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Articles

Case Reports

Made In Belgium

Paediatric Cochrane Corner

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Société Belge de Pédiatrie

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Références : 1. Careddu and Pettenazzo (2018), Pelargonium sidoides extract EPs® 7630: a review of its clinical efficacy and safety for treating acute respiratory tract infections in children. International Journal of general Medicine (11): 91-98 ; 2. Kamin et al. (2018), EPs® 7630 is effective and safe in children under 6 years with acute respiratory tract infections: clinical studies revisited, Current Medical Research and Opinion, 34(3): 475-485 ; 3. Anheyer et al. (2017), Herbal medicine in children with respiratory tract infection: systematic review and meta-analysis, Academic pediatrics (2017), doi: 10.1016/j.acap.2017.06.006. ; 4. Matthys H. et al. EPs® 7630 in acute respiratory tract infections. A systematic review and meta-analysis of randomized clinical trials. J Lung Pulm Respir Res, 3(1):00068-2016. ; 5. Kamin W et al., 2010, Efficacy and tolerability of EPs® 7630 in children and adolescents with acute bronchitis. A randomized, double-blind, placebo-controlled multicenter trial with a herbal drug preparation from Pelargonium sidoides roots ; 6. Matthys H et al. Safety and Tolerability of EPs® 7630 in Clinical Trials. Advances in Pharmacoepidemiology and Drug Safety. 2013;2(4):142–9

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Contents

De Belgische Vereniging voor Kindergeneeskunde

Omdat wij begaan zijn met
de gezondheid van onze kinderen

La Société Belge de Pédiatrie

Parce que nous nous soucions
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Editorial

Happy new year !

A new year begins and, with it, comes a multitude of wishes, greetings and good resolutions.

Shaken up by the successive crises of the last years, the world is in transformation. An evolution that our cartoonist, Serge Ernst, has drawn in the hollow of our hands.

Everywhere, big conferences and meetings are organized to decide and to coordinate protection, preservation, defense, development, recovery and reconstruction: the G7 Summit (June 26-28; Krun, Germany) the COP27 for climate (November 6-18; Sharm el-Sheikh, Egypt), the G20 Summit (November 15-16; Bali, Indonesia), the COP15 for biodiversity (December 7-19; Montreal, Canada), the Conference in support of Ukraine (December 13-14; Paris, France). Far away, plans and commitments are made to improve life on earth. The coming months will tell us if the will to carry them out is real.

Among the international gatherings of this year, we would like to come back to a particular event: the soccer world cup that took place in Qatar. There were many reasons not to mention it, or even to boycott it: non-respect of human rights, disastrous working conditions of the workers on the construction sites, catastrophic ecological costs, suspicions of corruption, ... As actors in the pediatric world, we must acknowledge that it was difficult to stay away from this widely publicized event. It is also contradictory to encourage the practice of sports among young people and to leave it under silence, when it takes place in a highly questionable context. Because yes, sport and soccer are very popular in children and adolescents. Yes, sport and physical activities are good for health. Yes, playing, setting goals and challenges, participating in competitions, recognizing the superiority of an opponent, and keeping the desire to win are important lessons in the development of a well-balanced personal and social life. Yes, celebrating a victory together and enjoying a shared accomplishment are unifying, resourcing and energizing moments. As adults, as pediatrician ambassadors for children, we must, more than ever, ensure that sport is not diverted from its founding values. And despite all the concerns mentioned above, it must be admitted that the competition played in December between the world's greatest soccer teams, delivered us some positive messages that inspired us to write this editorial. First of all, we would like to say that we have no footballing pretensions. Our biggest regret was not to see the Red Devils go further in the tournament. As many observers, we noticed that the teams that performed the best were those with a strong common will, a real collective game. Of course, there were individualities with exceptional qualities but, even in the grand finale, we saw that these players made the difference when they served the group, when they built collectively with their team. The twists and turns throughout the competition were also an illustration of the power of trust and confidence, of the importance of remaining determined, of not giving up. The team that won the tournament was the first negative surprise with a defeat in its initial match... As the matches went on and until the last minutes of the final game, we have seen players taking on themselves, observing, adapting, surpassing themselves and showing creativity to build with their teammates a new style of play and to find the key to success.

These are the messages we retain for this new year, these are the wishes we formulate for each of you. May 2023 give you the opportunity to always believe and the joy to contribute with your strengths and talents to the construction of a better world where it is good to live and to grow !

Once again, this December issue of the BJP is an illustration of the medical and scientific quality of our pediatric community and particularly of our young colleagues in training. This month, we are proud to publish several case reports about rare pathologies (triple A syndrome by T. Brose et al., congenital nasal pyriform aperture stenosis by L. Franssen et al., acute disseminated encephalomyelitis by M. Kwakernaat et al., chronic obstructive cholestasis associated with invasive fungal infection in a preterm neonate by A. Geurden et al.). Other articles also describe and discuss unusual clinical presentations in common pediatric settings: endocarditis and embolic complications by I. Aslanides et al., post-traumatic cortical blindness by T. Dominicus et al., acute focal cerebral lesions in children with diabetic ketoacidosis by A.L. Kolleger et al., Merkel diverticulum by N. Gerets et al. and tracheooesophageal fistula after ingestion of a button battery by D. Dinneweth et al.. E. Surgun and her team analyzed the impact of pneumococcal conjugate vaccine on the incidence of parapneumonic pleural effusion and report intriguing results in the Belgian population between 2000 and 2019. L. VanCamp et al. present the survey they made among Belgian paediatric trainees and recently graduated paediatricians about subspecialties in paediatrics. Our Cochrane corner section reviews which splinting strategies are best for the non-operative management of developmental dysplasia of the hip in children under six months of age. In the “Made in Belgium” section, we have invited Michael Aertsen from KULeuven to summarize his thesis about the brain magnetic resonance imaging in current fetal medicine.

Once again and on behalf of the entire board, we wish you a happy new year and a pleasant reading. We hope to see you in great shape in March at the next congress of the Belgian Society of Pediatrics.

Christophe Chantrain and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

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Intelligence artificielle et soins de santé : une révolution en cours. Comment l'intégrer au mieux ?

Réunion scientifique

Samedi 11 mars 2023

Inscription

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Organisation

Date et lieu

Samedi 11 mars 2023
Auditoire Maisin - (Auditoires Centraux)
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Accréditation

Rubrique 6 Ethique

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22 APRIL

VVK Voorjaarsvergadering

Allergie en astma bij kinderen: wat moet ik ervan weten?

Programma:

- **8:30 – 8:45 Verwelkoming**
  Prof An Bael, ZNA, Antwerpen. Voorzitter VVK.
  Dr Sophie Verelst, PeAACH, Jessa ziekenhuis, Hasselt
- **8:45 – 9:10 De allergische reactie: CAPtesten en componenten**
  Prof.Dr. Dominique Bullens, UZ Leuven
- **9:10 – 9:35 Praktische aspecten van voedingsallergie**
  Dr. Jasmine Leus, Maria Middelares, Gent
- **9:35 – 10:00 Allergie voor medicatie**
  Dr Athina Van Gasse, UZ Antwerpen
- **10:00 – 10:30 Algemene vergadering**
- **10:30 – 11:00 break**
- **11:00 – 11:25 Insectenallergie**
  Dr. Julie Willekens, UZ Gent
- **11:25 – 11:50 Immunotherapie en behandeling van aero-allergie**
  Dr. Katrien Coppens, Imelda Bonheiden
- **11:50 – 12:15 Laatste updates astma guidelines**
  Dr. Ine Van Dijck, PeAACH, Jessa ziekenhuis, Hasselt
- **12:15 – 12:30 Slotwoord**
  Prof An Bael, ZNA, Antwerpen. Voorzitter VVK.

Schrijf je snel in via de VVK website

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Moderator: dr Marc Raes, PeAACH, Jessa ziekenhuis, Hasselt

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CLIMATE CHANGES IN PEDIATRICS: FROM SOCIETY TO ENVIRONMENT

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Incidence and epidemiology of parapneumonic pleural effusion in children before and during pneumococcal conjugated vaccination era in Belgium (2000-2019)

Ebru Surgun [a], Philippe Lepage [b,c], Pierre Smeesters [a,b,c], Celine Mignon [b]

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Keywords

Pneumococcal conjugate vaccine, parapneumonic pleural effusion, pneumococcus

Abstract

Background:

Pneumococcal community-acquired pneumonia is frequently complicated by parapneumonic pleural effusion. In Belgium, three pneumococcal conjugate vaccines were introduced between 2007 and 2019. These are successively the heptavalent (PCV7), the 13-valent (PCV13) and the 10-valent (PCV10) pneumococcal conjugate vaccine. Our aim was to assess the effect of pneumococcal conjugate vaccines over time on the incidence of parapneumonic pleural effusion during the pre-vaccination (pre-PCV) and the three vaccination periods.

Methods:

The demographic and clinical-biological characteristics of hospitalized children with pleural effusion complicating community-acquired pneumonia were collected retrospectively between January 2000 and August 2019.

Results:

Among 474 children hospitalized for pneumonia with pleural effusion, Streptococcus pneumoniae was detected in 140 bacteriological samples. During the study period, the overall incidence of parapneumonic pleural effusion increased by 50.8% during the PCV10 period ($p<0.0001$). The incidence of pneumococcal pleural effusion was 27.2‰ during the PCV10 period and increased by approximately 60% compared to the pre-PCV period ($p=0.0005$) with a moderate decrease during the PCV13 period.

Conclusion:

Our study observes an increasing incidence of pleural effusions in children with pneumonia after the introduction of pneumococcal conjugate vaccines in Belgium. The reasons of these increased incidences remain unclear and should be confirmed in larger series of children. Pneumococcal vaccination in children remains however highly recommended by its favorable outcome on overall invasive pneumococcal disease.

Introduction

Community-acquired pneumonia (CAP) is a common pediatric infection and a major source of morbidity and mortality worldwide (1-4). According to data from the World Health Organization, 15% of deaths children under 5 years of age are due to pneumonia (5). In 2017, 808 694 pneumonia-related deaths were recorded in this age group worldwide (5).

Streptococcus pneumoniae (*S. pneumoniae*), is the most common pathogen causing invasive infections such as CAP with bacteremia or empyema, meningitis, osteomyelitis and sepsis (5-8). In 2000, 13.8 million episodes of pneumococcal pneumonia in children under 5 years of age were recorded worldwide (6). Parapneumonic pleural effusion (PPE) complicates nearly half of all pneumococcal pneumonia in some series. It results from microbial invasion and inflammation of the pleural space (9,10). It can progress to empyema corresponding to the accumulation of purulent fluid in the pleural cavity. CAP complicated by PPE or empyema often requires prolonged intravenous antibiotic therapy or even invasive management with percutaneous or surgical chest drainage.

Currently, more than 90 infection-related pneumococcal capsular serotypes have been described (3). Only high incidence invasive pneumococcal diseases (IPD) and antibiotic resistant serotypes are targeted by vaccines (11,12). Before the introduction of the pneumococcal heptavalent conjugate vaccine (PCV7, Prevenar®), 6 to 11 serotypes were predominant in IPD in the different regions of the world (13).

In Belgium, PCV7 was marketed in October 2004 and recommended in the vaccination schedule from January 2007 until September 2011 (Wallonia-Brussels Federation) or July 2011 (Flanders) (11,14). 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar® 13) was then introduced (11). From May 2016 to August 2019 (Wallonia-Brussels) and July 2015 to June 2019 (Flanders), PCV13 was replaced by the 10-valent pneumococcal conjugate vaccine (PCV10, Synflorix®) whose 8 serotypes are conjugated to a non-typable *Haemophilus influenzae* protein D and serotypes 18C and 19F are conjugated to tetanus toxin and diphtheria toxin, respectively (13,15,27). In the other two vaccines (PCV7 and PCV13), serotypes are conjugated to the modified diphtheria toxin (27).

PCV7 coverage includes serotypes 4, 6B, 9V, 14, 18C, 19F, 23F while PCV13 includes six additional serotypes 1, 3, 5, 6A, 7F and 19A (8,11). PCV10 covers PCV7 serotypes and serotypes 1, 5, 7F (13).

Children benefit from a vaccination schedule with 2 doses at 2 and 4 months followed by a booster at 12 months (11).

Many studies carried out in several countries have reported a remarkable decrease in the overall incidence of IPD caused by PCV7

vaccine serotypes (VTs) after its introduction, including pneumonia with pneumococcal bacteremia (2,4,16). But this observation was associated with some "replacement" of the seven VTs by non-vaccine serotypes (NVTs) in IPD (serotypes 1, 3, 5, 6A, 7F and 19A) (3,4,17). Similarly, recent epidemiological data demonstrate an increasing incidence of IPD caused by PCV13 VTs, especially serotypes 19A and 3 during the PCV10 recommendation period which justified the reintroduction of PCV13 vaccination (18,19).

Several studies in pediatric populations have also demonstrated an increasing incidence of pneumococcal empyema before and after PCV7 introduction, potentially associated to such circulating serotypes modifications (8,9,14,20). In contrast, the number of cases decreased after PCV13 introduction (2,8).

Our main objective was to compare the incidence of the demographic, clinical and biological characteristics of pleural effusions before and during the conjugate pneumococcal vaccination era in children in a Belgian pediatric hospital. Our second objective was to describe the evolution of its management.

Methods

Patient enrolment

This study was carried out at Hôpital Universitaire Des Enfants Reine Fabiola in Brussels, a tertiary pediatric hospital of 183 beds.

All children from 0 to 16 years old hospitalized for pneumonia and pleural effusions from January 2000 to August 2019 were identified using the international classification system ICD-9-CM (International Classification of Diseases-9-Clinical Modification) and ICD-10-CM (International Classification of Diseases-10-Clinical Modification). Data were collected retrospectively from their medical files. Demographic, clinical and biological data were encoded for eligible patients during the study period.

Four periods were defined based on vaccine recommendations in Belgium: "pre-PCV" from January 2000 to December 2006, "PCV7" from January 2007 to August 2011, "PCV13" from September 2011 to April 2016, "PCV10" from May 2016 to August 2019.

This study received the approval of the Hôpital Universitaire Des Enfants Reine Fabiola ethics committee (CEH file n° 62/21).

Inclusion criteria and definitions

We included all patients aged 0 to 16 years who were hospitalized for CAP and PPE.

CAP was defined as the association of cough and/or respiratory distress, a body temperature ≥ 38°C and the presence of a pulmonary consolidation on a chest X-ray (21).

PPE was confirmed by a chest X-ray and / or ultrasound.

The diagnosis of pneumococcal CAP was made based on identification of a *S. pneumoniae* by culture and/or polymerase chain reaction in pleural fluid or blood.

Penicillin susceptibility testing was performed on all *S. pneumoniae* isolates recovered. They were classified on report by minimum inhibitory concentration (MIC) as susceptible (MIC ≤ 0.06 µg/mL), intermediate (MIC = 0.12 - 1.0 µg/mL) or resistant (MIC ≥ 2.0 µg/mL) according to CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines.

The serotyping of *S. pneumoniae* was performed using the Quellung reaction capsular typing. Due to a failure to record data, pneumococcal serotypes could be identified only for isolates from patients admitted between January 2005 and August 2019.

Classification of parapneumonic pleural effusions

All ultrasound confirmed pleural effusions were sampled except those less than 10 mm thick (22). We distinguished three PPE categories (simple, complicated and empyema) according to the British Thoracic Society classification based on macroscopic appearance and biochemical and bacteriological characteristics of pleural fluid (9).

Pleural effusions with a macroscopic purulent aspect were considered as "empyema" even in case of negative bacteriological examination. Non-punctured and "unclassifiable" pleural effusions due to lack of information have been classified as "unknown".

Exclusion criteria

We excluded patients with non-parapneumonic pleural effusions, nosocomial pneumonia or in case of missing files. PPE of unknown etiology were not excluded. They were classified as "potential pneumococcal" PPE based on data showing that pneumococcus was the predominant etiological agent recovered in severe and complicated CAP with PPE at the same period in Europe (20).

Patients with more than 1 episode of CAP with PPE and chronic underlying diseases such as heart diseases, chronic respiratory diseases, neurological syndromes, malformative syndromes, hematological and oncological conditions, acquired or congenital immune deficiency or a history of prematurity were not excluded.

Statistics

Data were processed by SAS version 9.4© for Windows. Incidence rates were presented with a 95% confidence interval. Analyzes were performed by vaccination period, year, and age group. Continuous variables are expressed as mean ± standard deviation or median (IQR, interquartile range) and were analyzed by Kruskal-Wallis test. Categorical variables are presented with frequency distributions and were analyzed by Cochran-Armitage trend test. A p-value less than 0.05 was considered statistically significant.

Results

Global epidemiological data

Between January 2000 and August 2019, 6594 children were hospitalized with pneumonia. According to the 4 predefined vaccination periods, the number of cases were respectively: 3057 (January 2000 - December 2006), 1667 (January 2007 - August 2011), 1171 (September 2011 - April 2016) and 699 (May 2016 - August 2019). Vaccination data were not obtained individually but deduced from study periods. At the same period 1143 children were hospitalized with a pleural effusion. Based on the exclusion criteria, 669 cases were excluded (Figure 1). As shown in Figure 1, 474 children presented with a pleural effusion associated with CAP (7.2% of hospitalized pneumonia and 41.5% of pleural effusions all etiologies combined). They were divided into four groups according to the microorganism. A pleural fluid sample was taken from 250 children (52.7%) and a bacteriological pathogen was identified in blood culture and/or pleural fluid culture and/or polymerase chain reaction among 185 cases (39.0%). In 140 cases (29.5%), the microbiological sample revealed *S. pneumoniae*, which allowed them to be classified as CAP with pneumococcal PPE (pPPE). 267 other cases of PPE (56.3%) were classified as potential pneumococcal PPE (ppPPE) due to non-contributive microbiological analyzes.

The demographic, clinical and biological characteristics of the patients are shown in Table 1.

Parapneumonic pleural effusion incidence and characteristics

Between the beginning and the end of the study, the overall incidence of PPE among all hospitalized children with pneumonia increased from 56.3‰ during the pre-vaccination period (172/3057) to 114.4‰ during the 4th period (80/699) with a significant increasing trend of 50.8% ($p<0.0001$). This increase was most pronounced among children between 2 and 5 years old (47.5%; $p<0.0001$) and in males (49.4%; $p<0.0001$).

The pPPE incidence significantly increased, from 11.4‰ in the pre-

PCV period to 27.2‰ in the PCV10 period (p=0.0005). This represents a nearly 60% increase in CAP with PPE due to *S. pneumoniae*, especially in children 2 to 5 years old (p = 0.0003). This upward trend in pPPE is significant in both genders (female, p=0.01; male, p=0.02). The ppPPE also significantly increased, but in a lesser proportion (by 50.1%) with an incidence going from 35.0‰ to 70.1‰ (p<0.0001) between pre-PCV and PCV10 periods. Detailed data are available in Table 2 and Figure 2.

Among pPPE, complicated PPE had a significant upward trend (+ 81.3%) to reach a proportion of 47.4% of all PPE during the PCV10 period (95% CI, 5.6-58.7; p=0.001). On the contrary a significant decrease in empyema was observed among all PPE (-41.4%; p=0.03) and among pPPE (-64.8%; p=0.003). Detailed data are available in Table 3.

Parapneumonic pleural effusion treatment and short-term morbidity

The use of antibiotic therapy alone in the management of CAP complicated by PPE significantly increased by more than 30% throughout the study period (p=0.0002). The duration of intravenous antibiotic therapy significantly decreased with a median duration going from 14 to 7 days for total PPE and from 12 to 5 days for ppPPE (p<0.0001; p<0.0001). The decrease in intravenous antibiotic therapy duration for pPPE was not statistically significant, going from a median duration of 20 to 14 days between the pre-PCV and PCV10 periods (p=0.45). The use of thoracic drainage (percutaneous or surgical) decreased by 40.6% and 74.9% for total PPE (p=0.0004) and ppPPE (p<0.0001) respectively with a significant decrease in the duration of drainage (p<0.0001; p=0.02). However, a non-significant increase in thoracic surgery (VATS, video-assisted thoracoscopic surgery) was observed for pPPE (p=0.12).

The incidence of pulmonary complications varied over time with a non-significant decreasing trend for pPPE (p=0.64). A decreasing trend in pulmonary complications was found to be significant for ppPPE (p<0.0001) and for total PPE (p<0.0001) with reduction of pneumatoceles and pachypleuritis (Table 3).

Pneumococcal serotypes

Pneumococcal serotyping was obtained for 49 bacteriological samples isolated between 2005 and 2019. Except for two isolates, the serotypes identified were all VTs included in PCV13, in particular serotypes 1, 3, 5, 7F, 19A. There were 26 cases attributed to serotype 1, 2 cases to serotype 3, 7 cases to serotype 5, 1 case to serotype 7F, 1 case to serotype 8, 1 case to serotype 12F and 11 cases to serotype 19A. The serotypes distribution by vaccination period is shown in Table 4. Serotypes 1 and 19A were the most frequently found and represented approximately 75% of our identified cases (37 of 49 samples). PCV13 VTs were predominant during the PCV7 period. They decreased during the PCV13 period. Then, during the PCV10 period, serotype 19A increased slightly again and we observed cases due to serotypes 3, 8 and 12F. Among 10 patients admitted during the PCV13 period from whom serotypes were identified, 8 children had received three doses of PCV7 and 2 children had not been vaccinated against pneumococci. Among 6 patients in the PCV10 period, 3 children had received three doses of PCV13 and the other 3 children had received PCV10, one of whom had received only two doses. Serotype 1 was predominant during the first three periods and its incidence decreased to disappear during the PCV10 period (p=0.12) (Table 4). Serotypes 8 and 12F are not included in the VTs. The two patients from whom these serotypes were isolated had received a complete schedule of PCV13 vaccination.

S. pneumoniae identification and penicillin susceptibility

There was a significant increase in the use of polymerase chain reaction on pleural fluid as diagnostic tool for etiology of the PPE between the pre-PCV and PCV10 periods (0% to 57.9%; p<0.0001) (Table 4). The strains of *S. pneumoniae* isolated in culture and for which antibiotic susceptibility could be determined remained predominantly susceptible to first-line antibiotics during the vaccination periods (Table 5). Penicillin-resistant *S. pneumoniae* was identified in 3 children. All were 19A serotypes. Among the 3 patients, 1 had a penicillin allergy and was treated immediately with ciprofloxacin, 1 had a penicillin-resistant strain with an MIC of 1 µg/ml and was treated with high-dose penicillin and 1 died before receiving the antibiotic susceptibility profile.

Discussion

To assess the impact of pneumococcal vaccination on the occurrence of PPE, we performed a 20-year single-center retrospective study at Hôpital Universitaire Des Enfants Reine Fabiola, a tertiary pediatric hospital in Brussels. Our study suggests that the overall incidence of PPE among hospitalized children with CAP increased by 50.8% in 2019 compared to the pre-vaccination period.

This increase is primarily induced by the increased incidence of proven and potential pneumococcal PPE during vaccination periods. Moreover, we observe an increase of more than 50% in the incidence of the pneumococcal PPE after the introduction of pneumococcal vaccination, mainly in children under 5 years of age and in the category of complicated PPE. Nevertheless, based on short-term pulmonary complications, need for surgery and antibiotic duration the severity of pneumococcal PPE does not seem to vary over the different periods. This observation could be related with the decrease of the most aggressive serotypes by vaccination. To our knowledge, there is no study that has specifically evaluated the evolution of the number of PPE during the three pneumococcal vaccines periods even though reports of increased incidence of pneumococcal PPE before and following the introduction of PCV7 vaccine have already been published (8,23,12). The upward trend in the incidence of pneumococcal PPE before and after the PCV7 introduction in the vaccination schedule is also objectified in our study. This observation may be the consequence of a majority of complicated CAP related to non-PCV7 serotypes, notably 1, 3, 5, 7F and 19A (12). In addition, a study of serotype distribution in pediatric CAP showed that CAP associated with PCV7 serotypes are rare in PCV7 vaccinated children (21).

The consequences pneumococcal vaccines on the development of IPD in general have been widely analyzed in pediatric and adult populations around the world (15,24-26). Several recent studies show a decrease in the overall incidence of IPD after the introduction of PCV10 and PCV13 (24-26). On the contrary, a Belgian national retrospective observational study by Desmet et al. showed a pronounced upward trend in the incidence of IPD in children under 2 years of age after the replacement of the PCV13 by PCV10 between the years 2017 and 2018 (15). In Belgium, an increased rate of PCV13 non-PCV10 VTs has been identified in IPD in children after the introduction of PCV10 (15,27). Consequently, the national recommendation of pneumococcal vaccination has been modified towards PCV13 and a catch-up vaccination with PCV13 has been recommended for the patient with immunocompromising conditions at risk of IPD (18,27).

