strong age-dependent correlation between FENa cut-offs and the urinary sodium/urinary creatinine ratio (Una+/Ucreat) (7). In the future, monitoring UNa+/Ucreat will be important as variant-specific therapies in CF reduce salt losses via sweat. Salt supplements and diet will need to be adjusted accordingly.

" What's the impact of an impaired glucose metabolism on nutritional status and pulmonary function?"

CGM has revealed abnormal glucose profiles in pwCF even when fasting and post-OGTT glucose levels are normal. Glucose tolerance tends to decline over time, progressing from normal to impaired glucose tolerance and eventually diabetes. CFRD is associated with a worse nutritional status and pulmonary function (9). We observed in our study cohort disrupted circadian CGM-profiles in all but two adult patients. We found no significant associations between CGM-indices and FEV1pp or BMI in the paediatric cohort, but in our adult cohort, we observed a strong association between moderate hyperglycaemia during night and a worse concurrent pulmonary function. Specifically, every increase of 1% time > 140 mg/dL during the night associated with a 0.76% lower FEV1pp. Our study was the first to explore nocturnal and diurnal glycaemic profiles in children and adults with CF, revealing deviations from healthy individuals' profiles. While this is relevant in establishing CGM cut-offs, associations between CGM-indices and CF outcomes were absent in our small paediatrics cohort, suggesting the need for age-specific indices. Thirdly, the increase in nocturnal glycemia may challenge current CF nutritional interventions, warranting a reconsideration.

Conclusion

Therapy in CF has dramatically evolved in the last decade which is expected to increase life expectancy, but as a consequence, an increase in co-morbidities is expected. Optimizing nutritional status remains a pillar in CF therapy. Our findings can set the path for a further improvement of nutritional care in CF.

REFERENCES

1. Declercq D, Van Meerhaeghe S, Marchand S, Van Braeckel E, van Daele S, De Baets F, et al. The nutritional status in CF: Being certain about the uncertainties. Clinical nutrition ESPEN. 2019;29:15-21.
2. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr. 2016;35(3):557-77.
3. Wanyama S, Daneau G, Dupont L. Annual Report Belgian Cystic Fibrosis Registry (BCFR) 2019. Sciensano; 2019.
4. Libeert D, Declercq D, Wanyama S, Thomas M, Van Daele S, De Baets F, et al. The effect of enteral tube feeding in cystic fibrosis: A registry based study. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2018;17(2):264-70.
5. Declercq D, Huysentruyt K, Hauser B, De Wachter E, Van Daele S, De Baets F, et al. Long-term use of tube feeding in children with cystic fibrosis: results from two Belgian CF centers. European journal of clinical nutrition. 2020.
6. Declercq D, Van Braeckel E, Marchand S, Van Daele S, Van Biervliet S. Sodium Status and Replacement in Children and Adults Living with Cystic Fibrosis: A Narrative Review. Journal of the Academy of Nutrition and Dietetics. 2020;120(9):1517-29.
7. Declercq D, Peremans L, Glorieus M, Weygaerde YV, Schaballie H, Van Braeckel E, et al. Urinary sodium/creatinine ratio is a predictor for fractional sodium excretion and related to age in patients with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2021.
8. Declercq D, Helleputte S, Marchand S, Van Aken S, Van Braeckel E, Van Daele S, et al. Glycemic indices at night measured by CGM are predictive for a lower pulmonary function in adults but not in children with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2023;22(1):59-65.
9. Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: Pathophysiology, screening and diagnosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2019;18 Suppl 2:S3-S9.

Pampers premium protection™

Onze N°1 om de huid droog & gezond te helpen houden

ONMIDDELLIJKE ABSORPTIE

DERMA COMFORT Toplaag

Onze unieke derma comfort toplaag houdt urine en vloeibare stoelgang weg van de huid en houdt het vast in de kern.