The World Health Organization recommends either a 2+1 schedule with 2 primary doses and a booster between 9 and 12 months of age or a 3+0 schedule with 3 primary doses without a booster (28). Currently, there is no consensus on the optimal regimen (28). In Belgium, we apply the 2+1 schedule based on the opinion of the Superior Health Council (27). The booster has been shown to induce a longer and more effective immunogenicity against some serotype such as serotype 1 (28).

At the worldwide level, studies have shown how complex the relation is between pneumococcal vaccine formulation and IPD epidemiology (2,8,15,23-27,29).

Our serotyping data are too scarce for complete analyses of serotypes distribution but overall concordant with several studies showing that serotype 1 is the most prevalent in CAP and empyema in children

(7,11). During the PCV10 period, we also observed a re-emergence of PCV13 non PCV10 VTs as reported in the Belgian national study by Desmet et al. (15). But we have limited serotype data which makes difficult to conclude on the benefit of a catch-up vaccination and on the impact of a booster vaccination schedule [2+1].

Our study is subject to several limitations. The retrospective nature of the study is associated with the unavailability of some data. We recruited our patients using the international classification of diseases encoding system which remains imprecise. However, the analysis of all records was performed by a single author to eliminate interobserver variability in data encoding. It should be noted that a change in the management of pneumonia took place since 2008 at our hospital and resulted in shorter intravenous antibiotic treatment durations and in more frequent outpatient treatments with oral antibiotics. This could have affected the proportion of PPE among all hospitalized CAP since the presence of a PPE was considered a reason for hospitalization. This change also makes that the duration of intravenous antibiotics is an unreliable parameter to assess the severity of the infection. Likewise, the incidence of chest drainages is prone to overestimation due to inter-hospital transfers to our tertiary center for patients with an indication for chest tube placement. Our results can also be influenced by the use of polymerase chain reaction which has a greater sensitivity than conventional methods (culture of biological fluid) (30,31). It may partly explain the increase in the incidence of proven pneumococcal PPE, but is however not sufficient to explain the increase in the incidence of potential pneumococcal PPE. CAP without PPE were not considered, therefore our observations cannot be extrapolated to the general population of CAP.

Conclusion

Although the overall incidence of empyema remains low, our data suggest a significant increase in the incidence of PPE during vaccine periods compared to the pre-vaccination period. A moderate reduction of the incidence of pPPE was observed during the PCV13 period. But after the transition to PCV10 we observed an increased incidence of total PPE. The epidemiology of pPPE is influenced by multiple factors which makes it difficult to interpret the outcomes. Currently, it is recommended to continue pneumococcal vaccination with PCV13 based on evidence of decreasing IPD in children. However reporting programs such as Pedisurv in Belgium and national and international surveys remains crucial to understand the dynamics of the pPPE incidence in the future.

Disclosure of conflicts of interest

The authors have no conflict of interest to declare.

Table 1: Clinical, biological and demographic characteristics of patients

Variables	Total PPE (n = 474)	Pneumococcal PPE (n = 140)	Potential pneumococcal PPE (n = 267)
Age (month), median (IQR)	41 (22-68)	37 (23-60)	48 (24-72)
Age (groups), n (%)			
< 2 years old	80 (16.9)	25 (17.9)	34 (12.7)
2 – 5 years old	223 (47.0)	74 (53.6)	123 (46.1)
≥ 5 years old	171 (36.1)	41 (29.3)	110 (41.2)
Male sex, n (%)	264 (55.7)	75 (53.6)	156 (58.4)
Pneumococcal vaccination status, n (%)			
No vaccine	216 (45.6)	52(37.1)	132 (49.4)
PCV7	133 (28.1)	57 (40.7)	63 (23.6)
PCV13	64 (13.5)	18 (12.9)	36 (13.5)
PCV10	24 (5.1)	7 (5.0)	12 (4.5)
Unknown	37 (7.8)	6 (4.3)	24 (9.0)
Prematurity, n (%)	25 (5.3)	7 (5.0)	13 (4.9)
Antecedent of lower respiratory tract infection, n (%)	99 (20.9)	18 (12.9)	71 (26.6)
IPD risk factors, n (%)	65 (13.7)	11 (7.9)	45 (16.9)
Asthma, n (%)	16 (3.4)	4 (2.9)	12 (4.5)
Hemoglobinopathy, n (%)	22 (4.6)	2 (1.4)	17 (6.4)
Immunodeficiency, n (%)	8 (1.7)	0 (0)	7 (2.6)
Malformative syndrome, n (%)	9 (1.9)	3 (2.1)	5 (1.9)
Neurological disease, n (%)	9 (1.9)	2 (1.4)	4 (1.5)
Oncological condition, n (%)	6 (1.3)	1 (0.7)	3 (1.1)

Table 2: Evolution of the incidence of parapneumonic pleural effusions (n) among hospitalized patients with pneumonia (N) during vaccination periods

	Total PPE total (n = 474)						Pneumococcal PPE (n = 140)						Potential pneumococcal PPE (n = 267)					
	Periods						Periods						Periods					
Variables, n (% pneumonia)	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]	Pre-PCV (N = 2057)	PCV7 (N = 1667)	PCV13 (N = 1171)	PCV10 (N = 699)	Difference between pre-PCV and PCV10, %	p [a]
Total PPE	172 (56.3)	121 (72.6)	101 (86.3)	80 (114.4)	+ 50.8	<0.0001	-	-	-	-	-	-	-	-	-	-	-	-
Microbial agent																		
Pneumococcal PPE	35 (11.4)	57 (34.2)	29 (24.8)	19 (27.2)	+ 58.1	0.0005	-	-	-	-	-	-	-	-	-	-	-	-
Potential pneumococcal PPE	107 (35.0)	53 (31.8)	58 (49.5)	49 (70.1)	+ 50.1	<0.0001	-	-	-	-	-	-	-	-	-	-	-	-
Bacterial PPE *	22 (7.2)	9 (5.4)	8 (6.8)	6 (8.6)	+ 16.3	0.88	-	-	-	-	-	-	-	-	-	-	-	-
Viral PPE	8 (2.6)	2 (1.2)	6 (5.1)	6 (8.6)	+ 69.8	0.02	-	-	-	-	-	-	-	-	-	-	-	-
Age groups																		
< 2 years old	29 (9.5)	18 (10.8)	10 (8.5)	23 (32.9)	+ 71.1	0.0004	7 (2.3)	9 (5.4)	3 (2.6)	6 (8.6)	+ 73.3	0.06	13 (4.3)	7 (4.2)	4 (3.4)	10 (14.3)	+ 69.9	0.02
2 à 5 years old	78 (25.5)	55 (33.0)	56 (47.8)	34 (48.6)	+ 47.5	<0.0001	16 (5.2)	26 (15.6)	21 (17.9)	11 (15.7)	+ 66.9	0.0003	53 (17.3)	24 (14.4)	27 (23.1)	19 (27.2)	+ 36.4	0.06
≥ 5 years old	65 (21.3)	48 (28.8)	35 (29.9)	23 (32.9)	+ 35.3	0.03	12 (3.9)	22 (13.2)	5 (4.3)	2 (2.9)	- 25.6	1.00	41 (13.4)	22 (13.2)	27 (23.1)	20 (28.6)	+ 53.1	0.002
Sex																		
Female	77 (25.2)	53 (31.8)	43 (36.7)	37 (52.9)	+ 52.4	0.0002	14 (4.6)	29 (17.4)	13 (11.1)	9 (12.9)	+ 64.3	0.01	66 (21.6)	36 (21.6)	37 (31.6)	25 (35.8)	+ 39.7	0.04
Male	95 (31.1)	68 (40.8)	58 (49.5)	43 (61.5)	+ 49.4	<0.0001	21 (6.9)	28 (16.8)	16 (13.7)	10 (14.3)	+ 51.7	0.02	49 (16.0)	19 (11.4)	23 (19.6)	20 (28.6)	+ 44.1	0.0003

a Cochran-Armitage test for trend; p, p-value; n, number of parapneumonic pleural effusion cases; N, number of hospitalized cases with pneumoniae per vaccination period.

* Other than pneumococcus

Table 3: PPE characteristics and management

	Total PPE (n = 474)						Pneumococcal PPE (n = 140)						Potential pneumococcal PPE (n = 267)					
	Periods						Periods						Periods					
Variables, n (% PPE)	Pre-PCV (n = 172)	PCV7 (n = 121)	PCV13 (n = 101)	PCV10 (n = 80)	Difference between pre-PCV and PCV10, %	p a	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)	Difference between pre-PCV and PCV10, %	p a	Pre-PCV (n = 107)	PCV7 (n = 58)	PCV13 (n = 58)	PCV10 (n = 49)	Difference between pre-PCV and PCV10, %	p a
Variables, n (% PPE)																		
PPE categories																		
Unknown	93 (54.1)	48 (39.7)	63 (62.4)	52 (65.0)	+ 16.8	0.03	10 (28.6)	10 (17.5)	4 (13.8)	5 (26.3)	- 8.0	0.60	67 (62.6)	37 (69.8)	52 (89.7)	41 (83.7)	+ 25.2	0.0002
Simple	11 (6.4)	6 (5.5)	5 (5.0)	4 (5.0)	- 21.9	0.64	1 (2.9)	0 (0)	3 (10.3)	1 (5.3)	+ 45.3	0.25	9 (8.4)	3 (5.7)	1 (1.7)	3 (6.1)	- 27.4	0.32
Complicated	24 (14.0)	33 (27.3)	15 (14.9)	12 (15.0)	+ 6.7	0.96	3 (8.6)	17 (29.8)	11 (37.9)	9 (47.4)	+ 81.3	0.001	19 (17.8)	11 (20.8)	3 (5.2)	0 (0)	- 100	0.0003
Empyema	44 (25.6)	36 (29.8)	18 (17.8)	12 (15.0)	- 41.4	0.03	21 (60.0)	30 (52.6)	11 (37.9)	4 (21.1)	- 64.8	0.003	12 (11.2)	2 (3.8)	2 (3.4)	5 (10.2)	- 8.9	0.49
Treatment																		
Antibiotic alone	70 (40.7)	45 (37.2)	56 (55.4)	50 (62.5)	+ 34.9	0.0002	8 (22.9)	8 (14.0)	1 (3.4)	3 (15.8)	- 31.0	0.18	49 (45.8)	36 (67.9)	48 (82.8)	41 (83.7)	+ 45.3	0.0001
Single or repeated thoracocentesis	8 (4.7)	1 (0.8)	1 (1.0)	4 (5.0)	+ 6.0	0.71	1 (2.9)	0 (0)	0 (0)	0 (0)	- 100	0.39	6 (5.6)	0 (0)	0 (0)	2 (4.1)	- 26.8	0.36
Percutaneous chest tube	57 (33.1)	37 (30.6)	19 (18.8)	10 (12.5)	- 62.2	<0.0001	13 (37.1)	23 (40.4)	8 (27.6)	7 (36.8)	- 0.8	0.65	33 (30.8)	10 (18.9)	6 (10.3)	2 (4.1)	- 86.7	<0.0001
Surgery (VATS)	37 (21.5)	38 (31.4)	25 (24.8)	16 (20.0)	- 7.0	0.88	13 (37.1)	26 (45.6)	20 (69.0)	9 (47.4)	+ 21.7	0.12	19 (17.8)	7 (13.2)	4 (6.9)	4 (8.2)	- 53.9	0.04
Pulmonary complications	57 (33.1)	20 (16.5)	18 (17.8)	7 (8.8)	- 73.4	<0.0001	14 (40.0)	12 (21.1)	12 (41.4)	5 (26.3)	- 34.3	0.64	31 (29.0)	5 (9.4)	3 (5.2)	0 (0)	- 100	<0.0001
Pneumothorax	15 (8.7)	12 (9.9)	13 (12.9)	3 (3.8)	- 56.3	0.56	5 (14.3)	7 (12.3)	9 (31.0)	3 (15.8)	+ 9.5	0.30	7 (6.5)	3 (5.7)	2 (3.4)	0 (0)	- 100	0.07
Pneumatocele	18 (10.5)	8 (6.6)	3 (3.0)	4 (5.0)	- 52.4	0.03	4 (11.4)	5 (8.8)	3 (10.3)	3 (15.8)	+ 27.8	0.68	10 (9.3)	3 (5.7)	0 (0)	0 (0)	- 100	0.002
Pachypleuritis	26 (15.1)	6 (5.0)	3 (3.0)	0 (0)	- 100	<0.0001	6 (17.1)	5 (8.8)	1 (3.4)	0 (0)	- 100	0.02	15 (14.0)	1 (1.9)	1 (1.7)	0 (0)	- 100	0.0001
Lung abscess	9 (5.2)	4 (3.3)	1 (1.0)	3 (3.8)	- 26.9	0.26	4 (11.4)	3 (5.3)	1 (3.4)	2 (10.5)	- 7.9	0.74	4 (3.7)	0 (0)	0 (0)	0 (0)	- 100	0.04
Variables, median, day (IQR)						p b						p b						p b
Total length of stay	15 (9 – 20)	13 (7 – 18)	10 (5 – 16)	9 (4 – 16)	-	<0.0001	19 (13 – 23)	16 (13 – 19)	17 (13 – 28)	18 (12 – 22)	-	0.24	13 (8 – 19)	9 (5 – 14)	6 (4 – 11)	5 (3 – 12)	-	<0.0001
Duration of intravenous antibiotic therapy	14 (7 – 20)	14 (6- 18)	8 (4 – 14)	7 (3 – 14)	-	<0.0001	20 (15 – 21)	16 (13 – 19)	14 (12 – 23)	14 (10 – 19)	-	0.45	12 (7 – 17)	8 (5 – 14)	5 (3 – 8)	5 (2 – 10)	-	<0.0001

a Cochran-Armitage test for trend

b Kruskal-Wallis test

p, p-value; n, number of parapneumonic pleural effusion cases

Table 4: Evolution of identification methods and pneumococcal serotypes during vaccination periods

Variables, n (% pneumococcal PPE)	Periods				Difference between pre-PCV and PCV10, %	p *
	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)		
Identification of *S. pneumoniae*						
Blood culture	25 (71.4)	24 (42.1)	9 (31.0)	4 (21.0)	- 70.6	0.0001
Pleural fluid culture	8 (7.4)	5 (8.8)	3 (10.3)	3 (15.8)	+ 53.2	0.40
Blood and pleural fluid culture	2 (5.7)	5 (8.8)	2 (6.9)	1 (5.3)	- 7.0	0.92
Polymerase Chain Reaction	0 (0)	23 (40.3)	15 (51.7)	11 (57.9)	+ 100	<0.0001
Serotypes						
1	8 (22.9)	11 (19.3)	7 (24.1)	0 (0)	- 100	0.12
3	0 (0)	0 (0)	0 (0)	2 (10.5)	+ 100	0.01
5	1 (2.9)	4 (7.0)	2 (6.9)	0 (0)	- 100	0.81
7F	0 (0)	1 (1.7)	0 (0)	0 (0)	-	0.81
8	0 (0)	0 (0)	0 (0)	1 (5.3)	+ 100	0.26
12F	0 (0)	0 (0)	0 (0)	1 (5.3)	+ 100	0.07
19A	2 (5.7)	6 (10.5)	1 (3.4)	2 (10.5)	+ 45.7	0.88
No serotypes	24 (68.6)	35 (61.4)	19 (65.5)	13 (68.4)	- 0.3	0.94

a Cochran-Armitage test for trend; p, p-value; n, number of pneumococcal parapneumonic pleural effusion cases.

Table 5: Evolution of identification methods and pneumococcal serotypes during vaccination periods

Variable, n (% pneumococcal PPE)	Periods			
	Pre-PCV (n = 35)	PCV7 (n = 57)	PCV13 (n = 29)	PCV10 (n = 19)
Penicillin susceptibility				
Susceptible	28 (80.0)	29 (50.9)	12 (41.4)	8 (42.1)
Intermediate	5 (14.3)	3 (5.3)	0 (0)	0 (0)
Resistant	0 (0)	2 (3.5)	1 (3.4)	0 (0)

n, number of pneumococcal parapneumonic pleural effusion cases

Figure 2: Evolution of the annual incidence of parapneumonic pleural effusions

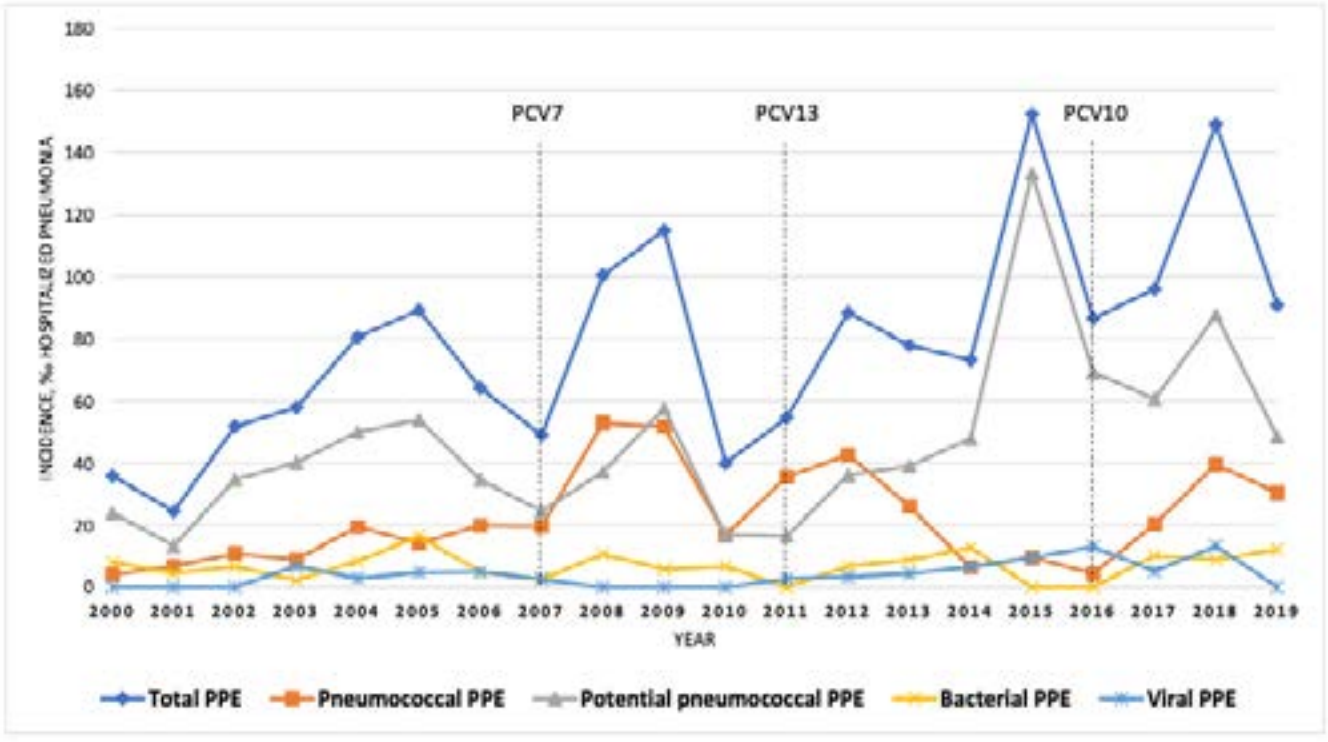
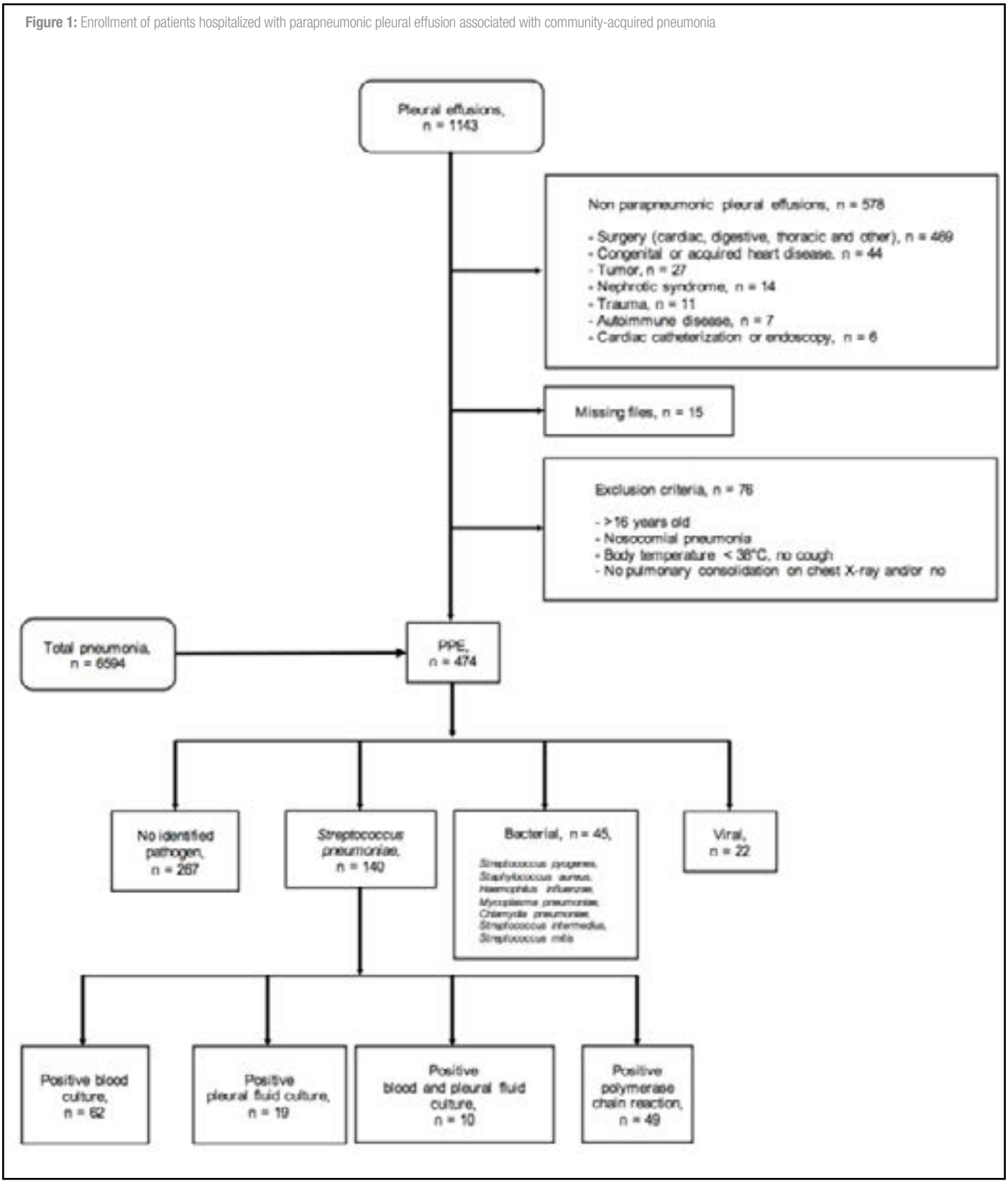


Figure 1: Enrollment of patients hospitalized with parapneumonic pleural effusion associated with community-acquired pneumonia



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VACCINEER MET VERTROUWEN TEGEN MenB

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.

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 B-vaccin (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. **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 B stammen. 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: 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). **Bijzondere waarschuwingen en voorzorgen bij gebruik:** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen (zie rubriek 5.1 van de volledige SPK). Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties (zie rubriek 5.1 van de volledige SPK). Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. Dit middel bevat minder dan 1 mmol natrium (23 mg) per dosis, dat wil zeggen dat het in wezen 'natriumvrij' is. Terugvinden herkomst: Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. **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 vaccinatie reeks. 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 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 - B-1000 Brussel - Madou - Website: www.eenbijwerkingmelden.be - e-mail: adr@fagg.be. **Luxemburg:** Centre Régional de Pharmacovigilance de Nancy - Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) - CHRU de Nancy - Hôpitaux de Brabois - Rue du Morvan - 54 511 Vandoeuvre Les Nancy Cedex - Tél.: (+33) 3 83 65 60 85 / 87 - e-mail: crpv@chru-nancy.fr ou Direction de la Santé - Division de la Pharmacie et des Médicaments - 20, rue de Bitbourg - L-1273 Luxembourg-Hamm - Tél.: (+352) 2478 5592 - e-mail: pharmacovigilance@ms.etat.lu - Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html. **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:** 25/02/2022 (v13). **AFLEVERINGSWIJZE:** Op medisch voorschrift. **Referentie:** SmPC Bexsero

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GSK

Paediatric subspecialties in Belgium: past, present, and future

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Keywords

Paediatrics; subspecialties; fellowships; training; organisation; future

Abstract

Objective: As paediatrics is a constantly evolving specialty, the interest in subspecialties has increased over the last decades. However, for a long time, only three paediatric subspecialties had official recognition criteria in Belgium (haematology and oncology, neurology, and neonatology) and recently infectiology was added to the shortlist. Importantly, the number of recognized subspecialties is varying between European countries. With this study, we aim to provide insights into the preferences of future paediatricians, especially on subspecialisation.

Methods: Between October 1st, 2021, and December 6th, 2021, the youth representatives of the Flemish Society of Paediatrics (Jong VVK) conducted a comprehensive survey on professional preferences among paediatric trainees and recently graduated paediatricians in Belgium. The survey included 34 questions and statements with an emphasis on subspecialisation and (future) work perspectives. The answers were compared with data from similar surveys in other countries.

Results: The survey was completed by 287 respondents. This survey was the first to include data from all universities in Belgium. In line with previous surveys among Flemish trainees, 80% of the respondents indicated wanting to subspecialize or having subspecialized and only 1% preferred working exclusively in private practice. The three most preferred subspecialties were neonatology, pulmonology, and infectiology. Interestingly, for two out of three respondents, the presence of official recognition criteria would affect their ambition to subspecialise.

Interpretation: Our unique dataset provides valuable insights into the future preferences of young paediatricians in Belgium. To optimize the career flow of the next generation of paediatricians, better structuring of subspecialties is warranted.

Introduction

Children are not miniature adults and a holistic approach is needed when treating paediatric patients. The higher survival rate of paediatric patients with severe and/or chronic conditions has led to an increasing prevalence of medically complex children (1, 2). Consequently, the paediatric workforce has been evolving towards more (sub)specialized medicine. Fellowships, i.e. additional training to become specialized in one or more subspecialties, are becoming increasingly important to support this evolution. Up until 2021, only three subspecialties had specific subspecialty criteria and were recognized by the Belgian government: neonatology, paediatric neurology, and paediatric haematology-oncology (3). Recently, infectiology was added to the shortlist, setting the final count of recognized subspecialties in Belgium on four subspecialties. In 2013, a mini-questionnaire among 46 different paediatric societies in Europe revealed the number of recognized subspecialties to vary from 0 to 20 in the 29 responding countries, of which 11 countries declared to recognize more than 10 different subspecialties (4). The approved syllabi for paediatric subspecialty training by the European Board of Paediatrics (EBP) provide guidelines for multiple subspecialties but not for all, and they are not yet associated with official recognition (5). These data demonstrate the lack of standardised and harmonised paediatric subspecialty recognition criteria in Belgium and Europe, with an impact on international mobility and collaboration.

Paediatric subspecialty criteria have been developed over time to standardise certain subspecialties within the field of paediatrics. These criteria allow paediatricians with expertise in a paediatric subspecialty to attract and treat patients with specific conditions, optimising patient care. Without these criteria, subspecialised paediatricians are unable to valorise their expertise. However, few studies have focused on the financial outcome of general versus subspecialised paediatricians. A study in 2011 in Atlanta (Georgia, USA) demonstrated that the financial returns of paediatric fellowship training varied greatly depending on which subspecialty fellowship was chosen. Pursuing a fellowship in most paediatric subspecialties was a negative financial decision when compared with practicing as a general paediatrician (6). Similar Belgian or European analyses are lacking in the current literature. The reasons for subspecialising are also very variable and differ from one country to another (7, 8).

To shape and standardise fellowships in Belgium and Europe, knowledge of the current profile and future expectations of paediatric trainees and young paediatricians is mandatory. In 2012 and 2015, youth representatives of the Flemish Society of Paediatrics (Jong VVK) surveyed their fellow paediatric trainees to map their profile and expectations (9). However, these surveys had some limitations. First, they were limited to the Flemish universities which complicated conclusions on a national level. Second, all respondents were paediatricians in training, lacking retrospective opinions of recently graduated paediatricians. Third, the emphasis of these surveys was on workload and future work conditions, rather than subspecialties and their recognition criteria. Therefore, in this context, we initiated a first national survey among paediatric trainees and recently graduated paediatricians of all Belgian universities about subspecialisation and future work preferences.

Methods

The survey was drafted by youth representatives of the Flemish Society of Paediatrics (Jong VVK). The content of the questions was based on previous surveys, as conducted in 2012 and 2015 (9), with the addition of

questions concerning paediatric subspecialisation. Questions were drafted after multiple internal review rounds and only approved by universal consensus. The survey was distributed electronically among all university and regional hospitals in Belgium. After the first version in Dutch, the survey was translated to French by a native speaker for distribution among all French-speaking universities. The filling-in period was from October 1st, 2021, to December 6th, 2021, and all replies were submitted electronically and anonymously.

The survey comprised 25 questions, of which 23 were multiple-choice questions, and 9 statements with 5 possible answers: *completely agree*, *agree*, *neutral*, *disagree*, and *completely disagree*. Apart from demographic questions, the emphasis was placed on subspecialisation and (future) work perspectives. After collecting all the results, sub-analyses were performed to compare Flemish respondents with French-speaking respondents, males with females, and universities. Statistics were performed using the Chi-Square with Benjamini Hochberg correction for multiple testing. The significance level for comparison analyses was set at a p-value of <0.05.

Results

General

The survey was completed by 287 respondents, of which almost 60% were trainees (see Figure 1). The average age of all respondents was 29.3 years old, and the majority were female (82.2%). All demographic characteristics are displayed in Table 1. Importantly, this survey was the first to include data from all universities in Belgium with a representative spread over the 7 different universities, besides a relative underrepresentation of Vrije Universiteit Brussels, KU Leuven, and Université de Liège.

Subspecialisation

Four out of 5 respondents (79.8%) indicated wanting to subspecialize or having subspecialized. The subspecialty preferences are shown in Figure 2. The 3 most preferred subspecialties were neonatology (15%), pulmonology (12.9%), and infectiology (11.8%), with 43 respondents (15.0%) not yet knowing which subspecialty they want to acquire. Males prefer to subspecialise more when compared to females (92.0% vs 77.1%, p=0,017). 'Interest in the field' was repeatedly (75.6%) declared as the primary motivation for subspecialisation. Interestingly, 41.5% of all respondents aspiring to subspecialise (95/229) prefer to do this at another university (domestic or foreign), while only 1 out of 3 (31.4%) respondents who have already applied for a fellowship, applied to an external department. Flemish-speaking trainees prefer a fellowship at their own university, in contrast to French-speaking trainees who prefer a foreign or other domestic universities (64.2% vs 39.2%, p<0,001). Noteworthy, 57.5% of all respondents (165/287) were not aware of all available fellowship positions, and 45.2% of all fourth- to seventh-year paediatric trainees (33/73) indicated they aspired to a fellowship, but lacked confirmation due to scarcity or absence of fellowship positions. Large majorities indicated a central overview of available fellowships would be very useful (93.7%) and a separate statute for fellows is mandatory (85.4%). For 2 out of 3 respondents (62.7%), the presence of subspecialty criteria would affect or has affected their ambition to subspecialise. Strikingly, 71.4% of all respondents would agree to a general training of 4 years, followed by a (mandatory) subspecialty training of 2 years, while only 13.9% would disagree.

Future

Next, we analysed future work expectations and preferences (Table 2); 65.5% preferred to work exclusively in a hospital, and only 2.4% in private practice. About one quarter (26.8%) still wants to combine their hospital activity with a private practice. Interestingly, an equal number (28.2%) of respondents wanted to work academically and regionally, and 58 respondents (20.2%) declared that subspecialising was or is needed for a future workplace. Half (51.7%) of these 58 respondents wanted to work academically, and only 10 (17.2%) of them regionally. One out of four (26.8%) respondents declared (wanting) to be self-employed, while 30.7% do not know yet. Moreover, 42.7% of the 199 paediatric trainees

Figure 1: Slice chart of the distribution in training of all respondents (n = 287).

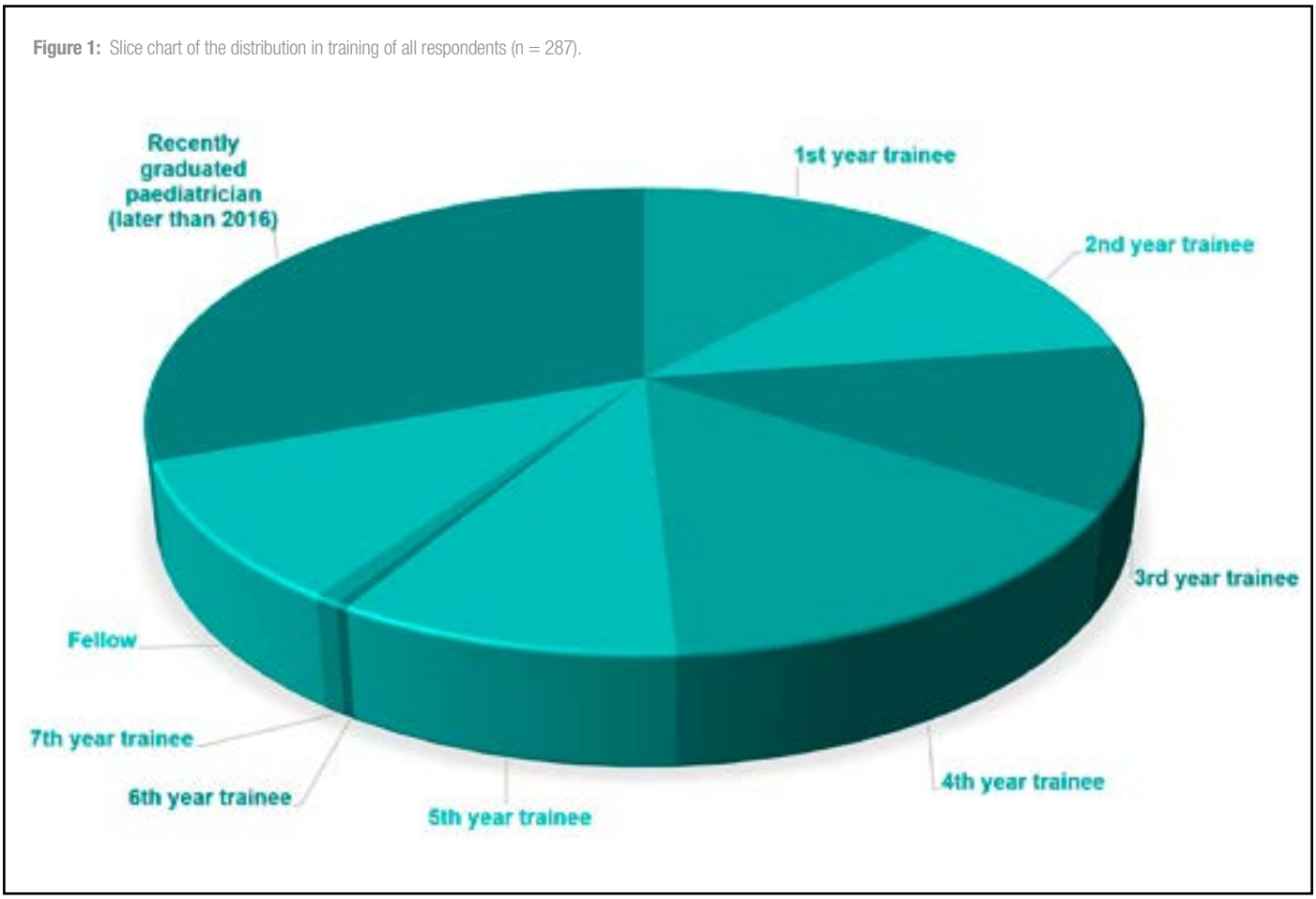


Table 1: Demographic characteristics of all respondents (n = 287) with number, percentage or mean, and response rate.

Characteristics	N	%	Mean	Response rate
Age	287		29.3y	
Gender				
Female	236	82.2		
Male	50	17.4		
Other	1	0.3		
Marital Status				
Married	85	29.6		
In a relationship	143	50.0		
Single	57	20.0		
Other	2	0.7		
Function				
Paediatric trainee	171	59.6		
In training for subspecialty/fellow	28	9.8		
Working as general paediatrician or subspecialist	88	30.7		
Geography				
Flemish/Dutch-speaking university	153	53.3		
Antwerp University	42	14.6		41.2%
Vrije Universiteit Brussels	25	8.7		25.3%
Ghent University	55	19.2		49.1%
KU Leuven	31	10.8		24,4%
French-speaking university	134	46.7		
Université libre de Bruxelles	48	16.7		43.6%
Université de Liège	28	9.7		25.7%
Université catholique de Louvain	58	20.2		50.4%

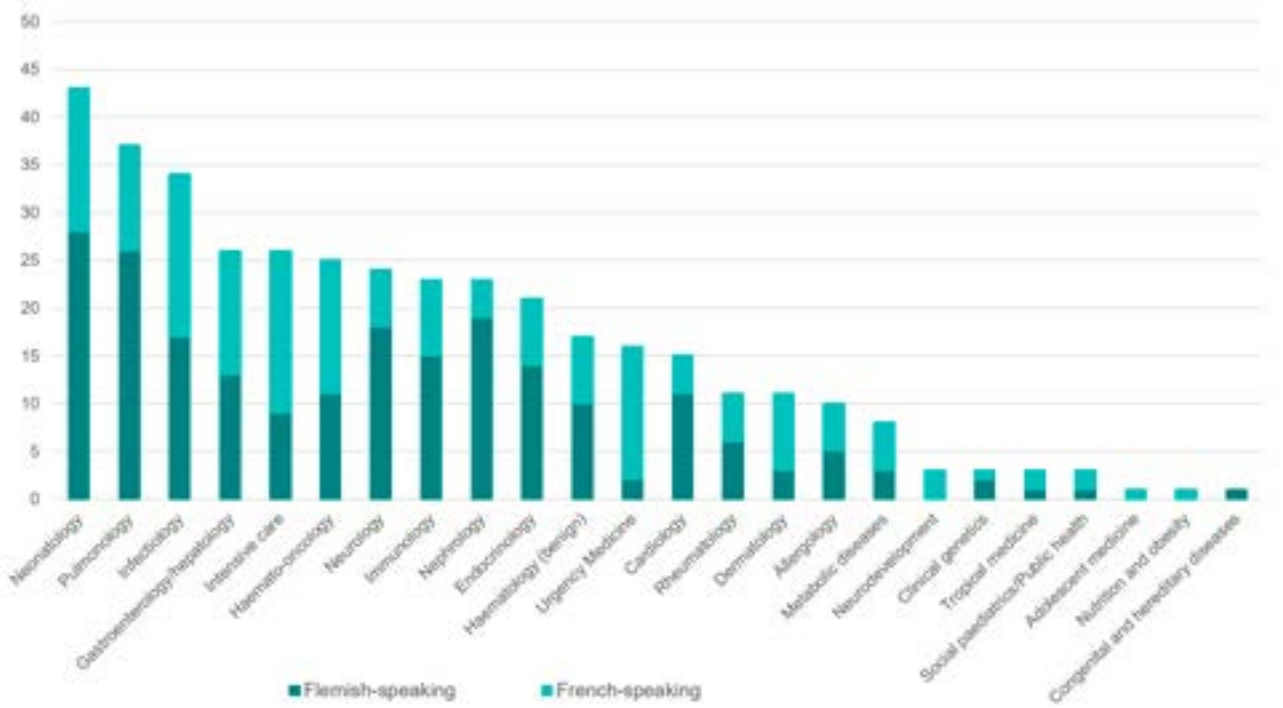
Table 2: Future work environment preferences of all respondents (n = 287) with number and percentage.

Future work environment	N	%
Hospital vs private practice		
Hospital	188	65.5
Private practice	7	2.4
Combination	77	26.8
Not (yet) known	15	5.2
Academic vs regional		
Academic	81	28.2
Regional	81	28.2
Combination	74	25.8
Not (yet) known	51	17.8
Statute		
Self-employed	77	26.8
Employee	67	23.3
Combination	55	19.2
Not (yet) known	88	30.7
Need for subspecialty		
Yes	58	20.2
No, but strongly recommended	57	19.9
No, not needed	51	17.8
Not (yet) known	121	42.2

Table 3: Timing of confirmation of a future workplace after graduation for all 5th to 7th year trainees, fellows, and recently graduated paediatricians (n = 146) with number and percentage.

Timing of confirmation	N	%
1st year	3	2.1
2nd year	2	1.4
3rd year	12	8.2
4th year	11	7.5
5th year	42	28.8
6th year	15	10.3
7th year	7	4.8
No confirmation yet	54	36.9

Figure 2: Slice chart of the distribution in training of all respondents (n = 287).



and fellows have not yet decided under which statute they want to work in the future. Flemish-speaking trainees and recently graduated paediatricians clearly prefer to work exclusively in a hospital or the combination, when compared to French-speaking trainees or recently graduated paediatricians (77.1% vs 52.2%, $p<0.001$). The timing of confirmation of a future workplace for all fifth-to seventh-year trainees, fellows and recently graduated paediatricians is displayed in Table 3. Critically, two out of three fifth-to seventh-year trainees and fellows (38/58) have no confirmation of a future workplace yet, among which 18 of the 28 fellows (64.3%). Additionally, 18,2% of all recently graduated paediatricians (16/88) had no workplace upon graduation.

Discussion

Paediatrics is a constantly evolving specialty, which warrants evaluating its progress over time. As more specialized care for paediatric patients is mandatory, paediatric subspecialties have increasingly gained interest over the last decades. However, few subspecialties in Belgium have official recognition criteria and a national framework to mitigate the transition from a paediatric trainee to a fellow or graduated paediatrician with a subspeciality degree is incomplete.

This survey was the first to comprise input from all paediatric trainees and recently graduated paediatricians about subspecialisation and future work perspectives on a national level. Importantly, almost 80% of all respondents indicated wanting to subspecialize or having subspecialized, confirming an increased interest in subspecialty of paediatric trainees and young paediatricians, when compared with previous surveys in 2012 and 2015 (42% and 62%, respectively) (9). In contrast, the estimated need for subspecialized paediatricians is lower, suggesting that data concerning the available subspecialist positions and the actual needs are absent. 'Interest in the field' was indicated as the most important factor for wanting to subspecialize, which is in line with previous American surveys among paediatric trainees (7). As infectious diseases is the third most wanted subspecialty, it is worth mentioning that this survey was conducted during the Covid-19 pandemic, possibly influencing the preferences of the respondents. Importantly, subspecialties such as social paediatrics, obesity and nutrition, and adolescent medicine seem to lack interest among the young generation of paediatricians. However, the implication of more paediatricians in those fields may have a major impact on the disease burden in adults in the long run.

As more than half of the respondents are not aware of all available fellowship positions, a central overview of available fellowships may be needed to facilitate the flow from trainee to fellow. In fact, 4 out of 9 fourth-to seventh-year paediatric trainees aspire to a fellowship, but declare that there is a scarcity or absence of fellowship positions. A substantial part of the respondents aspiring to a fellowship (41.5%) prefers to do this at another university, whether domestic or foreign. Nevertheless, only a smaller number of trainees is likely to apply to an external department. To fulfil the need for foreign fellowships and enhance international mobility, a central overview of all European fellowship positions and shared uniform recognition criteria may be very useful.

Nearly 3 out of 4 respondents (71.4%) indicated they would agree to a general paediatric training (*truncus communis*) of 4 years, pursued by a subspecialty training of 2 years. This would be similar to the training structure of internal medicine in Belgium, but also to the curriculum in The Netherlands for example. Whether or not these 2 years of subsequent subspecialty training would be mandatory, including for those pursuing a career in general paediatrics, remains to be elucidated. In any case, an organized structure may lead to a better flow and facilitate the recognition of all paediatric subspecialties, possibly including general paediatrics.

Official recognition criteria for subspecialties are highly needed, as the decision of whether or not to subspecialize depends or has depended on these criteria for 62% of all respondents. In the previous surveys, 84% of all respondents already acknowledged that recognition criteria for subspecialties are highly required (9). Furthermore, a special statute for fellows is expressed by the majority as very desirable. When comparing the statute of fellows in Belgium is compared to the statute in The Netherlands for example, considerable differences in terms of salary, education, workload, and more importantly recognition, are found. This again highlights the fact that there is a pivotal need for recognition criteria of

subspecialties, not only in Belgium but even more so in Europe. Nevertheless, a distinction should be made between paediatricians aspiring for additional training to expand their knowledge as general paediatricians and paediatricians aspiring for an academic career planning to treat almost exclusively patients in their subspeciality. At the moment, they both follow the same fellowship, although their future goals and perspectives are different. Keeping these differences in mind, an international consensus about the recognition criteria of subspecialties will be the keystone to streamlining subspecialty training and facilitating the career flow of all paediatric trainees in Belgium and in Europe.

The majority of respondents indicated wanting to work exclusively in a hospital, while 1 out of 4 (26.8%) prefer a combination of hospital care with private practice. In previous surveys among Flemish paediatric trainees, the percentage of trainees preferring to combine part-time hospital care with private practice differed from 63% in 2012 to 79% in 2015, with a decline in the importance of working in private practice. Comparing these numbers with the results of this national survey, we can see a shift in preferred future work environments towards hospital care instead of private practices. Working exclusively in private practice was only indicated by 7 French-speaking paediatric trainees (2.4%), while Flemish trainees still refrain from it (0%) (9). Noteworthy, the number of respondents who want to work academically was the same as the number wanting to work in a regional hospital. Moreover, subspecialising was needed or strongly recommended in view of a future workplace for 2 out of 5 respondents, emphasizing the urge for streamlined fellowship programs. Strikingly, more than three-quarters of the fourth- to seventh-year trainees and fellows lack confirmation of a future workplace, highlighting the need for an enhanced flow to and after graduation.

Limitations

Although this study revealed valuable data on the profile and (future) preferences of paediatric trainees, fellows, and young paediatricians in Belgium, there are also some limitations. First, this survey was only open for a short period (2 months) and not distributed equally by the different universities, possibly missing out on a higher response rate. Second, the survey was conducted solely by youth representatives of the Flemish Society of Paediatrics (Jong VVK) and not reviewed beforehand by external paediatricians or internship supervisors, which could have led to biased questions and/or statements. In addition, locoregional differences may explain some of the heterogeneity of the data set as well as limit its external validity. Consequently, conclusions should not be simply extrapolated and additional studies are warranted to map these findings on a European level. Third, detailed financial analyses of fellowships or working as a subspecialised paediatrician versus working as a general paediatrician in Belgium are lacking. Subsequent studies on the financial impact of career choices in paediatrics in Belgium and in Europe are needed.

Conclusion

This unique dataset provides valuable insights into the desires and needs of the future generation of paediatricians in Belgium. Additional studies about this topic on a European level are needed. Better structuring of fellowships and subspecialties is warranted to enhance the transition from training to graduation and optimize the career flow of future paediatricians in Belgium and Europe.

Acknowledgements

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Conflicts of interest

All authors have no financial or non-financial interests to disclose.

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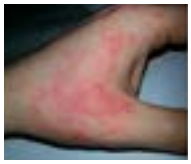
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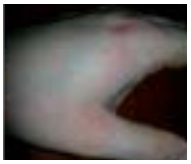
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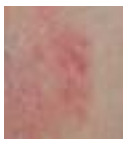
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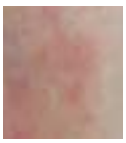
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Inhoud

Infective endocarditis with embolic complications caused by Abiotrophia defectiva. A case report.

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Keywords

Infective endocarditis, nutritionally variant Streptococcus, Abiotrophia defectiva, Shprinzten-Goldberg syndrome

Abstract

We describe the case of Abiotrophia defectiva infective endocarditis in a 13-year old boy with underlying cardiac abnormalities. Our patient presented with atypical symptoms, leading to delayed diagnosis and several complications. After antibiotical treatment, surgical intervention was indicated.

Infective endocarditis (IE) caused by nutritionally variant streptococci in pediatric population is rare. These fastidious microorganisms, growing very slowly in the laboratory, are known to be responsible for complicated IE.