Zie het verschil

ANDER TOONAANGEVEND MERK

Pampers premium protection™

Public health impact of environmental pollution on children in North and South. A focus on air and metal pollution in Antwerp (Belgium) and Lubumbashi (DR Congo)

PhD thesis presented on February 17th 2023 at Ghent University, Belgium

Daan Van Brusselen [a]

Promoters: Dirk De Bacquer [b], Koen Van Herck [c], Benoit Nemery [d], Dirk Avonts [e]

[a] Consultant Tropical Paediatrics and Paediatric Infectious Diseases, ZAS Hospitals, Antwerp Belgium; Department of Public Health and Primary Care, Ghent University
[b] Faculty of Medicine and Health Sciences, Department of Public Health and Primary Care, Ghent University, Belgium
[c] Cancer Institute, UZ Leuven, Belgium
[d] Department of Public Health and Primary Care, Centre for Environment and Health, KU Leuven, Belgium
[e] Faculty of Medicine and Health Sciences, Department of Family Medicine and Primary Health Care, Ghent University and Domus Medica, Antwerp, Belgium

Daan.VanBrusselen@gza.be

Keywords

Infant ; child ; environmental pollutants ; particulate matter ; vulnerable populations ; developing countries ; asthma.

Research in context

Emerging infectious diseases like Zika, COVID and Ebola have shown clearly that disrupting ecological systems can lead to epidemics and pandemics. Therefore WHO developed the 'One Health' concept, an 'interdisciplinary approach stressing connections between human, animal and environmental health' (1). The distressing amount of environmental health problems from the last 20 years clearly shows that we must broaden our definition of 'public health', and include '**Planetary (One) Health**', focusing on the *(human and animal) health impact of disrupted ecosystems.* Currently we are not only facing climate change and its health consequences, but also a lack of water and land, diminishing biodiversity and different kinds of pollution. All these problems are closely connected. To understand all these challenges – and react to them – we need to increase collaboration between disciplines and countries, if we want to keep our planet (and its inhabitants) healthy (2, 3).

The magnitude of the current environmental problems is endangering humanity itself (by nutritional crises resulting in population displacement and conflict, pandemics and the serious health impact of pollution) (3). **Air pollution** and '**chemical / toxic substances**' (of which metals are the most important) are the **two most important 'areas of work**' of WHO's 'Public Health and Environment' (PHE) strategy (4). The purpose of this PhD thesis was to fill a few knowledge gaps about the health impact of air and metal pollution on children in the Global North and South.

Evidence before this PhD

It is well known in paediatrics that the first 1000 days (from conception onwards) are very important in terms of proper nutrition and (psychosocial) development (5, 6). In this thesis we aimed to demonstrate that also environmental '**early life exposures**' are very important. South African researchers from the 'Drakenstein Child Health Study' have shown that **antenatal exposure** to household air pollution (HAP) already affects the incidence and severity of '*lower respiratory tract illness*' (remark that they call it LRT 'illness' and not 'infection') in their offspring (7, 8). Antenatal outdoor 'ultrafine particle' (UFP; with an aerodynamic diameter < 0.1 micrometre) exposure was also linked to '*asthma development in children*' in the US (mostly when the exposure took place late in pregnancy) (9). Foetuses and infants are extremely vulnerable to pollution exposure because of their rapid development and immature immune system, particularly those in Low- and Middle-Income Countries (LMIC) where poverty and lack of resources compound the effects (10).

Environmental health effects are the largest in **disadvantaged or vulnerable populations**: this can be because of age (the youngest and the oldest are more 'fragile'), disease, race and poverty (11). There is a clear link between poverty and unhealthy living environment, also in Belgium (12). People in 'low resource settings' are even a lot more 'exposed' to several environmental pollutants than disadvantaged people in the global North, because there are less stringent environmental laws in LMIC (13).