This case report illustrates the atypical presentations of IE. It also reminds us that IE should rapidly be raised in patients with predisposing factors, such as structural congenital heart disease, and emphasizes the importance of blood cultures.

Introduction

Infective endocarditis (IE) is very rare, especially in children, with an estimated annual incidence of 0.43 cases per 100.000 children (1).

IE caused by Abiotrophia defectiva, a nutritionally variant streptococcus (NVS) species, is characterized by a subacute atypical clinical presentation. Only a dozen cases have been previously reported in children, of which a majority with underlying cardiac disease (2). Early diagnosis and adequate treatment are crucial.

In this case report, we describe an unusual presentation of IE due to Abiotrophia defectiva in a 13-year old boy with underlying cardiac abnormalities. By the time of diagnosis, complications had already occurred, and led to mitral valve plasty. Management by a multidisciplinary team was required.

Case report

Clinical presentation

A 13-year old boy was seen in the emergency room with a 4-month history of fatigue and intermittent inflammatory symptoms of the inferior limbs, notably swelling and warmness. His ankles were swollen and painful. In the last weeks, he presented two episodes of petechial lesions on the lateral malleolus which disappeared spontaneously (figure 1).

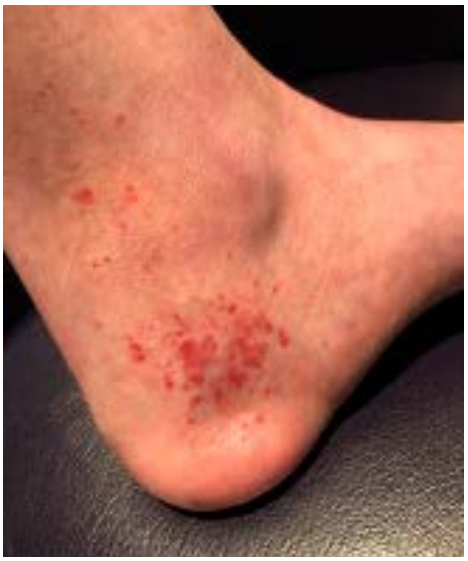
Interestingly, our patient was diagnosed with Shprintzen-Goldberg syndrome (SGS), a rare genetic disorder characterized by delayed global development, marfanoid features, a characteristic facies, skeletal abnormalities and cardiovascular anomalies (3). Cardiovascular anomalies include mitral valve prolapse, secundum atrial septal defect and aortic root dilatation. SGS results most frequently from de novo mutations of the SKI gene. Approximately sixty cases have been described in the literature.

Our young patient had all these features. He was followed up annually by the pediatric cardiologist and geneticist. His last yearly cardiac follow-up was a year ago and showed a stable atrio-ventricular valve prolapse with mild mitral valve and tricuspid valve regurgitation and a discrete aortic root dilatation.

Since the onset of symptoms, he had consulted his family doctor on several occasions for arthralgia and petechial rash, without fever. Symptomatic treatment with painkillers was initiated. He was then referred to an orthopedic surgeon who ordered a Doppler-US and an MRI of the lower limbs. They showed no abnormalities. Due to persistent complaints, he was referred to our hospital. Of note, he had undergone a dental procedure 1 year before and received adequate antibiotic prophylaxis, though he did not meet the criteria.

On initial examination he was afebrile with tachycardia (heart rate 128/minute), normal blood pressure (100/67 mmHg) and a saturation of 100% in room air. Clinical examination showed the known dysmorphia with arachnodactyly and finger clubbing, general amyotrophia and pallor. Petechial lesions were seen on his left foot. Heart auscultation revealed a

Figure 1: Initial examination : petechial lesions on exterior malleolus of the right foot.



systolic murmur grade 3/6 in the mitral area, increased compared to his last cardiologist's report. Respiratory examination was normal. No Janeway lesions, Roth's spots and Osler nodes were found. Abdominal palpation revealed splenomegaly. Orthopedic examination showed painful palpation and mobilization of his left upper and lower limbs. He suffered from severe back pain which prevented him from walking. A left hemiparesis was found on neurological examination. On the day of admission, he presented two fever spikes.

Investigations

His initial laboratory workup showed moderate microcytic anemia (hemoglobin 9.0g/dl [N 11.7-17g/d]), elevated erythrocyte sedimentation rate (28 mm/hour [N 0-11mm/h]), elevated CRP (31.78 mg/L [N < 5mg/L]) and normal leucocyte count. One blood culture was drawn on admission. His SARS-Cov2 swab was negative. Abdominal ultrasound confirmed a splenomegaly.

On admission, the differential diagnosis included rheumatic diseases, multifocal osteitis and infective endocarditis. Therefore, a bone scintigraphy was performed that showed no argument in favor of osteitis, but a mild uptake at the vertebral junction L3-4 was detected.

After 36 hours growth of gram-positive cocci, which were later identified as Abiotrophia defectiva colonies, was observed in every blood culture drawn on admission.

A transthoracic echocardiogram was performed and showed thickening of the mitral valve with two vegetations causing severe mitral valve regurgitation (grade ¾) with left atrial and ventricle enlargement (figure 2). Cardiac contractility was preserved.

According to the modified Duke criteria, the diagnosis of definite IE was made. Our patient was transferred to the university hospital (Cliniques universitaires Saint-Luc, Brussels), where additional work-up was performed. A cerebral CT-scan showed a hemorrhagic stroke in the posterior parietal region, probably due to septic aneurysms (figure 3). MRI of the lumbar region revealed spondylodiscitis of L3-4 vertebrae.

Management

Antibiotherapy consisted of gentamicin and ceftriaxone initially. After obtaining the antibiogram, he was switched on ampicillin high dose for 6 weeks after the first negative hemoculture.

According to the current recommendations, urgent surgical treatment was proposed. He underwent resection of the vegetations and mitral valve plasty with annuloplasty after 10 days of intravenous (iv) antibiotics (4). Prolonged preoperative antibiotherapy was performed because, due to his fragile aortic root, the peroperative canulation could have led to defect and necessity of reparation, which would predispose our patient to further infection if not treated appropriately. Postoperatively low molecular weight heparin (LMWH) at curative dose and enalapril were started. LMWH was continued during 6 weeks post-intervention, then replaced by acetylsalicylic acid.

A weekly follow-up echocardiogram was performed during hospitalization. Postoperatively, there was initially mild left ventricular dysfunction, which improved with time and a persistent mild mitral valve regurgitation (grade ¼). Fortunately, the mitral vegetation removed during surgery was sterile.

For the spondylodiscitis, an antalgic corset, painkillers and physiotherapy follow-up were set up. He regained his ability to walk a few weeks after cardiac intervention. The analgesics were gradually decreased.

Follow-up

Our patient evolved well and was discharged home after six weeks of iv antibiotherapy. He remained afebrile and the blood cultures remained negative after antibiotic discontinuation. Longer term cardiac follow-up will include clinical evaluation, blood cultures and echocardiography twice a year for one year, then yearly.

Figure 2: Transthoracic electrocardiogram :
Thickening of the mitral valve with two vegetations (the largest measuring 1.5x1.2cm attached to the anterior cusp, the smallest measuring 0.4x0.5cm attached to the posterior cusp) causing severe mitral regurgitation.

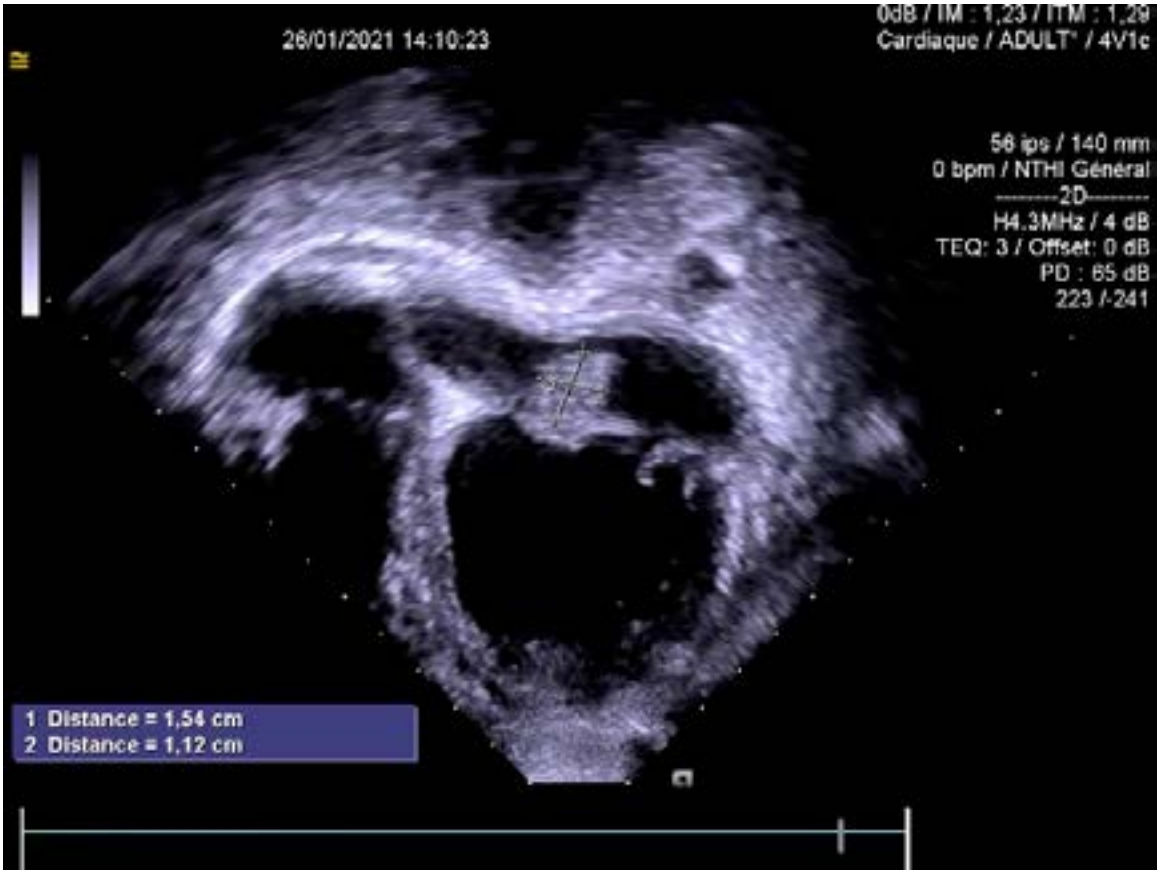
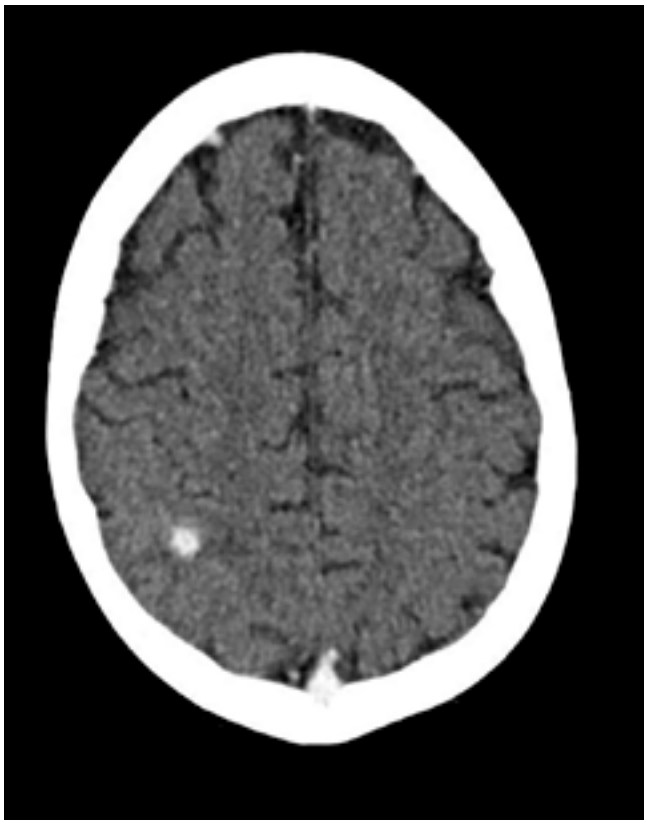


Figure 3: Cerebral CT-scan with injection :
Hemorrhagic stroke in the right posterior parietal lobe, due to septic emboli.



Neurologically, our patient evolved well. On discharge, he kept a light left asymmetry but could stand upright and walk on his own.

Of note, our patient is now eligible for antibioprophylaxis during at-risk procedures (dental procedures requiring manipulation of gingival or periapical region of the teeth or perforation of the oral mucosa) because of his first episode of IE.

Discussion

IE is a rare diagnosis in pediatric population. IE can present with an acute or subacute course, depending on the causative microorganism. Subacute endocarditis is difficult to diagnose, leading to long delay between the first symptoms and the treatment. Cases reports from worldwide literature show a time-to-diagnosis ranging from five days to one year.

Patients with the highest risk of IE are : patients with a prosthetic valve or prosthetic material, patients with a central venous catheter, patients with history of IE and patients with congenital cardiopathy.

The clinical presentation of IE in children is related to four underlying phenomena:

- bacteremia : fever (in 90% of patients), chills, weight loss
- valvulitis : heart murmurs (+- 85% of patients), heart failure
- immunologic responses : glomerulonephritis, Osler nodes, Janeway lesions, splenomegaly, petechial rash, Roth spots
- emboli : present at diagnosis in 30% of patients.

Investigation should include laboratory workup, blood cultures, and echocardiography. Echocardiography plays a key role in diagnosis and management of IE and should be performed as soon as IE is suspected.

The importance of blood cultures in the investigation process needs to be emphasized. Indeed, they are the cornerstone of diagnosis. The current recommendations advise that in case of suspicion of IE, blood cultures should be drawn daily and should not be delayed awaiting a febrile peak (4). Three pairs, taken at 30-min intervals, each containing 10ml are to be collected before any antibiotherapy. In case antibiotics have already been started, they are to be withdrawn for minimum 48 hrs. before repeating blood cultures. It is advised to notify the microbiology laboratory that IE is suspected and that fastidious organisms should be looked after. Testing for antibiotic susceptibility is critical.

After initiating the antibiotic treatment, blood cultures should be drawn after 48-72 hrs. to assess its efficiency and repeated until they become negative.

Modified Duke criteria (figure 4) are used to categorize the patient with confirmed IE, suspected IE and excluded IE.

IE is difficult to diagnose and treat, therefore an 'endocarditis team' with cardiologists, infectiologists and cardiac surgeons, is largely recommended.

In case of IE caused by NVS, prompt large antimicrobial therapy should be initiated, usually beta-lactam or vancomycin plus gentamycin, secondarily adapted to the antibiogram results (4). Antibiotherapy lasts minimum 6 weeks after the first negative blood culture. Surgical treatment is often necessary.

Given IE caused by Abiotrophia defectiva has a high risk of relapse, a clinical, biological and echographical follow-up is recommended every 6 months during the first year, then yearly. After discharge, the patient and his parents should be advised of the symptoms of IE and of the risk of relapse. Good dental hygiene is also recommended (4).

After the neonatal period, the most frequent pathogens identified in the blood cultures are, firstly, the viridans group streptococci and, secondly, Staphylococcus aureus (5).

Abiotrophia defectiva is a member of the NVS species, a subgroup of the viridans group streptococci. They are gram-positive cocci that grow as satellite colonies around other microorganisms. It is a member of the normal mouth flora, urogenital and intestinal tracts. It causes infections such as bacteriemia, brain abscess, septic arthritis and rarely infective endocarditis (6).

NVS are said to be responsible of 1-3% of all IE and are a common cause of culture-negative bacterial endocarditis (7). Blood culture-negative IE refers to IE in which no causative microorganism can be grown using the usual blood culture methods. NVS growth's is a challenge because they grow in small satellite colonies near larger colonies of "helper" bacteria. Therefore, microbiologists use agar surfaces inoculated with mixed bacterial flora. Their role in IE is likely underestimated. IE caused by NVS usually presents with large vegetations, high rates of complications and relapse.

Song et al. reported nine pediatric cases of IE caused by Abiotrophia defectiva (7). Three of them had underlying cardiac disease (33%). Eight patients out of nine presented embolic complications (89%).

The high rate of complications, especially embolic events, can be explained by two main factors. Firstly, IE caused by Abiotrophia defectiva is often belatedly diagnosed due to its subacute course. Secondly, Abiotrophia defectiva is highly infective and forms large biofilms, leading to large vegetations, more prone to embolization.

Conclusion

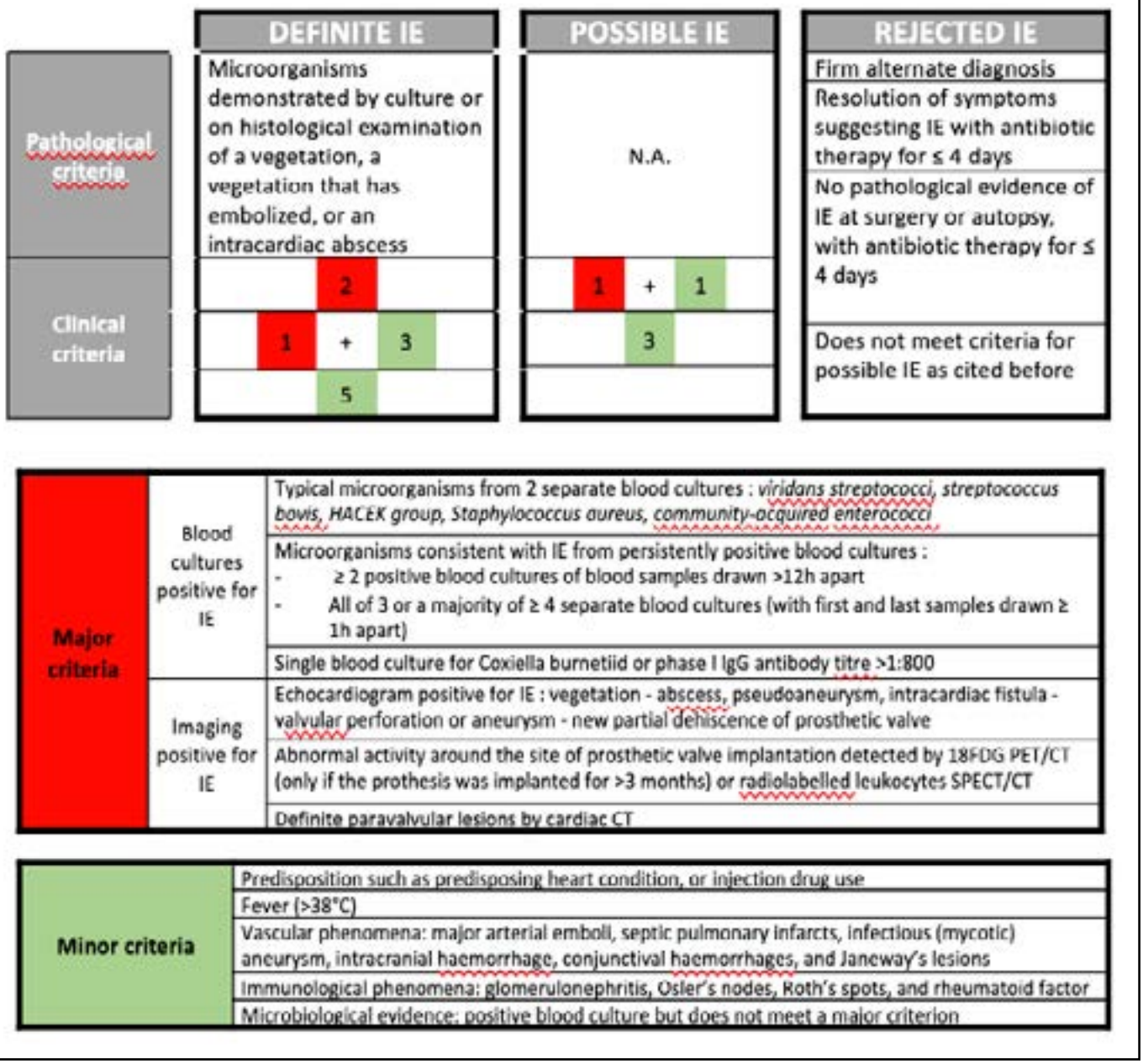
This case report discusses a subacute presentation of IE caused by Abiotrophia defectiva in a 13-year old boy with underlying cardiac abnormalities. The atypical clinical presentation led to a delayed diagnosis. At time of diagnosis, several complications were present. After combined antibiotic therapy and surgical management, the evolution was favorable.

With this case report, we hope to have emphasized the importance of clinical examination in the diagnostical approach of IE. Rheumatological and skin manifestations are rare but clearly described. Therefore, in the presence of known valvulopathy, these symptoms should raise a low threshold of IE suspicion. Blood cultures are cornerstones of the diagnostical approach.

Conflict of interest

The authors have no conflict of interest to disclose concerning this manuscript.

Figure 4: Definition of IE according to modified Duke criteria" the text is underlined as if the words were not correctly written. Do you think it would be possible the erase the underlining ?



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NUTRICIA

Triple A syndrome, a challenging race for the diagnosis in a potentially lethal pathology: a case report

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Keywords

Triple A syndrome – Allgrove syndrome – Esophageal achalasia – Alacrima – Adrenal insufficiency

Abstract

Triple A syndrome is a rare disease that associates achalasia, alacrima and adrenal insufficiency. Here we report a case of a 15 year-old girl presenting this typical triad. The symptoms being aspecific, diagnosis was delayed, with a major impact on her growth and development. Despite the rarity of this syndrome, diagnosis must be made as early as possible to avoid lethal consequences (acute adrenal insufficiency, denutrition). We confirmed the diagnosis with imaging and genetic analysis. The patient underwent surgical and medical treatments and was followed to prevent potential complications.

Introduction

The triple A syndrome (TAS, Allgrove syndrome) is a rare disease characterized by a symptomatic triad of esophageal achalasia, adrenal insufficiency and alacrima (1). Achalasia is a primary motor disorder with absence of peristalsis and incomplete relaxation of the lower esophageal sphincter (LES) (2, 3). A few cases of TAS have been described in children and adolescents. Its incidence varies according to the continents and is approximately 0,1/100,000. Diagnosis is often delayed in children because of lower incidence and unspecific symptoms (1, 4).

Case report

A 15-year-old girl was admitted for weight loss and loss of appetite. She had presented feeding difficulties, postprandial vomiting and dysphagia since her third year of life. She had not started puberty. The patient was born at term with intrauterine growth restriction (birth weight: 2500g). She was the fourth of five children of a Moroccan family with consanguineous parents. Her brother died at the age of 13 with similar clinical symptoms. At first clinical examination, she was underweight and pale with muscular hypotrophy (anthropometric measurements: weight 28.7kg (-4SD), height 140cm (-4SD), BMI 14kg/m² (-2SD)), late onset puberty (Tanner stage P1M2) and dental cavities. Additional history showed an absence of tears (Schirmer's test not performed), nighttime gastroesophageal reflux, amenorrhea and an already supplemented primary adrenal insufficiency (hydrocortisone supplementation initiated in 2016 in Morocco at the dose of 15mg/day, corresponding to 16mg/m²/day). Laboratory evaluations showed primary adrenal insufficiency (cortisol 6.5µg/dL [Normal value: 9-21µg/dL] and ACTH 559pg/mL [Normal value: 7.2-63pg/mL] measured in the morning), normal serum sodium (sodium 142mmol/L [Normal value: 136-145mmol/L] and potassium 3.9mmol/L [Normal value: 3.5-5.1mmol/L]), normal glucose (fasting serum glucose 69mg/dL [Normal value: 60-100mg/dL]), anemia, hypoproteinemia, negative inflammatory bowel disease antibodies, negative celiac disease antibodies and normal thyroid function. The high resolution esophageal manometry could not be performed due to poor compliance. The barium swallow (Figure 1) and upper gastrointestinal endoscopy (Figure 2) showed a dilated esophagus and low peristalsis with delayed emptying of the esophagus and gastric inflammation. Anatomical and functional criteria were compatible with esophagus achalasia. The combination of achalasia, adrenal insufficiency and alacrima suggested triple A syndrome. DNA sampling (*AAAS* gene, chr 12q13, mutation ALADIN) identified a homozygous intronic mutation 14 c.1331 + 1G>A (the most common mutation in North Africa). A treatment by proton pump inhibitors (omeprazole 40mg), artificial tears and a high caloric diet was initiated and adrenal supplementation was pursued. After a multidisciplinary discussion, Heller procedure with anti-reflux surgery (Dor gastroplasty) was performed. In the short and medium term, the course of the disease was satisfactory, with a decrease of dyspepsia, dysphagia, postprandial vomiting and food impaction. The growth in height and weight progressed harmoniously with a significant increase of the BMI and the first signs of puberty appeared. After a few years, the evolution was fine without distant complications. Digestive tolerance was good due to the absence of gastroesophageal reflux and dysphagia. The esophageal impedancemetry was normal one year after the surgery.