Added value of this PhD and knowledge gaps

In our 'health impact assessment' (HIA) of 'Ringland' we have calculated that the impact of improved air quality by moving the entire Antwerp Ring Road into a tunnel, would especially have a significant impact on 'all cause' mortality (21 deaths, 95%CI 7-41, avoided annually in the population living in a perimeter of 1500m around the ring road), and on child lung function development (forced vital capacity improvements of 3-64ml in 356 of the 430 schools around the ring road) (14). In the 'BronchiolAir' study (in publication), we found a trend that children hospitalized for bronchiolitis appear to be more exposed to air pollution, but the study was too small to draw definite conclusions. This trend does however confirm that the already existing evidence from the US on the association between bronchiolitis and air pollution, does probably also count for the urban environment of Antwerp. Larger studies are needed to consolidate the impact of air pollution on bronchiolitis in Europe; and even more so in LMIC.

In a case-control study in a mining area in southern Katanga (Democratic Republic of the Congo, DRC), we were able to associate paternal occupational mining (OR 5.5; 95%CI 1.2-25), and concentrations of Mn (OR 1.7; 95%CI 1.1-2.7) and Zn (OR 1.6; 95% CI 0.9-2.8) in cord blood and placental tissue, with the incidence of (visible) birth defects in newborns (15). Prospective studies could help to establish a causal relationship between metal pollution and congenital malformations.

We have added data to the increasing evidence that 'early life exposure' to environmental pollutants, is harmful in the Global North and South. Until a few decades ago, pollution was not considered a major determinant of health among children. The health impact of air and metal pollution on children is becoming more clear in recent years. And even if some things (like the relationship between metals and birth defects in DRC that we have shown) are just associations, according to the 'precautionary principle', this is enough to start protecting children from environmental 'early life exposures'. Even if there is uncertainty about the nature and magnitude of potentially harmful effects of several pollutants, the credible threat of these agents to the paediatric population provides a rationale for taking precautionary measures to prevent this exposure (16).

Policy implications of all the evidence available

WHO, UNICEF and The Lancet recently called for action to put '**children in all policies**' to build a healthier and more equitable world for future generations. This is especially important for policies on environmental pollution (17). Fossil fuel combustion has become one of 'the world's most significant threats to children's health' (10). The 'Ringland' and 'BronchiolAir' studies confirm that the **individualized motorized traffic** (and the liberty associated with it) has become one of society's largest problems. Air pollution, but also pollution of water and soil (by fossil fuels, but recently also by metals for batteries), global warming, destruction of biodiversity and liveable urban space for roads and car parks are just a few of the negative effects of the automobile industry (18).

It is exaggerated to state that lithium-ion batteries are '*the new oil*', but – as part of the 'low-carbon future' – high amounts of cobalt and smaller amounts of copper are needed. They are extracted in countries like DRC. The increased production makes that more children (and adults) are exposed to high amounts of metals, especially in vulnerable countries like DRC. Our 'Katanga Malformations Congénitales' study has shown that even unborn children are at risk. We must therefore prevent that batteries destroy more lives than they save the climate (19, 20). On a *global scale* **Big Tech companies should be held responsible** not only for where their metals come from, but also become key stakeholders in a real circular economy, by becoming accountable for the recycling of their own mobile devices, laptops, etcetera, when they can no longer be used (cf. the Recupel initiative) (21).

An important component of environmental health in *LMIC*, is '**better housing**'. Better housing means that dwellings are *climate-proof*, i.e. less hot and mosquito-free, but also free of *household air pollution (HAP)*. HAP can be reduced by cooking on porches that are well ventilated, with nets not only to keep mosquitos out, but also to let the smoke escape (22).