Discussion

The triple A syndrome is a rare disease usually characterized by a clinical triad of esophageal achalasia, adrenal insufficiency and alacrima (1). Although its name is defined by the triad, the syndrome is phenotypically heterogeneous. Fewer than the three features may be present. Additional features not originally identified, include progressive autonomic (central and peripheral) nervous system deficits (1, 4). The latter symptoms were

not present in our patient, who presented with the usual triad. The etiology of achalasia in TAS appears to be distinct from other forms of achalasia. Although it is a rare condition and epidemiologic data are scant, symptoms of swallowing difficulty and achalasia in TAS usually manifests by the end of the first decade of life and can begin in infancy in contrast to idiopathic achalasia, where a very small minority of patients manifest symptoms before the age of 10. Our patient had presented dysphagia since her third year of life (2, 3).

Mutations in the *AAAS* gene (which codes for the ALADIN protein), located on chr 12q13, accounts for the majority of cases (5). Consanguinity is often described. Transmission is autosomal recessive pattern. In our patient's family, an older brother died at the age of 13, possibly of adrenal insufficiency. Indeed, he presented the same clinical symptoms. The penetrance of biallelic mutations in *AAAS* approaches 100%, though expressivity is variable, possibly due to allelic variation or the existence of yet unidentified genes (1, 5, 6). Diagnosis is often delayed because of the aspecificity of symptoms (vomiting, dysphagia, weight loss, failure to thrive, chest pain, regurgitated food), lower incidence of achalasia than other more frequent pathologies (gastroesophageal reflux disease). Our patient presented with severe growth retardation, probably due to the combination of partial primary adrenal deficiency for years and a long-standing undernutrition (Figure 3). The differential diagnoses that must be excluded when faced with similar symptoms are gastroesophageal reflux, eosinophilic esophagitis, foreign-body ingestion, intrinsic esophageal stenosis, leiomyomatosis, external compression of the esophagus (e.g. esophageal duplication, mediastinal tuberculosis, malignant neoplasms), and eating disorders (anorexia nervosa). The diagnosis must be made as early as possible since long-existing achalasia can cause severe undernutrition, which can be potentially lethal (2, 3). The workup includes biochemistry, X-ray (barium swallow X-ray), esophageal manometry and upper endoscopy. Esophageal manometry allows definitive diagnosis and grading of the achalasia. In our case, radiological and endoscopic characteristics, as well as the alacrima and the primary adrenal deficiency are sufficient to establish the diagnosis. Furthermore, the genetic analysis brought formal confirmation (1, 7, 8). The three primary types of treatment are pharmacological and nutritional (adrenocortical hormone supplementation, symptomatic treatment of alacrima, high caloric diet), endoscopic (botulinum toxin injection into the LES, pneumatic dilatation and stenting, peroral endoscopic myotomy) and surgical (Heller procedure with anti-reflux surgery and feeding gastrostomy) (9,10). Our patient was granted a surgical treatment as first line therapy, due to severe anatomical and nutritional repercussions as well as the late diagnosis. Gastrostomy was not immediately necessary thanks to good surgical tolerance with improving symptomatology, satisfying semi-liquid refeeding leading to acceptable weight gain. Patients should be regularly followed-up to prevent progression toward esophageal cancer or motor disorders with malnutrition.

Conclusion

Triple A syndrome is rare and its prevalence varies among continents. Achalasia in Triple A syndrome may appear earlier in life than isolated achalasia. The symptoms are rather aspecific and the diagnosis is difficult and often delayed. It is essential to quickly confirm diagnosis because the disease can be fatal (acute adrenal insufficiency, malnutrition). Long-term patient follow-up is essential in view of distant complications.

Conflict of interest

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

Figure 1: Barium swallow radiography: major distension of the superior 2/3 of the esophagus with delayed emptying and food stagnation, thin aspect of the inferior 1/3 of the esophagus and of the esogastric junction (« bird's beak »).

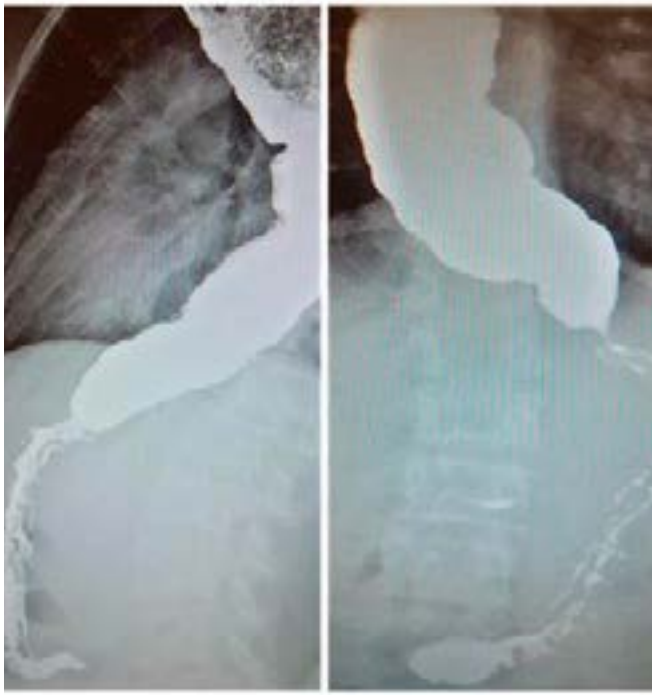


Figure 2: Upper gastrointestinal endoscopy: dilated esophagus and gastric inflammation (nodular aspect).

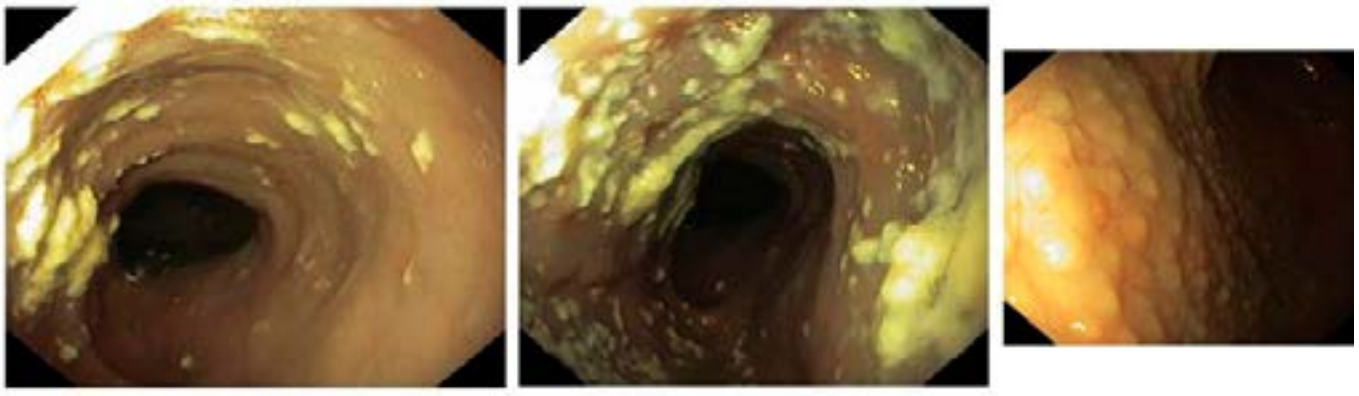
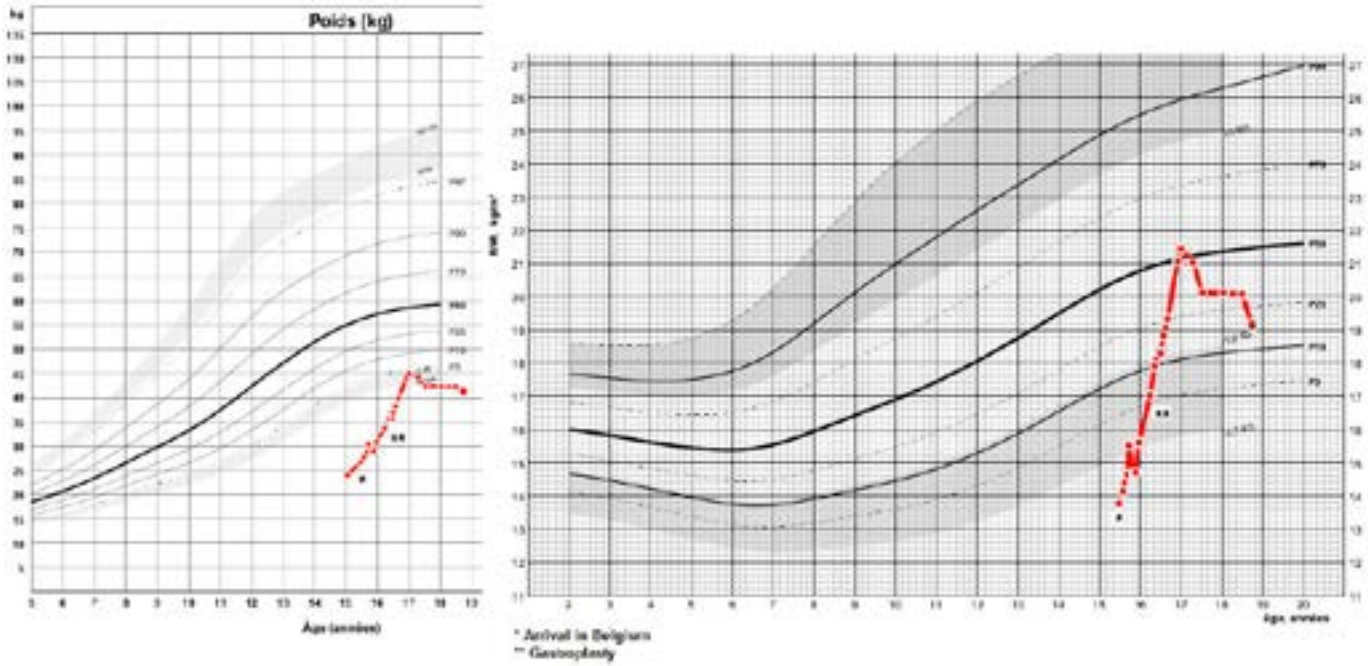


Figure 3: Growth and BMI curve with arrival in Belgium and gastroplasty.



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Congenital nasal pyriform aperture stenosis in a three-week old girl: a case report and discussion of current treatment strategies

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Keywords

Congenital nasal pyriform aperture stenosis, CNPAS, nasal obstruction, treatment

Abstract

Congenital nasal pyriform aperture stenosis (CNPAS) is a rare form of nasal obstruction in infants. It can cause respiratory distress and feeding difficulties, as neonates are obligate nasal breathers. The incidence of CPNAS seems to be underestimated. We report a case of CNPAS diagnosed in a three-weeks old neonate. She was initially started on conservative treatment based on topical nasal medication and humification, but without good clinical result. At the hospital heated humidified high-flow nasal cannula (HHHFNC) was started as a temporary treatment. After surgical treatment through sublabial approach, she could be weaned from high flow therapy.

Introduction

Nasal airway obstruction in a newborn can cause respiratory distress and feeding difficulties, as neonates are obligate nasal breathers (1-7). Congenital nasal pyriform aperture stenosis (CNPAS) is a form of nasal obstruction characterised by abnormal narrowing of the anterior inlet of the nasal cavity. It is a condition caused by overgrowth of the medial nasal process of the maxilla (1, 3, 4, 6, 8, 9). It can mimic the clinical findings of choanal atresia, which is the most common cause of neonatal nasal obstruction (1, 3, 6, 9). The incidence of CPNAS seems to be underestimated (7). We report the case of a three-week old girl with CPNAS.

Case report

A three-week old girl, born full term through normal vaginal delivery in a different hospital, presented at our hospital with nose congestion, laboured breathing and feeding difficulty. There were no clear apnoeas or cyanotic incidents. Clinical evaluation showed respiratory distress with inspiratory stridor and subcostal retractions. A notable finding was that we couldn't pass a nasopharyngeal swab. A capillary blood gas demonstrated respiratory acidosis without complete metabolic compensation. Heated humidified high-flow nasal cannula (HHHFNC) without additional oxygen was started. A capillary blood gas showed a clear improvement a day later.

Detailed history showed she had symptoms of obstructive breathing with subcostal and jugular retractions and inspiratory stridor starting shortly after birth. Conservative treatment with rinsing and oxymetazoline drops was initiated, but resulted in no clinical improvement. Upon follow-up consultation it was almost impossible to pass a nasopharyngeal swab. There was suspicion of a choanal atresia and the patient was referred to their ENT department. Initial tests showed there was air passage through both nostrils and no further plan of action was postulated. The patient came to our centre for a second opinion.

As stated above we started with HHHFNC in our hospital on day one. Because weaning from this therapy was not possible without the baby getting very uncomfortable, she was transferred to the ENT department at the University Hospital of Antwerp. Fibreoptic endoscopy showed a bilaterally narrow pyriform aperture and bilateral patent choanae. A computerized tomography (CT) scan confirmed a stenosis of the pyriform aperture with a maximum diameter of 5mm and a generally narrowed nasal cavity, as shown in Figure 1. There was no central mega incisor.

At the age 32 days the pyriform aperture was surgically dilated through a sublabial approach with a placement of stents. Unfortunately, the stents were afunctional because of blockage after one day and, therefore, removed. HHHFNC was restarted and the nose was rinsed and washed with budesonide nasal drops four times a day. She was successfully weaned from HHHFNC after seven days.

As CNPAS can be associated with midline defects, additional technical tests were requested. An echocardiogram showed no abnormalities. MRI of the brain showed no midline defects, but did reveal unrelated sequelae from an earlier birth-related subarachnoid haemorrhage.

Discussion

The exact incidence of CNPAS is unknown. It is said to be a rare form of nasal obstruction, but its frequency is probably underestimated since it has been diagnosed more frequently since it was first described in 1989 by Brown et. al (1). Symptoms include nasal congestion, respiratory distress with retractions, inspiratory stridor, episodes of apnoea and/or cyanosis, difficulty feeding and failure to thrive. These symptoms can occur straight after birth or after a few weeks and are often triggered by an upper respiratory infection which narrows the already compromised airway even further (2, 4-6, 8). Our patient already showed obstructive breathing with subcostal and jugular retractions and inspiratory stridor shortly after birth.

Diagnosis of CNPAS is suspected when the anterior nasal fossae are narrowed upon physical examination and/or when it is difficult to pass a five French catheter or a nasopharyngeal swab. The golden standard tool to establish the diagnosis is a CT scan. The CT scan would show stenosis at the bony nasal inlet. However, there is currently no consensus about the minimal dimensions for CNPAS, as literature describes the dimensions ranging from a width of less than eight millimetres to less than eleven millimetres (2, 4, 6, 8-10). In our case the pyriform aperture width was maximum five millimetres. This would be a definite diagnosis according to both cut off values.

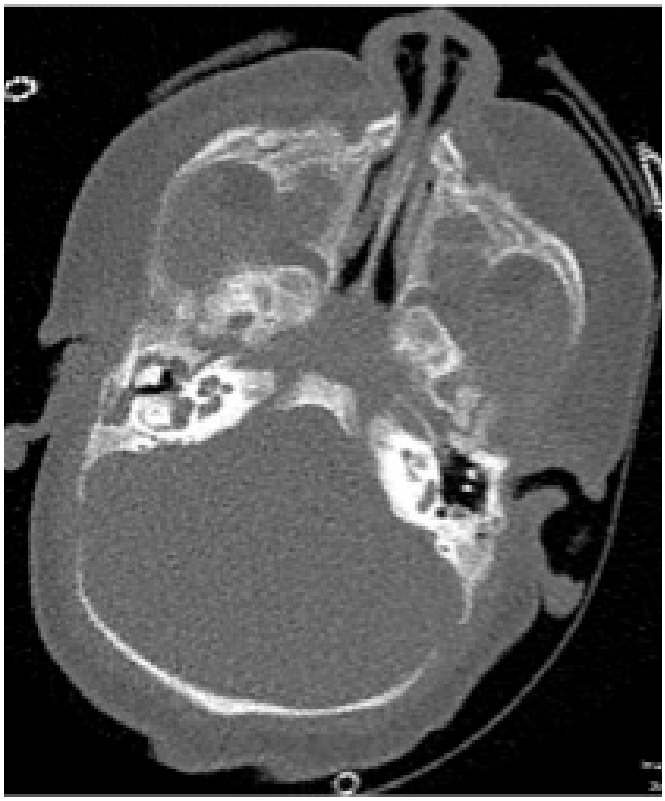
CNPAS can be an isolated phenomenon or it can occur together with other abnormalities. It is associated with midline anomalies, including central nervous system, endocrine and craniofacial abnormalities. Examples of associated anomalies are holoprosencephaly, facial haemangiomas, clinodactyly, pituitary dysfunction and a single central maxillary incisor (2-10).

It is also often associated with a mid-nasal stenosis. Patients with CNPAS should be evaluated to exclude midline anomalies because of this association, especially if there is a single central maxillary incisor, which is seen in up to 60% to 75% of cases (6, 9). Further evaluation includes chromosomal analysis, MRI of the brain and an echocardiogram (2-10).

The choice of treatment is based on the severity of the obstruction and clinical symptoms, as the width of the aperture cannot always predict the need for surgery (3, 9, 10). Initial treatment should include humidification, topical nasal decongestants and steroids. If patients can tolerate conservative management, it is continued until the craniofacial growth improves the nasal airway with time. When patients do not respond to medical treatment alone, they should undergo a surgical procedure. Indications for surgical treatment are respiratory distress or failure to thrive (2-7, 9). The classical surgical technique is widening of the pyriform aperture through a sublabial approach (1, 4, 5, 9, 10). In recent literature, a less invasive dilatation technique using a balloon has also been described. However, this technic carries a risk to the integrity of the nasal septum. (4, 8, 9). Our case was started on conservative management, but without enough improvement. At 32 days old she underwent surgery with the sublabial approach.

In 2020 Fuzi et al. (2) came with a high-flow nasal cannula treatment as a novel method of respiratory support in children with CPNAS. It delivers warmed and humidified gas with or without supplementary oxygen to the nasal airways, combined with some positive airway pressure. Treatment with high-flow nasal cannula decreases the work of breathing by improving oxygenation, increasing the end-expiratory lung volume and dilating the radius of the nasopharyngeal airway which reduces the airway resistance. It also increases the functional residual capacity and alveolar recruitment and flushes the nasopharyngeal dead space. Furthermore, it has been shown to be safe to use and well tolerated in neonates. Its use, however, has been limited by a relative lack of evidence and the high costs associated with the device. As it is still a relatively new method, access to the machines is also limited. In the case mentioned in Fuzi et al. the parents needed to purchase the device privately. In our case, HHHFNC treatment was used temporarily during the hospitalisation period.

Figure 1: CT Scan showing a narrow pyriform apertura of maximum 5mm with a globally narrow cavum nasi.



Conclusion

Congenital nasal pyriform aperture stenosis (CNPAS) is a rare form of nasal obstruction in infants, but it should be part of the differential diagnosis along with (unilateral) choanal atresia. The golden standard to establish the diagnosis is a CT scan revealing stenosis at the bony nasal inlet. As CNPAS has been associated with midline defects, additional evaluation should be performed. Conservative measures, such as nasal decongestants, may be sufficient to improve nasal patency and bridge the time until craniofacial growth improves the nasal airway. In more severe cases, surgical management is necessary. Heated humidified high-flow nasal cannula can be used as a temporary treatment in the hospital setting.

Consent

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

Conflicts of interest disclosure

There are no conflicts of interest.

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Post-traumatic transient cortical blindness in a three-year old

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Keywords

post-traumatic, head trauma, cortical blindness

Abstract

Post-traumatic transient cortical blindness after trivial head trauma occurs in rare instances in children and typically resolves in a matter of hours. We present a case of a three-year old girl who presented with a transient but complete loss of vision after a minor fall on her head.

Introduction

Post-traumatic transient cortical blindness (PTTCB) is a documented entity of complete loss of vision that can occur in children after minor head trauma. It has been described in several cases throughout history however it is still poorly known among health-care providers. It is a transient and benign condition but can be very distressing for patients, their family and health-care workers. Here, we describe a case of PTTCB in a three-year old girl and give a summary of cases described throughout history.

Case

A three-year-old girl with no relevant medical history was brought to the emergency department suffering from a complete loss of vision occurring 30 minutes after a minor head trauma. There were no direct witnesses of the trauma itself, although the child could consistently reconstruct what happened, namely a fall on the back of her head after being pushed over by another child. Around 30 minutes after the fall the patient repeatedly exclaimed: 'I can't see anything!'. Neurological examination upon admittance was normal except for a complete bilateral loss of vision. Speech, pupillary reflexes and vital signs were normal. There were no external signs of trauma. Glasgow Come Scale was 15. Urgent MRI scan showed no intracranial hemorrhage, mass or skull fracture. During ophthalmological examination about three hours after the event she slowly regained vision. The patient could identify presented shapes and started to make eye contact. She was admitted to the pediatric department for cardiorespiratory monitoring and neurological observation throughout the night which were uneventful. Neurological examination performed the next day was completely normal, as was a visual-evoked potential test. Thorough ophthalmological evaluation showed a complete recuperation of the patient's vision. She was discharged after 24 hours. Follow-up examination was performed 5 days later and was completely normal. A phone-consultation was performed 2 months after the event which showed no residual signs in our patient.

Discussion

PTTCB following minor head trauma is a known entity and several cases have been described in literature. Bodian et al. first described 6 cases in 1964, since then, over 35 cases have been published in modern literature (1). It is a benign, completely reversible condition that can cause a great amount of stress among patients, parents and caregivers. It occurs most frequently in children. Age of affected patients ranges from 18 months up to 24 years old (2). As the condition can go unnoticed, due to the visual problems being falsely attributed to hysteria and/or post-traumatic confusion or the patient being too young to complain of vision loss, its incidence is most likely understated. Some sources claim an incidence of up to 4.8% in all patients admitted to the emergency department with trivial head trauma, while others place the incidence around 0.4-0.6% (3,4). There is often a delay in occurrence of the blindness after the trauma, ranging from minutes up to an hour. In PTTCB, pupillary reflexes and intracranial imaging are normal. Voluntary eye movements remain intact. Vision loss can be partial and complete recovery is nearly always achieved within a matter of hours, cases of prolonged blindness have however been described (5,6). Weisz et al. published a prospective follow-up study on 4 patients and included repeated ophthalmological, neurological and psychiatric examinations during a 5-year period. All patients had a completely recovery and follow-up visits were uneventful (7). The differential diagnosis of PTTCB includes intracranial hemorrhage, (bilateral) retinal detachment, optic nerve or chiasmal trauma, hysteria and intracranial masses. True cortical blindness can be differentiated from hysteria by using threatening gestures or checking for optokinetic nystagmus, as the latter can't be suppressed voluntarily.

There is much debate about the etiology of PTTCB. Some authors claim a vascular cause, i.e. a vasospasm along the ocular tract, given the sudden onset, brief nature of the condition and the fact that there appears to be an increased incidence of migraine in patients experiencing PTTCB (4). Another possible explanation is a contusion of the occipital brain with secondary focal edema and ischemia. EEGs performed on patients experiencing PTTCB generally show slowing of occipital alpha waves which is consistent with this theory although these EEG findings are also seen in patients with minor head trauma without PTTCB (8). Secondary edema would explain the delay in onset of blindness but this theory fails to explain why some patients experience blindness immediately upon impact (9). It is reasonable to assume that PTTCB would occur most frequently after traumatic impact on the occipital region of the skull, given the function of the occipital lobe, however this is difficult to prove as it can be challenging to determine the exact point of impact in a fall, especially when unwitnessed as in the presented case.

We suggest that every patient with post-traumatic loss of vision be given a complete neurological examination as well as immediate cranial imaging i.e., CT-scan or MRI-scan where possible. Ophthalmological examination should be performed as soon as possible. Referral to a neurosurgeon should be done when in doubt. In the event of complete loss of vision after minor head trauma with an otherwise normal ophthalmological and neurological examination and normal cranial imaging, it is reasonable to

assume PTTCB and to expect a complete recovery within hours. Patients should be monitored for at least 24 hours and frequently checked for signs of raising intracranial pressure or neurological abnormalities. Given the current evidence, there seems to be no need for a systematic long-term follow-up.

Conclusion

Physicians, especially pediatricians and emergency physicians, should be aware of PTTCB and be able to recognize it adeptly. Further research is needed to better understand the pathophysiology of this condition.

Conflict of interest

The authors have no potential, real or perceived conflict of interest to disclose.

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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

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. • **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: 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 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: 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 doit 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. **Contre-indications:** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1. **Mises en garde spéciales et précautions d'emploi:** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entrainer le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vasovagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contreindication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation (voir rubrique 5.1 du RCP complet). Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles postvaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique (voir rubrique 5.1 du RCP complet). Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à *Neisseria meningitidis* du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Ce médicament contient moins de 1 mmol (23 mg) de sodium par dose, c'est-à-dire qu'il est essentiellement « sans sodium ». Traçabilité: Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **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 - B-1000 Bruxelles - Madou - Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be. **Luxembourg:** Centre Régional de Pharmacovigilance de Nancy - Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) - CHRU de Nancy - Hôpitaux de Brabois - Rue du Morvan - 54 511 Vandoeuvre Les Nancy Cedex - Tél.: (+33) 3 83 65 60 85 / 87 - e-mail: crpv@chru-nancy.fr ou Direction de la Santé - Division de la Pharmacie et des Médicaments - 20, rue de Bitbourg - L-1273 Luxembourg-Hamm - Tél.: (+352) 2478 5592 - e-mail: pharmacovigilance@ms.etat.lu - Link pour le formulaire : https://guichet.public.lu/fr/entreprises/sectoriel/sante/medecins/notification-effets-indesirables-medicaments.html. **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:** 25/02/2022 (v13). **MODE DE DELIVRANCE:** Sur prescription médicale. **Référence :** SmPC Bexsero

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GSK

Rare but not to be missed : acute focal cerebral lesions in two children with new-onset diabetes mellitus

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Keywords

pediatric diabetes, diabetic ketoacidosis, cerebral edema, stroke

Abstract

Type 1 diabetes mellitus can present with ketoacidosis, a severe condition responsible for most of the morbidity and mortality. Neurological complications arise in approximately 1% of cases, essentially in the form of cerebral edema, and less frequently ischemic or hemorrhagic stroke. Here we report two cases; both children had severe ketoacidosis at onset of the disease and were admitted with altered consciousness. The first child presented with cerebral edema rapidly diagnosed and treated; he developed left hemiparesis with evidence of ischemic sequelae on the brain MRI. The second child presented a Parinaud syndrome which led to diagnosis of ischemic stroke.

Introduction

Type 1 diabetes Mellitus (T1DM) is a leading cause of chronic disease in children, often presenting with ketoacidosis. In the context of ketoacidosis (often with severe metabolic disruption), children may present with an altered level of consciousness and require intensive resuscitation and care. Although most patients rapidly recover with fluid and insulin therapy, neurological complications may occur. We describe two cases illustrating these unfortunate outcomes.

Case 1

A 5-year-old boy with an altered level of consciousness was admitted to a general hospital. The child had been examined twice the previous day (firstly by his family doctor and secondly by a pediatric fellow in the emergency department), with symptoms of vomiting, abdominal pain and weight loss, On both occasions, he had been discharged with the diagnosis of viral gastroenteritis.

On his third presentation, and then admission in the emergency department, vital signs were within normal range except for a raised respiratory rate for age (tachypnea). Investigations revealed severe hyperglycemia (697 mg/dL[NL 60-100]) and ketoacidosis (pH 6,95 [NL 7.35-7.45], undetectable HCO3, PCO2 14 mmHg [NL 32-48], ketonemia 7 mmol/L), leading to the diagnosis of new-onset T1DM and diabetic ketoacidosis (DKA).

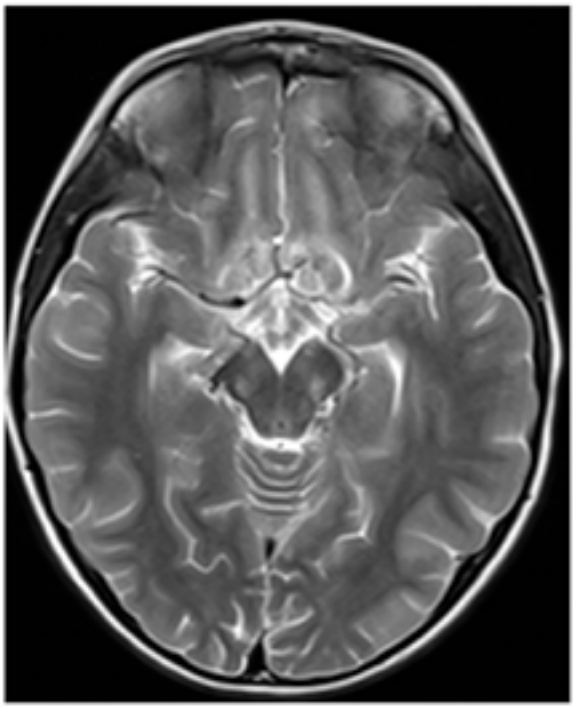
His Glasgow coma scale (GCS) was 13/15 at that time, and the child received one bolus of 20 ml/kg of NaCl 0,9%, followed by a second bolus of 10 ml/kg after 1 hour. At that time, insulin was started at a rate of 0,1 U/kg/hour. This precipitated his blood glucose to drop to 276 mg/dL, 4 hours after admission. He was transferred to the pediatric intensive care unit (PICU) in a referral hospital, where the GCS progressively deteriorated to 4/15. A head CT-scan revealed global cerebral edema with subfalcine and tonsillar herniation. Hypertonic therapy using mannitol, followed by hypertonic saline (NaCl 3%) improved his clinical signs over a few hours. Over the next 24 hours, the patient returned to a normal neurological status. He was transferred back to the general hospital after 48 hours, where he was switched to subcutaneous insulin therapy and diabetes education started. Three days later, the child developed a left hemiparesis with steppage and pyramidal signs. Additionally, sleep-related bradycardia and hypotension developed. The child was readmitted to the intensive care unit for 48 hours where cerebral MRI revealed extensive ischemic lesions suggestive of post-herniation ischemia due to cerebral oedema (Fig. 1 A-D). A week later, the child presented with short episodes of hypotonia and pallor, which led us to suspect seizures. Prolonged EEG showed no signs of epileptic activity and he did not require any anti-seizure treatment. No further episodes were observed. He was discharged home with rehabilitation for his hemiparesis and ongoing diabetic management.

Case 2

A 6-year-old boy with no relevant medical history presented to the emergency department with abdominal pain and vomiting for the preceding 48 hours, and on history revealed 2 months of symptomatic polydipsia. Vital signs showed a raised respiratory rate for age, tachypnoea (27 breaths/minute), fever (38°c) and tachycardia (127 beats/minute). On initial clinical examination, he was found not only to have signs of acute weight loss (estimated 3kg weight loss) but examination revealed a confused and stuporous patient with a response to verbal stimuli (GCS 14/15). Investigations showed a severe acidosis (pH 6.9, HCO3 3.6 mmol/L [NL20-28], PCO2 23 mmHg) and hyperglycemia (406 mg/dl), leading to the diagnosis of new-onset T1DM with severe DKA. Additionally, he had hypokalemia (2.3 mmol/L [NL 3.4-4.7]), prior to the commencement of insulin therapy. Screening for Covid-19 (PCR) was positive, with the child demonstrating mild covid manifestations (cough and one temperature spike).

Treatment was started in the emergency room with a 10 ml/kg bolus of NaCl 0,9% followed by an IV insulin infusion at a rate of 0,1 U/kg/hour. The child was admitted to the PICU, where IV insulin was continued, and fluid management for his maintenance, rehydration and ongoing losses carefully corrected over 48 hours. Supplemental potassium was also administered. His vital signs rapidly normalized and his neurological condition improved over the next 48 hours, at which time he was transferred to the pediatric diabetic ward. Subcutaneous insulin was started, within the context of a multidisciplinary education protocol for new diabetic patients and their families. At this stage the little boy's level of consciousness was fully restored, enabling a thorough neurological examination. On examination a vertical gaze palsy was revealed (Parinaud syndrome). A cerebral MRI confirmed an ischemic lesion of the left thalamus extending to the left cerebral peduncle (Fig. 2 A-C). Over the following weeks, repeated neurological examination highlighted an almost complete resolution of the Parinaud syndrome. The child developed no other symptoms from the SARS-CoV2 infection.

Figure 1 A-D: T2 (A) and FLAIR (B-C) axial MRI of the brain of a 5 year-old-boy (patient 1) obtained nine days after onset of symptoms showing several ischemic lesions : basifrontal bilateral (A-B) and in the posterior arm of the right internal capsule (C). Figure D shows diffusion sequences of the basifrontal lesions.



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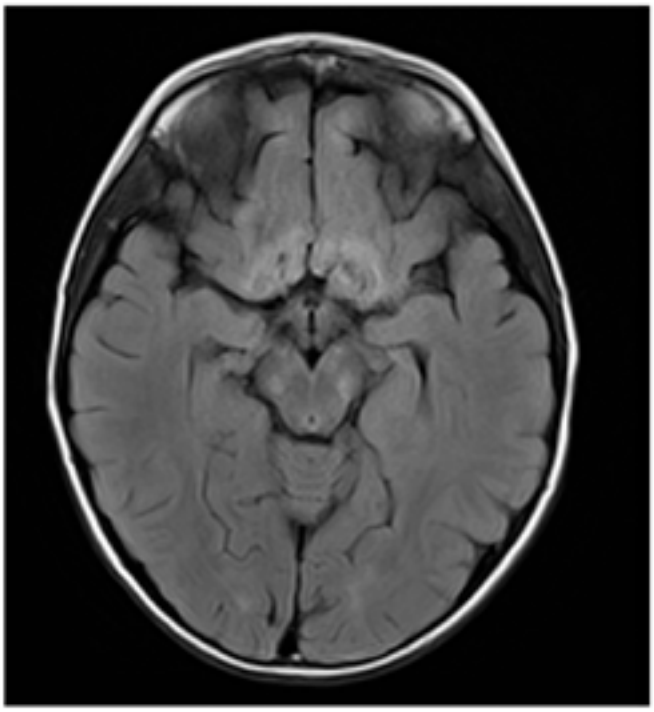

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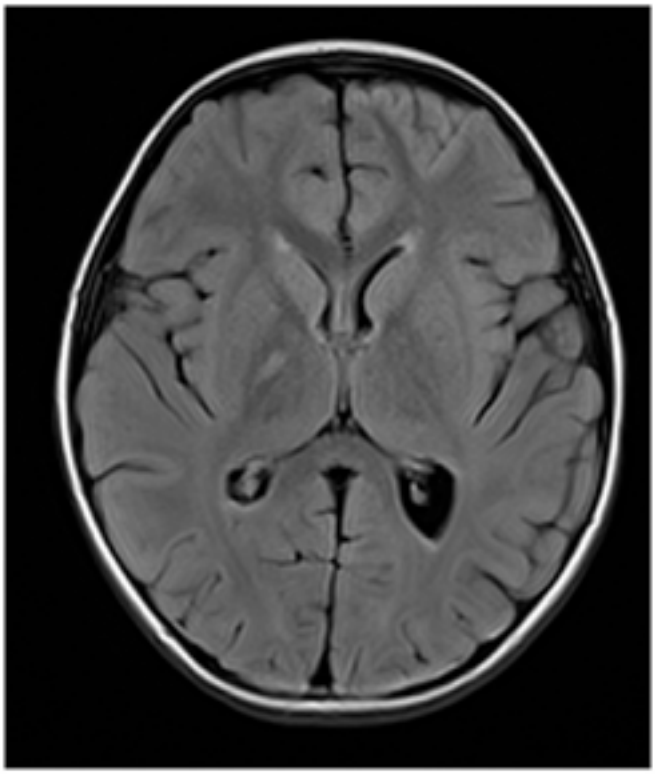

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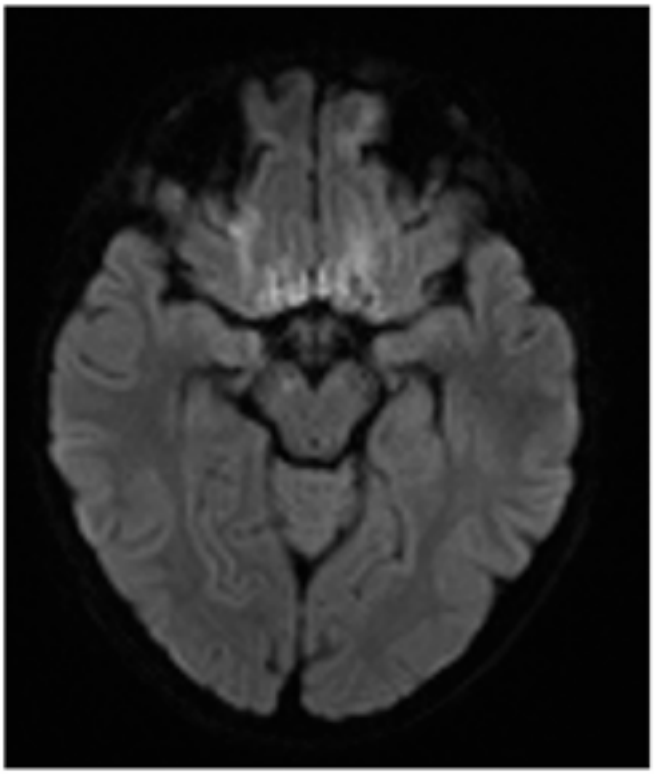

D

Discussion

T1DM is a well-known condition in children and one of the most frequent causes of chronic disease (1). Approximately one-third of children present with diabetic ketoacidosis (DKA) at diagnosis, which significantly impacts on the morbidity and mortality. Ketoacidosis is a state of insulin deficiency leading to catabolism and lipolysis, resulting in hyperglycemia and ketonemia. This results in hyperosmolality, metabolic acidosis and dehydration due to osmotic diuresis. Ketoacidosis is defined by hyperglycemia (glucose >200 mg/dl), ketonemia (blood ß-hydroxybutyrate ≥3 mmol/L) and/or ketonuria, and acidosis (pH <7,3 and/or HCO3 <15 mmol/L).

Neurological complications of DKA are rare but potentially severe and life threatening. The most frequent complication is cerebral edema (CE), observed in less than 1% of patients but estimated to be present in 10% of those presenting with severe ketoacidosis (pH <7.1) (2). Furthermore, evidence of subclinical edema on imaging suggests that there is a clinical spectrum in CE, with only the most severe cases being clinically detected (3). The diagnosis of CE remains challenging, especially in younger children. The Cushing's triad (bradycardia, irregular respirations, and a widened pulse pressure) is seen only late in the evolution of CE and physicians should be alert even in cases where these parameters are within normal range. Furthermore, imaging can be falsely negative in the early first few hours. Another diagnostic challenge arises from the fact that CE has long been thought to be a complication of mis-managed fluid resuscitation, with the quantity of fluids administration and the use of hypotonic solutions being pinpointed as causing or aggravating CE. The PECARN FLUID trial, published in 2018 and the first randomized control trial to evaluate this risk, has not confirmed this belief (4). In response, current guidelines have been recently reviewed and advocate for an IV fluid replacement adapted to the degree of dehydration (1). Use of sodium bicarbonate is still discouraged, with current evidence suggesting it may increase risk of CE.

Knowledge of risk factors for developing CE is incomplete. Low PCO2 on admission, higher blood urea nitrogen and more severe acidosis are current presented risk factors (5). Younger age and new-onset diabetes are also considered risk factors as smaller children's brains are more susceptible to hypoxia and reduced cerebral perfusion. This is supported by the growing research on the pathogenesis of CE which hypothesizes that CE could be due to a defect of cerebral autoregulation leading to hyperemia and vasogenic edema, as well as brain hypoperfusion and reperfusion injury (6,7).

Other neurological complications of DKA that may be observed include: cerebral vein thrombosis, arterial ischemic stroke and hemorrhagic stroke. In children, stroke accounts for 10% of intracerebral complications from DKA and although rare, they are responsible for severe morbidity.

Whilst stroke can be a consequence of CE due to vascular compression, it can also occur independently. The pathogenesis can be linked to several mechanisms well demonstrated in a state of acidosis and hyperglycemia. These mechanisms include (a) a systemic inflammatory state with high levels of cytokines and complement activation, resulting in vascular injury; (b) a disruption in the normal coagulation pathway which is not well understood (some studies showing enhanced platelet activation and higher levels of procoagulant factors during DKA); and (c) impaired cerebral autoregulation, with studies suggesting it could be specifically due to DKA (8,9,10). Furthermore, studies in the adult population show a link between stroke and hyperglycemia, with a well-known higher risk of stroke in patients with T1DM. Such evidence in children is still lacking. Bharill et al. recently reported a pediatric case of stroke associated to T1DM without DKA, suggesting this association could also exist in children (11).

Clinical focal signs are found in less than 30% of cases of stroke, with children having largely non-specific symptoms and signs (lethargy, behavioral changes, confusion, blood pressure and/or heart rate changes). This makes the differentiation between acute stroke from CE difficult. Prompt diagnosis using neuroimaging techniques (preferably MRI) is essential, especially if focal signs are present. Imaging should also be considered in cases of a change in neurological examination or a slower than normal improvement of neurological symptoms with normalizing blood parameters. CT is less efficient in diagnosing strokes and can be falsely negative in the first hours of CE (12).

Our two cases illustrate the overlap between the two clinical entities of CE and stroke. In the first case, MRI showed post-herniation lesions as well as asymmetric ischemic lesions accounting for the hemiparesis. In this case, CE was diagnosed during the acute phase incorrectly accounting for both lesions. Our second case raises other clinical learning points. Firstly, the delay of imaging does not allow us to discriminate a stroke from vascular compression caused by early undetected cerebral edema and secondly, Covid-19 infection could be considered a confounding factor, as cases exist demonstrating associations between strokes and a severe form of the infection (13,14). In this case however, the Covid-19 related symptoms were mild, supporting DKA as the most likely etiology.

Conclusion

DKA is a frequent and severe condition in children, which every clinician is susceptible to encounter. Acute and patient tailored treatment is essential in managing those children. The knowledge that neurological complications may appear should induce clinicians to monitor neurological status for at least 48h after starting the treatment, even if DKA symptoms are resolved. The higher risk of stroke in these patients should be remembered and motivate imaging in case of focal signs, or lack of improvement of neurological status.

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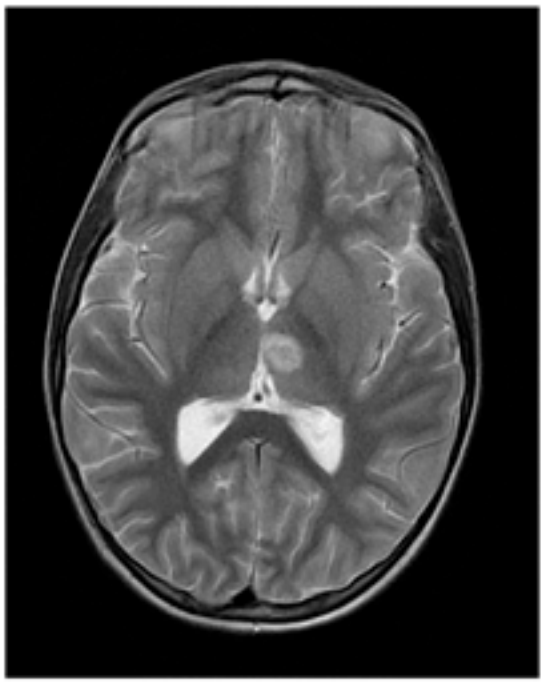
Figure 2 A-C: T2 (A), FLAIR (B) and diffusion sequence (C) MRI of the brain of a 6 year-old-boy (patient 2) obtained 1 week after DKA treatment showing an infarction of the left thalamus extending to the left cerebral peduncle.



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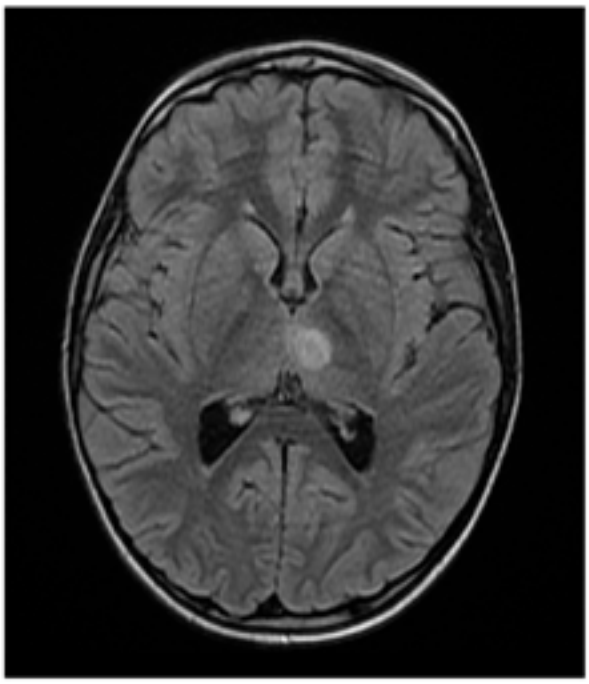

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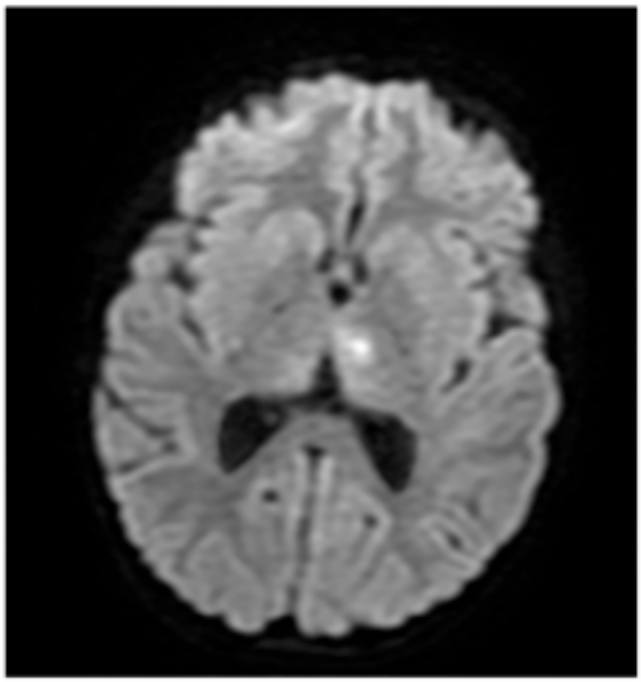

C

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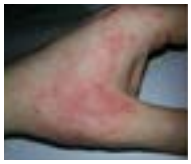
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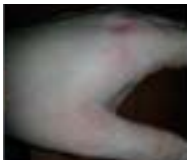
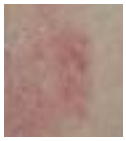

D3

VERLICHT DE SYMPTOMEN VAN DE PATIËNTEN IN 3 DAGEN TIJD[1]**:**

-26% JEUK
-33% PRIKKELING
-47% BRANDERIG GEVOEL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D7


D14

VERMINDERDE SCORAD:

-43% NA 7 DAGEN
-68% NA 14 DAGEN

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Acute Disseminated Encephalomyelitis: a Case Report

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Keywords

Case report; acute disseminated encephalomyelitis; ADEM; children; corticosteroids; plasmapheresis

Abstract

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory and demyelinating disorder of the central nervous system. In this case report, we describe a ten-year-old-boy who presented with weakness in the legs. After work-up, a post-viral ADEM was diagnosed, possibly caused by Bocavirus. This case illustrated how mild signs of encephalopathy as part of the presenting symptoms of ADEM can easily be missed. When treating ADEM, beyond initial therapy, early initiation of physical, occupational and speech rehabilitation can help facilitate more timely and complete recovery.

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating disorder of the central nervous system (CNS) (1-5). Diagnosis requires both multifocal involvement of the CNS and encephalopathy (1, 3-8). ADEM is commonly preceded by a viral infection, but can be seen after vaccination (1-6, 8, 9). Corticosteroids are considered the first-line treatment. Other treatments include intravenous immunoglobulins (IVIg) and plasmapheresis (1, 3-6, 8). ADEM has a favourable prognosis, with low mortality (1, 3, 4, 6). However, reports have shown that most patients suffer from a variety of cognitive deficits post-ADEM (1-4). To reduce these deficits rehabilitation therapy should be initiated early on (3, 4).