In HIC technical solutions that reduce industrial emissions, proper urban cycling networks, good public transport systems, clean power sources (wind, water, sun) and isolation of houses are essential (10). A '**Modal Shift**' towards more active transport and '**Road pricing**' (these two are currently part of the 'Ringland' plan), but also '**Low Emission Zones**' **(LEZ)**, preferably associated with 'circulation plans', are only first steps. More and more cities recommend to leave personal cars (especially for non-urban residents) in '*park and ride zones*' outside of the city. These zones should be equipped with charging stations (for electric cars) and be a lot better connected to the heart of the city by public transport and shared bicycle systems. **Transforming 'car parks' into 'real parks'** could also have additional salutogenic effects. The WHO recommendation is that all people should have access to ≥ 0.5 hectare (ha) open green space within 300 m linear distance from their home. Recently, the '**3-30-300 rule**' (or 'Vancouver rule') has been proposed by urban planners: they state that 'everybody should be able to see at least 3 trees from their home, that all neighbourhoods should have at least 30% tree cover, and that everyone should have access to "a green area of at least one hectare" within 300 metres' (23). Adding blue spaces to this '3-30-300 rule', could even increase its impact.

It has already been shown many times that investing in Public Health works. The 'fiscal multiplier' for investments in public health is 4.3. This means that for every euro invested in Public Health, the society in the end gains 4 euros (24). So, societies investing in healthier (pollution free) environments for children will also benefit financially from this. For example, Copenhagen is planning **Cycle Super Highways**, to improve mobility and reduce air pollution in the capital region. The planned 'Bicycle Super Highways', around the city (>500 km of bike paths), could reduce public health expenses by 40 million euro every year (25). 'Historically, cycle paths are an artifact of car thinking' (26). Originally streets were 'meeting places'. In a lot of cities worldwide pedestrians and cyclists are 'reclaiming the streets', by initiatives like the 'Critical Mass Bike Ride' (26).

Traffic remains an important cause of diverse forms of pollution that harm children. When planning transport, the purpose should be to maximize social/health benefits, and to minimize harm. Therefore some people argue that we should 'phase out' cars from our lives. For almost all journeys cars can easily be substituted (think of Pontevedra, Amsterdam or Copenhagen) (27).

Measuring works: 'Clear indicators' can be helpful to identify which populations are most vulnerable (and where you should act first). In New York City, e.g., the city council mapped green space and the 'urban heat island' effect: on this basis they decided which communities are the most at risk for heat-related mortality/morbidity and where they should thus prioritize cooling policies (28). The same could be done for places and populations most at risk for air pollution.

You can be unlucky with your genes and get cancer despite living an ultra-healthy life. But statistically, with a healthy lifestyle you are 79% less likely to develop a chronic condition. 'Quick wins' are not smoking, exercising, keeping your BMI under 30 and a healthy diet (no red meat and prepared meat; lots of vegetables and seeds) (29). It is now becoming increasingly clear that a healthy lifestyle also includes avoiding 'early life exposures' to a combination of pollutants. Pollution is like a symphonic orchestra: there's only a concert when several instruments play together.

'Bird perspective' on this PhD

We have to broaden our definition of 'public health' with the concept of 'planetary health'. Everything is connected. Climate warming, loss of biodiversity, but also environmental pollution are closely related to global health problems like infectious disease outbreaks (COVID-19, LRTI…) and 'non-communicable diseases' (malnutrition, asthma, allergies, renal problems, several cancers…) (30).

We must mutualize the 'commons' again. 'Commons' or 'le bien commun' are the things that are not supposed to be anyone's property; it's what we all inherit from our parents and pass on to our children. It's about air, water, the underground (and by extension also our climate) (31). We have an intergenerational responsibility to keep them clean. These 'commons' are important in the Global North, but perhaps even more so in the Global South, because there are less stringent environmental laws in LMIC.

This doctoral research was needed because we often do not realize how early in life an unhealthy living environment can already have long-lasting consequences. Since foetuses and young children cannot do anything about this themselves, society has a tremendous responsibility. The trend to more sustainable cities and a healthier world has been set. It can be slowed down by some politicians and policy makers (often protecting privileges of a selected group), but it cannot be stopped anymore. A 'tailored approach' depending on where you are, is needed. Think global, act local.