Case Report

A ten-year-old boy, previously known with developmental dysphasia, presented with weakness in his legs and inability to sit independently. Two days prior he suffered from back pain and pain and stiffness in his legs. There was no urinary or faecal incontinence. There were no signs of concurrent infection. Three weeks prior he suffered a common cold. At clinical examination he was alert, yet quiet, and showed minimal interaction. Apart from minimal movements of the toes of his right foot, he was unable to move his legs and feet, nor could he stand. He had no motor response in his left leg and had minimal response in his right quadriceps, being unable to move against gravity. Patellar and Achilles reflexes were absent bilaterally. Plantar reflexes were normal. Sensibility of the legs was preserved, as were strength and sensibility of the arms. There were no meningeal signs. There was no photophobia, pupils were equal and reactive to light. Examination of the cranial nerves was normal. Examination of the heart, lungs and ENT-region was normal. During hospitalisation he attained urinary- and faecal retention, with need of bladder catheterisation, laxatives and rectal enema's.

Based on this, the differential diagnosis included acute infection of the central nervous system (CNS), an acute demyelinating syndrome, auto-immune encephalitis and malignancies of the CNS (1-3). Therefore, lab-work up, a lumbar puncture and brain/spinal MRI were performed. Laboratory findings showed C-Reactive Protein <5mg/L, sedimentation 5 mm/h, leukocytes 13.22x10E9/L. Serology was negative for Cytomegalovirus, Borrelia, Treponema, Herpes simplex virus, Mumps virus, Rubella virus, Coxsackievirus, Parvovirus, Mycoplasma pneumoniae and SARS-CoV-2. Serology for Epstein-Barr virus and Measles virus was IgG positive, indicating immunity or old infection. PCR for Bocavirus was positive on nasopharyngeal swab, but PCR of the liquor came back negative. The lumbar puncture showed 5 white blood cells/microliter, < 100 red blood cells/microliter, total protein 48 mg/dL, CSF-serum glucose ratio of 0.62 and absence of oligoclonal bands. Liquor cultures were negative for Herpes simplex virus, Varicella zoster virus, Enterovirus and Mycoplasma pneumoniae. Auto-immune work-up showed borderline antinuclear antibody positivity, with a titre of 1:80, which was considered irrelevant. Antibodies for myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 were negative. An MRI of the spinal cord showed longitudinal central inflammation of the thoracic part (figure 1a and b), and was considered most likely to be due to longitudinally extensive transverse myelitis. In further work-up of the extent of CNS lesions, MRI of the brain was performed, showing multiple diffuse nodular white matter lesions, mostly located subcortically (figure 2). This, combined with the longitudinal inflammation at the thoracic spinal cord, confirmed the diagnosis of ADEM.

Initially, a five day cycle of high-dose intravenous corticosteroids; methylprednisolone 30 mg/kg/day, was started. This showed an unsatisfactory response with only slight improvement of the symptoms, i.e. improvement in strength of the right leg, yet inability to move the left leg, unchanged urinary- or faecal incontinence and persistent minimal interaction. Therefore, plasmapheresis was started. In total five cycles were performed, showing good clinical response, with the boy regaining strength of the legs, a significant improvement in interaction and some improvement of urinary- and faecal incontinence. Aetiology was deemed post-viral, potentially due to a Bocavirus infection, considering an otherwise negative work-up. No EEG was performed in this case as his quiet behaviour was initially considered to be part of his personality. After the plasmapheresis it was noticed that this represented a mild sign of encephalopathy, which had thus been misinterpreted at first.

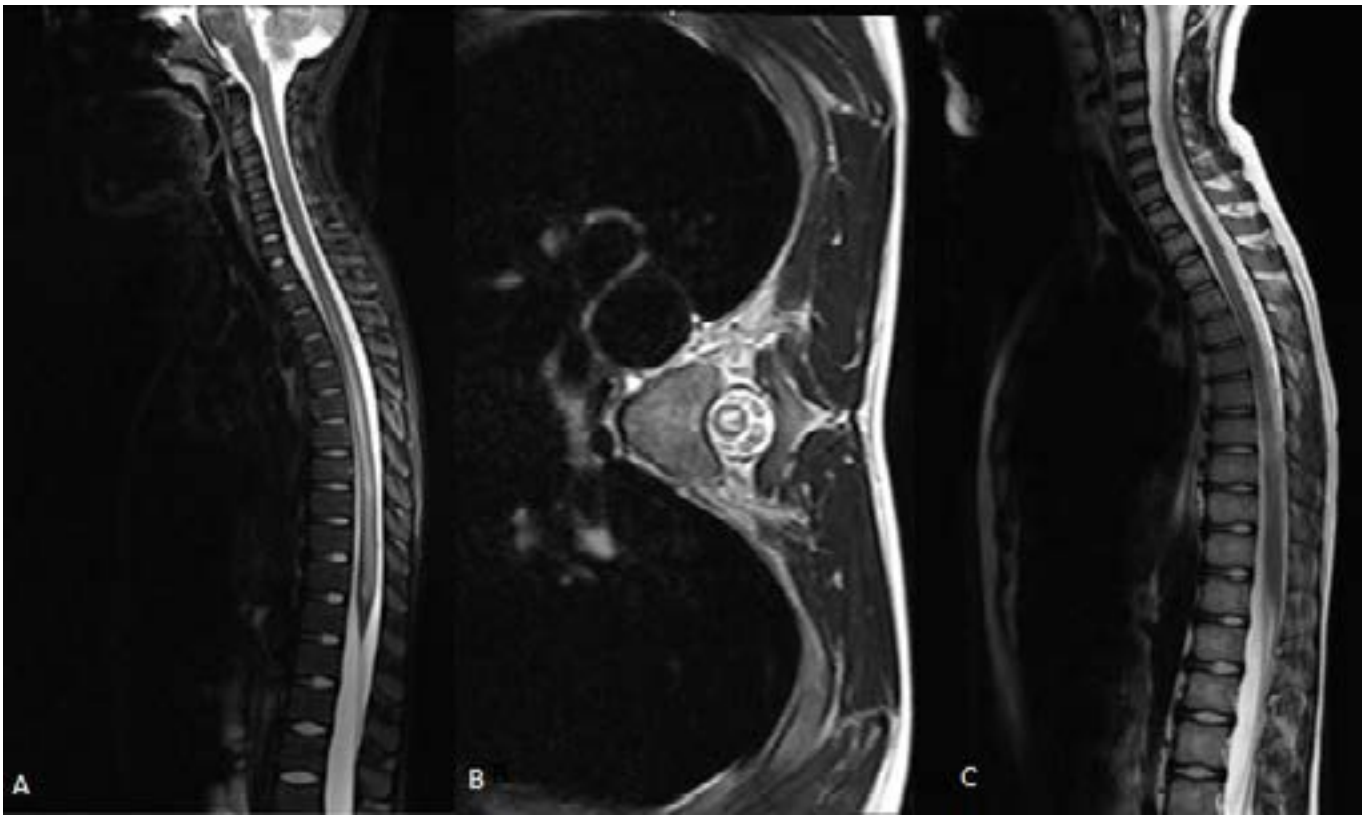
Two weeks after onset of the symptoms he was discharged from the hospital and started clinical rehabilitation in a specialised centre, which focussed on somatic, motor, urological and communicative rehabilitation. He was discharged after eight weeks. He fully regained strength in his legs. At discharge no lasting cognitive defects had been observed. There are however, residual complaints of a neurogenic bladder. Six-month follow-up showed a normal neurological examination. The MRI showed disappearance of the white matter lesions of the brain and considerable regression, yet no resolution, of the inflammation of the spinal cord (figure 1c).

Discussion

Definition and pathogenesis

ADEM is an immune-mediated inflammatory demyelinating disorder that mainly affects children, with a reported incidence of 0.23-0.6/100.000

Figure 1 A-C: Figure 1a and b: MRI of the spinal cord. It shows longitudinal central myelopathy from T2 to T12-L1.Figure 1c: MRI of the spinal cord. It shows regression of the inflammation from T2 to T12-L1. Images obtained with STIR which is a technique most sensitive for inflammatory spinal cord lesions.



per year (1-6). Mean age at presentation is between five to eight years (5, 7). It is commonly preceded by a viral infection, but can be seen after vaccination (1-7).

The precise aetiology of ADEM is unknown. Evidence suggests that it results from a transient autoimmune response triggered by an environmental event toward myelin or other self-antigens through activation of T-cell clones in genetically susceptible individuals (1-4). One protein known to play a role in ADEM is myelin oligodendrocyte glycoprotein (MOG), a protein exclusively expressed in the CNS, that is part of the myelin sheath. Expression of MOG antibodies are associated with different inflammatory diseases of the CNS such as ADEM, optic neuritis and transverse myelitis. In ADEM, 64% of children have positive MOG-antibodies. Ninety-six percent of those children turn out to have relapsing ADEM. A decline in MOG-antibodies to undetectable levels after treatment is associated with a smaller chance of future relapse and thus a better long-term prognosis (1, 2, 6, 8).

In our patient, the preceding viral infection could have well been a Bocavirus infection considering the positive nasopharyngeal PCR. Bocavirus has been associated with neurological sequalae such as encephalitis and epileptic convulsions (9). However, we found no previous literature describing association of Bocavirus with ADEM.

Clinical and biochemical findings

As ADEM is a polyfocal disease, initial presentation is highly variable. It typically has a monophasic course, but a multiphasic course is described (1, 4). Clinical presentation of ADEM may resemble other demyelinating diseases. Mortality is rare, with most studies reporting no deaths, and some with a maximum of 3% (1, 2) . However, up to 25% of children require admission to the paediatric intensive care unit due to respiratory failure (1-4, 7). Encephalopathy is a required criterion for the disease, varying from altered behaviour such as irritability, sleepiness or confusion, to altered consciousness such as lethargy, stupor or coma (1, 2, 4-8). Patients with polyfocal onset of symptoms without encephalopathy are categorised under 'Clinically isolated syndrome' (CIS). Multiple studies have shown that these patients are at higher risk of developing Multiple sclerosis (MS) (1, 7).

ADEM is diagnosed on clinical grounds and MRI, which shows demyelinating lesions. The abnormalities found are large, asymmetric patchy, poorly marginated areas of increased signal intensity in the white matter tracts of the cerebral hemispheres, brainstem, optic nerves and spinal cord (1-7).

Other investigations in the work-up of ADEM are to exclude other diagnoses such as infectious, neoplastic and metabolic disorders (4-6). Cerebrospinal fluid may be normal or show a mild pleocytosis with, or without, elevated protein levels (1-3, 6, 7). In the acute phase, the majority of EEG's are abnormal, with nonspecific findings. Most commonly, diffuse slowing of the background pattern is found (2).

Treatment

There are no randomized controlled trials regarding the treatment of ADEM. Therefore, advice is based on case reports and expert opinions (1-3, 6). High dose intravenous methylprednisolone is widely accepted as the first line treatment of choice. A 3 to 5-day course of 30mg/kg/day is started, followed by oral tapering during 4-6-weeks. Other treatments with beneficial effects include IVIg and plasmapheresis. They are considered when corticosteroids are contra-indicated or ineffective (1-7). As ADEM is not associated with the development of new lesions on follow-up, it is important to have long-term clinical and radiological follow-up to exclude a multi-phasic disorder, such as MS, and to mitigate any potential neurological of psychosocial sequelae of the condition. The international Study Group suggested reassessing the patient with at least two additional MRI's after the first normal MRI, over a period of 5 years from the initial episode (1, 2, 4).

Prognosis

ADEM has a favourable prognosis, as complete recovery is reached in most cases and mortality is rare (1-4, 7). Recovery is typically seen between 26-34-days after onset (2, 3, 6). However, few reports are available on

the cognitive outcomes of ADEM. Several studies have shown that patients frequently suffer from a variety of mild cognitive deficits: up to half of the children may have mild deficits, and moderate-severe deficits can be seen in up to 18% (2-4). Early initiation of physical, occupational and speech therapy might prevent this and can help facilitate more timely and complete recovery (3, 4).

As mentioned above, encephalopathy is a main criterion for the diagnosis of ADEM. In this case, as there were minimal symptoms, it could be argued that the correct diagnosis would have been CIS. CIS constitutes a polyfocal onset, but no encephalopathy. It has a less favourable outcome, with a high risk of developing MS (1, 7). However, during the initial days the boy was notably quieter and more withdrawn, showing minimal interaction with other people, which improved significantly after treatment.

Conclusion

We report the case of a ten-year-old boy with ADEM, provoked by a preceding viral infection, possibly due to Bocavirus, treated with corticosteroids and plasmapheresis. Because signs of encephalopathy as a presenting symptom of ADEM may be mild, they can easily be missed. For good clinical outcome early initiation of physical, occupational and speech therapy is important.

Conflict of interest: The authors declare no conflict of interest.

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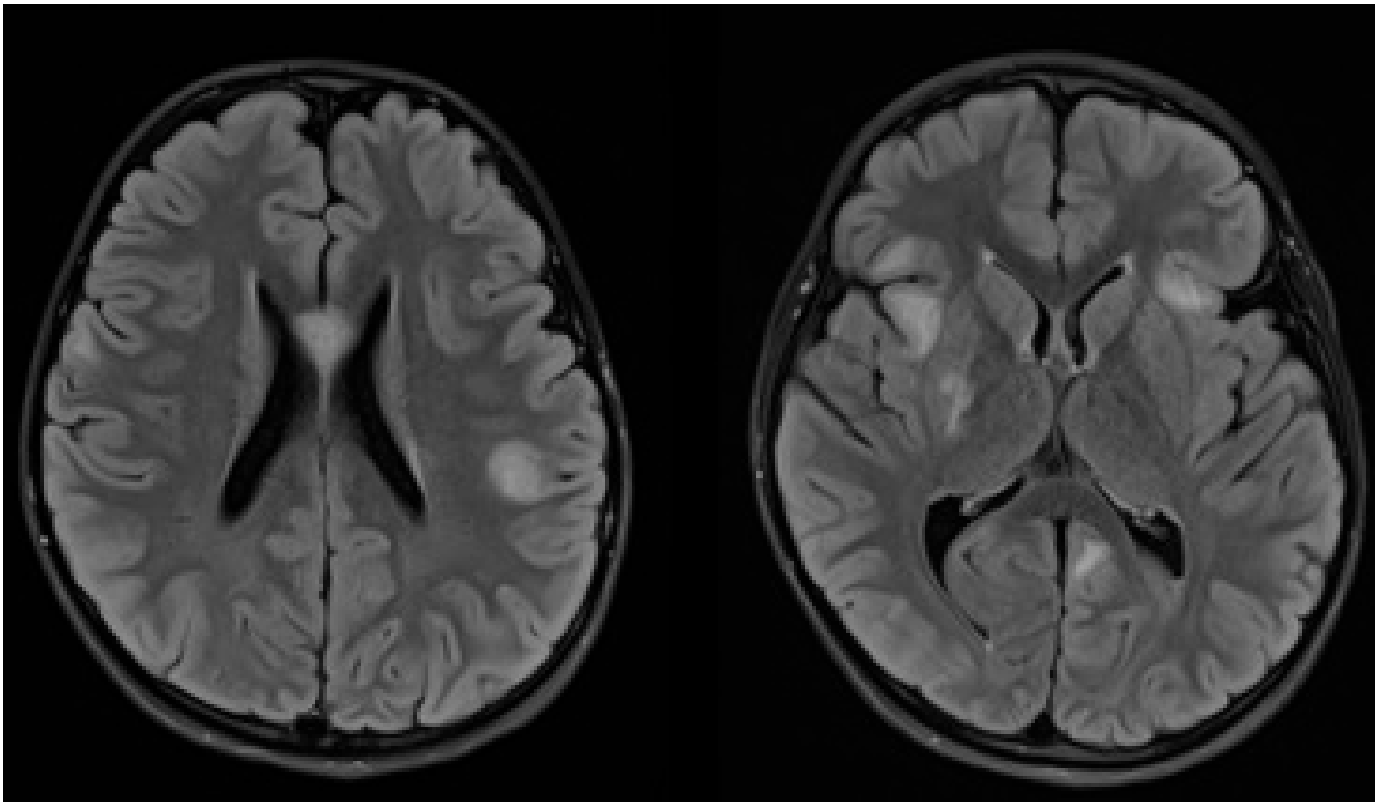
Figure 2: MRI of the brain. Diffuse white matter lesions, mostly sub- and juxtacortical and in the basal ganglia, corpus callosum and brainstem. Images obtained with FLAIR which is a technique most sensitive for white matter lesions in the brain.



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Meckel's diverticulum: sometimes a hidden pitfall

Noor Gerets [a], Astrid Jeunen [a], Eveline Box [a], Robrecht Ceulemans [b], Patrice Givron [a]

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Keywords

Meckel's diverticulum

Abstract

Meckel's diverticulum is the most common congenital abnormality of the small intestine, resulting from incomplete obliteration of the vitelline duct leading to the formation of a true diverticulum. The clinical presentation ranges from an asymptomatic course up to life-threatening complications. We report the case of a 3-years-old boy, initially diagnosed with an acute gastritis. Additional diagnostics showed the need for urgent surgical treatment due to a small bowel obstruction. This case report addresses the importance of adding additional diagnostics if the patient is not clearing up within acceptable time with the initiated therapy.

Introduction

Meckel's diverticulum (MD) is a common congenital true diverticulum on the ileum, resulting from incomplete atrophy of the vitelline duct (1). This vitelline duct contains pluripotent cells, which can give rise to heterotopic tissues (if the duct does not disappear), of which gastric mucosa is the most common, followed by pancreatic and rarely colonic and biliary mucosa. The acid secretion of the ectopic gastric tissue causes tissue changes in the adjacent mucosa (erosion and ulceration), which are accountable for the main pathological reason behind complications (2). Various complications can arise in the form of intestinal obstruction, hemorrhage, diverticulitis, perforation and rarely vesicodiverticular fistulae and tumors. We report a case of intestinal volvulus with strangulation, caused by a fibrovascular band arising from MD. The aim of this article is to highlight the clinical index of suspicion leading to this diagnosis, the possible additional examinations and suggested management.

Case report

A 3-year-old boy presented to the emergency department because of non-bilious vomiting up to 10 times and severe anorexia since one day. At presentation there were no complaints of abdominal pain.

His personal history was uneventful and there was no history of previous abdominal surgery.

Clinically, the boy was pale with sunken eyes and dry lips. On examination, a hyperperistaltic non-distended abdomen without guarding, tenderness or masses was found. Furthermore, no clinical abnormalities were found. Laboratory findings showed a leukocyte count of 16.90 (5-15x109/l), a CRP value of <1 (<5mg/l) and electrolytes and hemoglobin within normal limits. He was diagnosed with an acute gastritis, for which he was hospitalized, and intravenous fluid treatment was started.

A few hours later, given insufficient recovery on intravenous fluid with emerging pain, further diagnostics were initiated. He remained afebrile. Abdominal ultrasound showed an increased amount of intra-abdominal free fluid and distended small bowel loops filled with fluid. To identify the cause, computerized tomographic imaging (Figure 1) was performed which revealed the whirlpool sign, a rotation of the bowel around its mesentery leading to whirls of the mesenteric vessels, with striking dilatation of small bowel loops and a collapse of ileal intestinal loops (3). Laboratory findings showed a leukocyte count of 31.5 (5-15x109/l), a CRP value of 45 (<5 mg/l) and a hyponatremic (sodium 133 (135-145 mmol/l)) metabolic acidosis (HCO3- 16.7 (22-29 mmol/l)). Blood gas showed an elevated lactate level of 18 (<11.3 g/dl).

In dialogue with the surgery department, the decision was made to perform an emergency exploratory laparotomy under general anesthesia. In entering the peritoneal cavity, a mesodiverticular fibrovascular band, extending between the tip of MD and the visceral peritoneum of the small bowel mesentery, was seen. This fibrovascular cord caused independently prominent stenosis of the terminal ileum, which resulted in an intestinal volvulus causing obstruction and strangulation. The fibrovascular band was cut and the diverticulum resected. The compromised intestinal loop gradually recolored with marked pulsations and capillary refill (Figure 2). No segmental bowel resection was necessary.

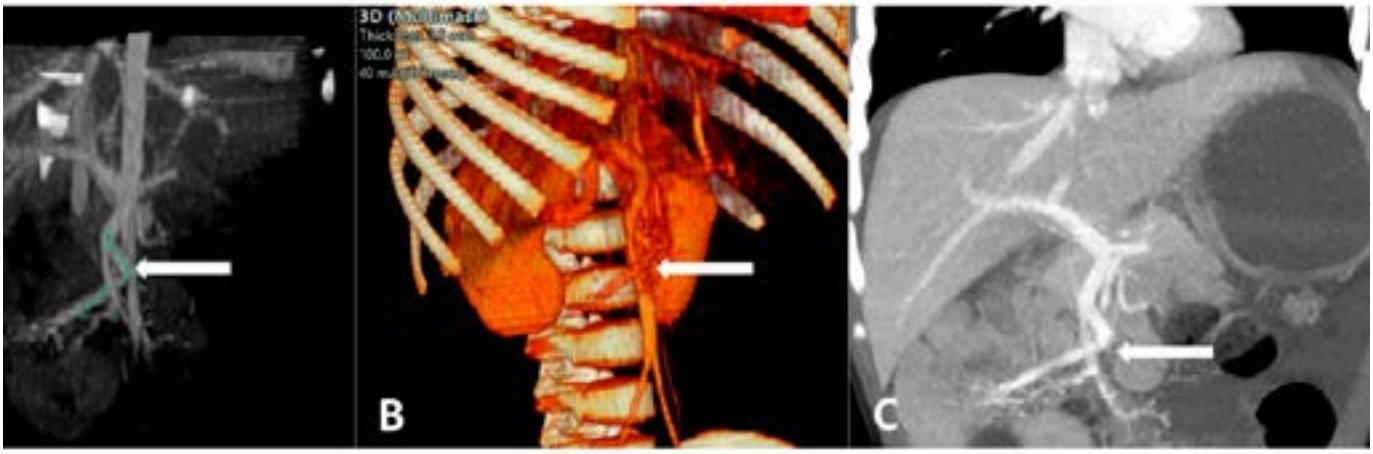
The diverticulum was sent for histological examination. No heterotopic tissue was found, but the image is compatible with a MD. Early ischemic changes were already noticed. Postoperative antibiotic therapy (piperacillin/tazocin) was initiated. The patient recovered without any complication and was discharged one week later.

Discussion

It has been stated that MD follows the 'rule of 2s', as it occurs in 2% of the population, is usually discovered before 2 years of age, is situated within 2 feet (61cm) of ileocecal valve, measures 2 inches (5cm) in length and 2cm in diameter (2).

The life-time risk of diverticulum complications is approximately 4-9% (1). This embryologic remnant may cause different kinds of complications. Combining the largest pediatric patient series, 46.7% of children presents with obstruction,25.3% presents with gastro-intestinal-hemorrhage and 19.5% presents with inflammation (4). Rarer forms of symptomatic MD, including umbilical abnormalities involving the vitelline duct, parasite-infections, Meckelian cancers and uncertain cases, account for the remainder (1). Studies agree there are more men than women presenting with symptomatic MD and that the most common presentations of symptomatic MD are caused by obstruction, gastro-intestinal hemorrhage, and inflammation with or without perforation. Ectopic gastric tissue is associated with symptomatic MD in general and with gastro-intestinal hemorrhage in particular (1,5). Complications are frequently associated with younger ages, as 40% of these complications are seen below the age of ten years (2). An explanation why symptomatic MD presents more often in young patients, comes from the decrease in nerve fiber density with age. Higher nerve fiber density leads to more intense local peristalsis which may cause intussusception.

Figure 1 (Panel A-C) : Radiological images of the abdomen with visualization of the mesenteric swirl sign (arrows).



In contrast, acid production in ectopic mucosae increases with age, which could explain why children with hemorrhage are older (1).