REFERENCES

1. Rabinowitz PM, Pappaioanou M, Bardosh KL, Conti L. A planetary vision for one health. BMJ global health. 2018;3(5):e001137.
2. Planetary health alliance: goals 2021. Boston MA, USA2021 [cited 2023 Aug 02]. Available from: https://www.planetaryhealthalliance.org/planetary-health.
3. Myers SS, Pivor JI, Saraiva AM. The São Paulo Declaration on Planetary Health. Lancet (London, England). 2021;398(10308):1299.
4. WHO Public Health & Environment (PHE) Global Strategy Overview Geneva, Switserland: WHO; 2011 [cited 2023 Aug 02]. Available from: (http://www.who.int/phe/publications/PHE_2011_global_strategy_overview_2011.pdf?ua=1).
5. Barker DJ. Fetal origins of coronary heart disease. BMJ (Clinical research ed). 1995;311(6998):171-4.
6. Singh BSK, Danckaerts M, Van den Bergh BRH. Helping Families of Infants With Persistent Crying and Sleep Problems in a Day-Clinic. Frontiers in psychiatry. 2021;12:591389.
7. Nemery B, de Marie Katoto P. Protecting children's lungs by providing clean air during pregnancy? The Lancet Planetary health. 2017;1(8):e309-e10.
8. Vanker A, Barnett W, Workman L, Nduru PM, Sly PD, Gie RP, et al. Early-life exposure to indoor air pollution or tobacco smoke and lower respiratory tract illness and wheezing in African infants: a longitudinal birth cohort study. The Lancet Planetary health. 2017;1(8):e328-e36.
9. Wright RJ, Hsu HL, Chiu YM, Coull BA, Simon MC, Hudda N, et al. Prenatal Ambient Ultrafine Particle Exposure and Childhood Asthma in the Northeastern United States. American journal of respiratory and critical care medicine. 2021;204(7):788-96.
10. Perera F. Pollution from Fossil-Fuel Combustion is the Leading Environmental Threat to Global Pediatric Health and Equity: Solutions Exist. International journal of environmental research and public health. 2017;15(1).
11. United_Nations_Environment_Programme. Sixth Global Environment Outlook (GEO-6) Summary for Policymakers. Singapore: Cambridge University Press; 2019 [cited 2023 Aug 02]. Available from: (https://wedocs.unep.org/bitstream/handle/20.500.11822/27652/GEO6SPM_EN.pdf?sequence=1&isAllowed=y).
12. Hoe gezond is de lucht in Brussel? Ontdek de resultaten van CurieuzenAir. De Standaard. 2021.
13. Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. The Lancet Commission on pollution and health. Lancet (London, England). 2018;391(10119):462-512.
14. Van Brusselen D, Arrazola de Oñate W, Maiheu B, Vranckx S, Lefebvre W, Janssen S, et al. Health Impact Assessment of a Predicted Air Quality Change by Moving Traffic from an Urban Ring Road into a Tunnel. The Case of Antwerp, Belgium. PloS one. 2016;11(5):e0154052.
15. Van Brusselen D, Kayembe-Kitenge T, Mbuyi-Musanzayi S, Lubala Kasole T, Kabamba Ngombe L, Musa Obadia P, et al. Metal mining and birth defects: a case-control study in Lubumbashi, Democratic Republic of the Congo. The Lancet Planetary health. 2020;4(4):e158-e67.
16. Tickner JA, Hoppin P. Children's environmental health: a case study in implementing the precautionary principle. International journal of occupational and environmental health. 2000;6(4):281-8.
17. Dalglish SL, Costello A, Clark H, Coll-Seck A. Children in All Policies 2030: a new initiative to implement the recommendations of the WHO-UNICEF-Lancet Commission. Lancet (London, England). 2021;397(10285):1605-7.
18. Descamps P. Dossier: La ville défigurée. Ravages de l'automobilisme Le Monde Diplomatique. 2021.
19. Sovacool BK, Newell P, Carley S, Fanzo J. Equity, technological innovation and sustainable behaviour in a low-carbon future. Nature human behaviour. 2022;6(3):326-37.
20. Watts J. How the race for cobalt risks turning it from miracle metal to deadly chemical. The Guardian. 2019.
21. Sovacool BK, Turnheim B, Hook A, Brock A, Martiskainen M. Dispossessed by decarbonisation: Reducing vulnerability, injustice, and inequality in the lived experience of low-carbon pathways. World Development. 2021;137:105116.
22. Knudsen J. How to design houses in Africa that reduce diseases. 39th Annual ESPID Meeting; Geneva2021.
23. Konijnendijk C. The 3-30-300 rule for urban forestry and greener cities. Biophilic Cities Journal. 2021;4(2):2.
24. Reeves A, Basu S, McKee M, Meissner C, Stuckler D. Does investment in the health sector promote or inhibit economic growth? Globalization and health. 2013;9:43.
25. Cadence_team. Denmark's first cycling superhighway London, UK 2017 [cited 2023 Aug 02]. Available from: https://www.cadencemag.co.uk/news-denmarks-first-cycling-superhighway/
26. Schipper F, Emanuel M, Oldenziel R. Sustainable Urban Mobility in the Present, Past, and Future. Technology and culture. 2020;61(1):307-17.
27. Monbiot G. Cars are killing us. Within 10 years we must phase them out. The Guardian. 2019.
28. van den Broek d'Obrenan H, Huxley R. Measuring what matters: supporting cities in tackling climate and health challenges. The Lancet Global health. 2022;10(6):e788-e9.
29. Deschepper R. Je levensstijl als medicijn. Tielt, Belgium: Lannoo; 2022.
30. 3The_Lancet_Planetary_Health. Editorial. Turning point? . The Lancet Planetary health. 2020;4(12):e544.
31. Lotens W. De nieuwe coöperatie: tussen realiteit en utopie. Tielt, Belgium: Lannoo Campus; 2013.

Vitamine D pour les enfants:

Il existe une solution plus simple que de compter les gouttes

VISTA-D3™

PETITS COMPRIMÉS FONDANTS

MADE IN BELGIUM

5 DOSAGES DIFFÉRENTS (UI)

- **400 – 600 – 800 – 1000 – 2000 –** (**3000** pour adultes)
- **DOSAGE PRÉCIS:** Pas de risque que la maman donne trop ou trop peu

ADMINISTRATION TRÈS PRATIQUE

- **PETITS COMPRIMÉS FONDANTS:** diamètre 7 mm
- **MICROGOUTTELETTES D'HUILE + VIT.D À L'INTÉRIEUR DU COMPRIMÉ** Bonne absorption tout en évitant l'huile en bouche
- **ENFANTS:** sucer ou croquer
- **ENFANTS AVEC MALABSORPTION:** laisser fondre sous la langue
- **BÉBÉS:** dissoudre dans une petite cuiller d'eau ou dans le biberon

TRÈS BIEN ACCEPTÉ

- **GOÛT FRAIS ET NEUTRE**
- **SANS:** lactose, gluten, sucre, édulcorant synthétique, colorants

MOINS DE 5€ PAR MOIS

- **VISTA-D3 400:** 120 comprimés fondants
- **VISTA-D3 600:** 120 comprimés fondants
- **VISTA-D3 800:** 120 comprimés fondants
- **VISTA-D3 1000:** 180 comprimés fondants
- **VISTA-D3 2000:** 180 comprimés fondants
- **VISTA-D3 3000:** 180 comprimés fondants

VISTA-D3, avec vista pour vos petits patients

BESOIN D'ECHANTILLONS ?

Envoyez votre choix et votre adresse postale par mail à office@vistalife.be

VISTA®