Obstruction caused by the MD, can be caused by different mechanisms. In children, volvulus and intussusception appear to be the most common etiologies (1). In our case a fibrovascular cord was the cause of the intestinal volvulus. It is an extremely rare condition; we found only nine cases reported before this one (6). It is believed that the connection between the mesodiverticular band and adjacent mesentery establishes an axis for diverticular torsion and an opening for bowel to herniate, thus propagating the important mechanism for this pathology (7).Other mechanisms are torsion of the diverticulum (8), a Meckel's diverticulitis which results in reduced intestinal luminal diameter, an inversion of MD into the bowel lumen or an incarceration of the MD in an abdominal wall of internal hernia (2). This latter complication is also reported as a cause of sudden infant death syndrome (9).

Common symptoms of MD complications are fever, vomiting, abdominal pain and bloody stools. These symptoms and its underlying pathological processes are not unique to MD. MD represent a diagnostic challenge and are often incidentally found (1,2).

MD can be diagnosed by using imaging modalities as ultrasound, angiography, scintigraphy (Tc-99m), CT and MRI. When observed on ultrasound and CT, the MD takes the shape of a cyst or blind pouch diverging from the ileum. Angiography may identify the source of gastro-intestinal hemorrhage and the vitelline artery branching off the superior mesenteric artery, when present, is pathognomonic for MD. Nuclear scans with Tc-99m visualize the MD by accumulation of the tracer in the ectopic gastric tissue. The sensitivity and specificity of most of the diagnostic test is low and one needs to actively search for it (1). However, complications are easily diagnosed and can lead to indispensable surgical interventions. In a study of Kawamoto and all, a MD was detected on CT in 57.1% of symptomatic patients (10). Nuclear scans with Tc-99m visualize the MD by accumulation of the tracer in the ectopic gastric tissue and have a respectively sensitivity and specificity of respectively 89.6% and 97.1% (1).

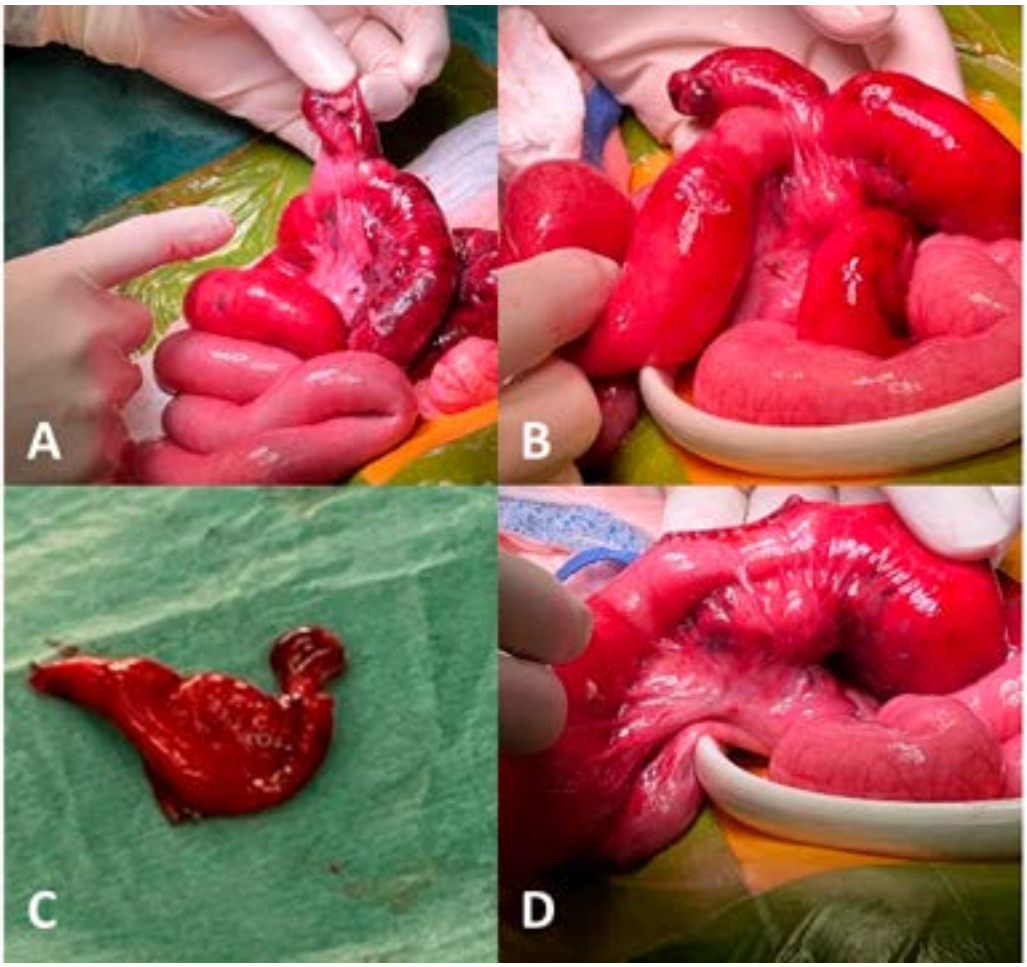
Symptomatic MD should be managed surgically by performing a diverticulectomy using hand-sewn or stapling techniques through an open or laparoscopic approach (11). A laparoscopic approach is feasible and safe and a review of the national Surgical Quality Improvement Program-Pediatric (NSQIP-Ped) database confirmed that the laparoscopic approach is associated with a shorter length of hospitalization. If a conversion from a laparoscopic to an open procedure is required, the risk of complication is not affected (12). Diverticulectomy is most easily performed using a linear gastrointestinal stapler applied to the base of the diverticulum (13). A segmental resection is suggested if the small bowel lumen is in jeopardy of being narrowed, a palpable abnormality is present at the base of the diverticulum, the neck of the diverticulum is wide (>2 cm) or if the diverticulum is short, broad-based with features warranting resection due to the risk of leaving behind ectopic tissue at the base (11). When gastrointestinal bleeding is the primary clinical manifestation, it is likely that both segmental small bowel resection and simple diverticulectomy are effective surgical approaches (14,15,16).

As illustrated in our case, a MD can mimic other abdominal diseases such as an appendicitis gastro-enteritis or an intussusception (17). If the patient does not respond as expected to the initiated therapy for the presumptive diagnosis, other differential diagnoses, among which a MD, should be considered.

Conclusion

MD can present itself in a broad clinical spectrum, ranging from an asymptomatic course up to life-threatening complications for which a high suspicion for timely diagnosis and surgical intervention should be kept. In our case, the diagnosis of a MD with intestinal volvulus and strangulation was made within 24 hours after presentation, without any complication, even with non-suspicious clinical examination and normal blood analysis with presentation. Take home message: as pediatricians we are familiar with the common presentation of a gastritis and its treatment. However, if the patient is not clearing up within acceptable time frame after correctly initiated standard therapies, the patient should be reassessed, and additional diagnostics should be promptly added.

Figure 2 (Panel A-B) : On the series of photo's, the strangulation by the fibrovascular band resulting in a cyanotic ileal segment can be seen. A diverticulectomy was performed with a linear gastro-intestinal stapler at the base of the diverticulum. The ileal segment recovers with good capillary refill and pulsations.



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NUTRICIA

Chronic obstructive cholestasis with gallbladder masses associated with invasive fungal infection in a preterm neonate: a case report

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Keywords

invasive fungal infection, obstructive cholestasis, preterm, beta-D-glucan, case report

Abstract

A preterm boy, born at the gestational age of 26 weeks, developed a sepsis followed by obstructive cholestasis at the age of 4 weeks despite broad spectrum antibiotic and fluconazole treatment. Abdominal ultrasound showed masses of unknown origin in the gallbladder. An invasive fungal infection was diagnosed via serum (1,3)-beta-D-glucan. After initiation of the echinocandin caspofungin, inflammation and cholestasis parameters subsided quickly and the patient recovered.

Accumulation of fungal balls in the gallbladder has been described as a cause of chronic obstructive cholestasis in immunocompromised adults, this is the first reported case in a preterm neonate.

Introduction

Neonatal cholestasis and invasive fungal infections are both associated with important morbidity and mortality in preterm neonates. Neonatal cholestasis is defined by a serum conjugated bilirubin of more than 1 mg/dL or more than 20% of the total serum bilirubin. Up to 10 to 20% of premature babies will develop cholestasis due to various causes, including but not excluded to those mentioned in figure 1. Some of these require urgent interventions so a prompt and full diagnostic work up of neonatal cholestasis is key (1).

Invasive fungal infections are mostly caused by *Candida* species. Risk factors include presence of central venous catheters, use of broad-spectrum antibiotics, intravenous lipid emulsion, endotracheal tubes and antenatal antibiotics (2). The gold standard for microbiological diagnosis is a fungal culture, but this lacks sensitivity (3). Therefore, additional culture-independent tests such as galactomannan and (1,3)-beta-D-glucan (BDG) can be of added value for diagnosing invasive fungal infections. BDG is a major cell wall constituent of most pathogenic fungi (including *Candida* and *Aspergillus* species) which is released in serum in case of an invasive fungal infection. The most important diagnostic value of a BDG assay is its high negative predictive value (4). In case of invasive *Candida* infections in neonates, the first choice of empirical antifungal therapy is still under debate. Amphotericin B deoxycholate, fluconazole and echinocandins are appropriate choices. If a non-*albicans Candida* species is being isolated such as *C. glabrata*, or *C. krusei*, which are intermediate or resistant to fluconazole, amphotericin or an echinocandin should be administered. This is also recommended when the patient has received fluconazole prophylaxis (3). Although it is under discussion as studies have shown that there is no increase in fluconazole resistance after prophylaxis (5).

In adult immunocompromised patients the accumulation of fungal balls in the gallbladder during a systemic fungal infection has been described to cause chronic obstructive cholestasis (6). To this day, this had not yet been reported in preterm neonates.

Patient information

A male baby was born at the gestational age of 26 weeks, weighing 800 grams, through spontaneous vaginal delivery. APGAR scores were 8-10-10. He received surfactant and respiratory support through nasal continuous positive airway pressure. Regarding premature labour of unknown origin antibiotics were administered for 5 days. Blood culture remained negative. Fluid intake consisted solely of breast milk by the age of 10 days and there were no more central lines. No major particularities were reported during the first month.

At the age of 4 weeks, he developed a clinical late onset sepsis of unknown origin with hypothermia, a distended abdomen and a septic appearance for which broad-spectrum antibiotics were initiated. C-reactive protein (CRP) rose to 23 mg/L (normal < 4 mg/L) and blood culture became positive for *S. epidermidis*. A central venous catheter was placed and empirical therapy with amikacin and piperacillin-tazobactam initiated for which the antibiogram confirmed sensitivity. Therapy was subsequently narrowed to vancomycin monotherapy for a total of 10 days. The patient improved clinically, nevertheless CRP remained elevated. Therapy was switched again to various (broad-spectrum) antibiotics: vancomycin, cefotaxime, piperacillin-tazobactam and the antifungal azole drug fluconazole. Despite this, CRP increased to a value of 109 mg/L at the age of 7 weeks. Echocardiography showed no signs of endocarditis. Serial blood and urine cultures remained sterile. The central catheter was removed and replaced, no pathogens were cultured from the catheter tip. A viral

Figure 1: Flowchart for management of neonatal cholestasis and when to suspect an invasive fungal infection.
HSV = herpes simplex virus, CMV = cytomegalovirus, HAV = hepatitis A virus, HBV = hepatitis B virus, HCV hepatitis C virus, BDG = beta-D-glucan

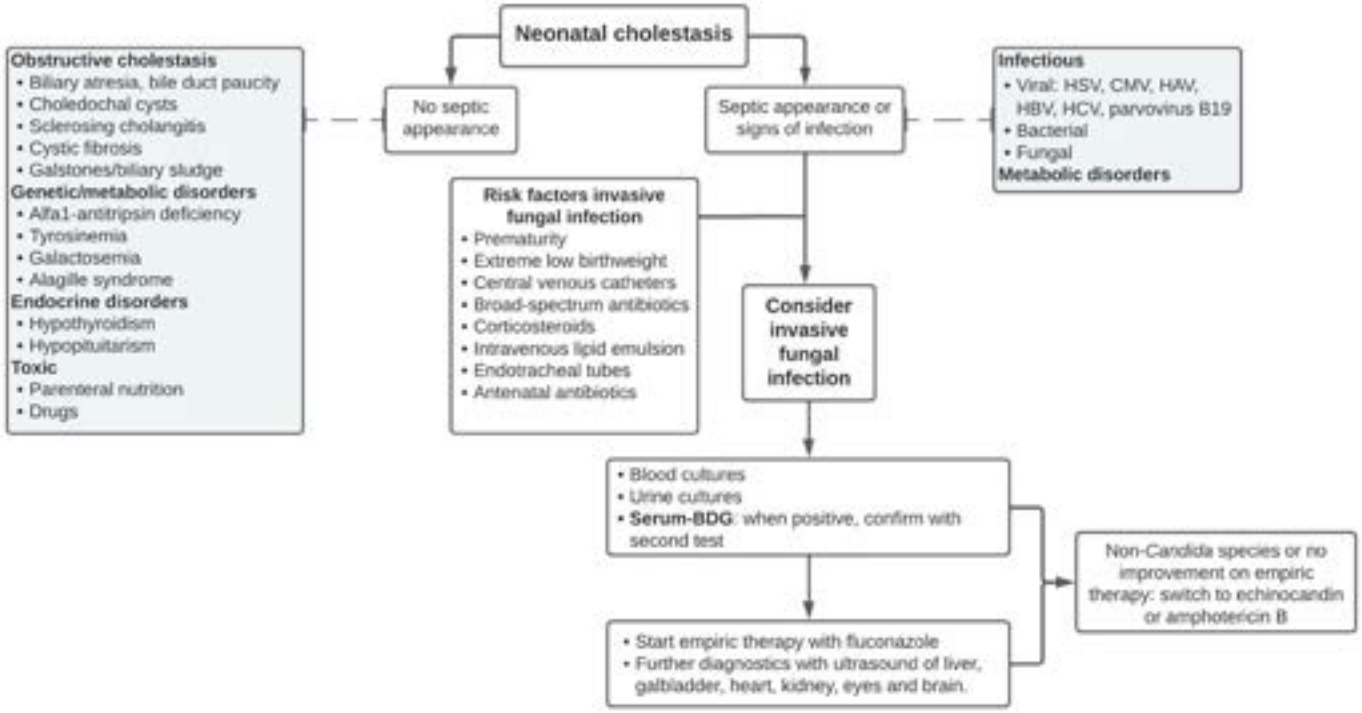
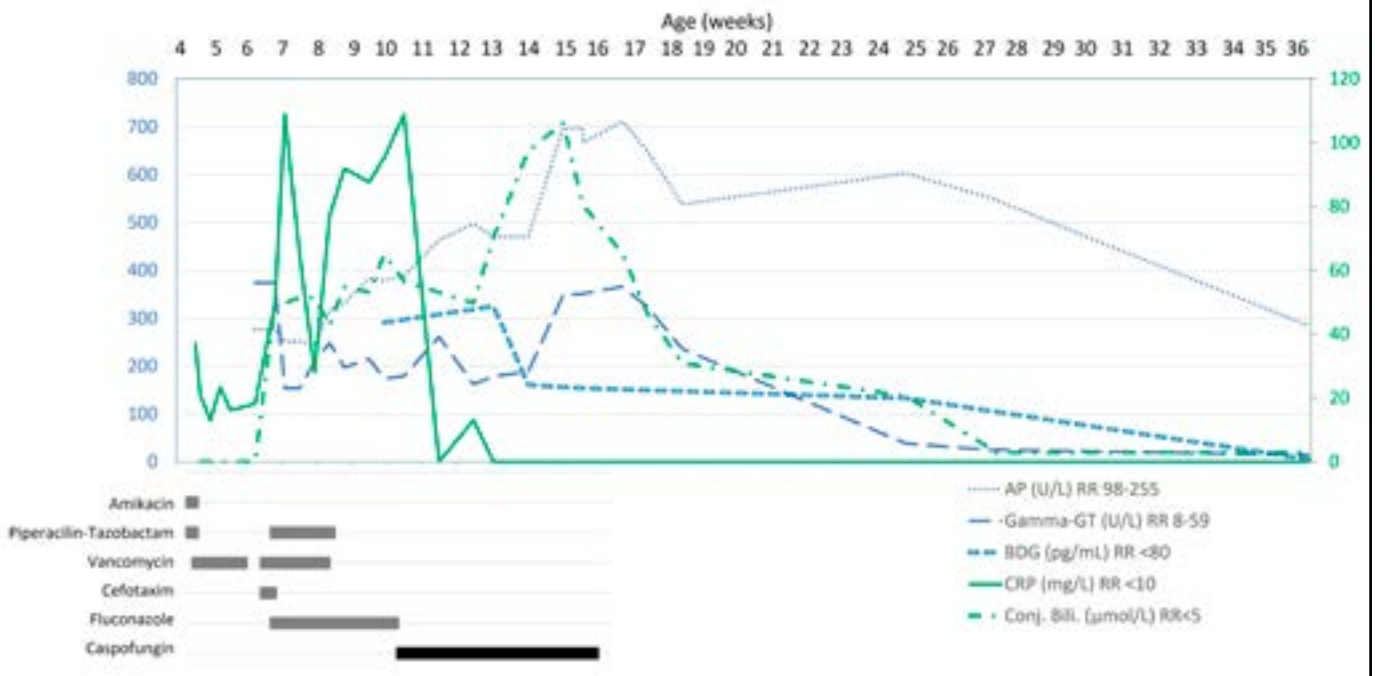


Figure 2: Evolution of laboratory results and reaction to antibiotic and antifungal treatment. AP, gamma-GT and BDG are displayed on the left axis, CRP and Conj. Bili. in the right axis.
AP = alkaline phosphatase, BDG = beta-D-glucan, CRP = C-reactive protein, Conj. Bili. = conjugated bilirubin, Gamma-GT = gamma-glutamyl transferase, RR = reference range.



respiratory multiplex molecular panel performed on a nasopharyngeal aspirate could not identify any pathogens.

During this period, his stool became acholic and he developed jaundice and failure to thrive. Further investigations revealed cholestasis with a conjugated hyperbilirubinemia, elevated gamma-glutamyl transpeptidase and liver alkaline phosphatase. The evolution of the biochemical parameters is visualised in figure 2.

Furter diagnostic tests could not indicate any viral cause for the cholestasis and screening for alfa1-antitripsin deficiency, cystic fibrosis, tyrosinemia and galactosemia came back negative. An abdominal ultrasound showed hyperechogenic material in the gallbladder and magnetic resonance imaging confirmed cholecystolithiasis without distention of the biliary tract.

Weight gain was already insufficient from the age of 4 weeks despite enriching breast milk with human milk fortifier and medium chain triglycerides. At 7 weeks of age breast milk was substituted for total parenteral feeding. After a small catch up in weight the evolution ceased again by 8 weeks.

As no bacterial or other cause could be found for the cholestasis, inflammation and failure to thrive, at the age of 8 weeks all antibiotics were stopped and fluconazole continued in therapeutic dosages. There was no effect on the clinical evolution or growth. Blood cultures taken within this antibiotic free window remained negative. At the age of 10 weeks, a serum BDG test (performed at the Belgian mycosis reference centre at the laboratory of University Hospital Leuven) suggested an invasive fungal infection with a value of 294 pg/mL (cut-off value for positivity = 80 pg/mL) while receiving fluconazole in therapeutic dosages for over two weeks (7). Subsequently, therapy was switched to intravenous caspofungin (an echinocandin) at a dosage of 2 mg/kg/day, once daily. Within one week CRP normalized and a remarkable catch up growth could be noted (figure 3). The serum BDG rose further to a maximum of 325 pg/mL, followed by a gradual decrease (figure 2). Transaminases declined slowly under the ongoing therapy, though the cholelithiasis remained visible on ultrasound exams up to 7 months after therapy. We believe this history is compatible with the presence of fungal collections in the gallbladder. This could however not be confirmed. Firstly, because endoscopic retrograde cholangiopancreatography (ERCP) was not feasible at his young age and low body weight, and secondly, because it was decided to hold off on cholecystectomy given the clinical improvement following initiation of caspofungin.

Caspofungin was discontinued after 6 weeks. Afterwards, our patient was observed for another 2 weeks at the neonatology ward, without signs of relapse. The boy could be discharged from the hospital in good clinical condition at the age of 18 weeks (postconceptional age of 44 weeks).

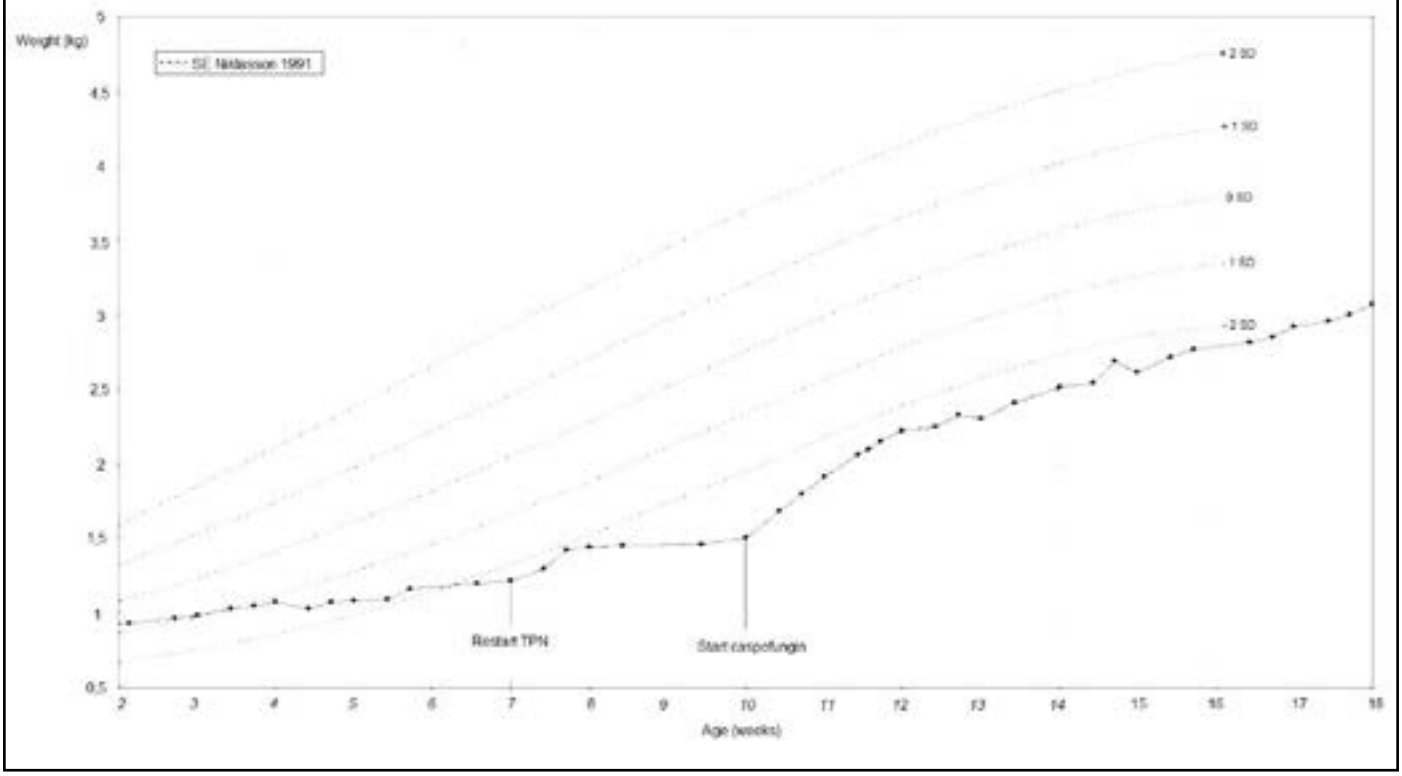
Over the following weeks cholestasis parameters declined to normal values. His growth curve returned within the normal range. BDG became negative at the age of 36 weeks (20 weeks after termination of caspofungin therapy).

Discussion

The presence of fungal balls in the gallbladder, obstructing bile flow, as a result of a systemic fungal infection have been described in adult immunodeficient patients but is very rare (6). One case report describing a *Candida tropicalis* infection with gallbladder masses in a term neonate has been published but to our knowledge systemic fungal infections with gallbladder concrements have not been described in preterm neonates (8).

Diagnosis of a systemic fungal infection can be challenging. *Candida* sensitivity of blood cultures has been reported to be only 50%, and most only become positive after 48 hours of incubation. BDG is a component of the fungal wall of the *Aspergillus*, *Candida*, *Pneumocystis*, *Coccidioides* and *Histoplasma species* and its presence in serum can be an indication for an invasive fungal infection. BDG can be positive up to 10 days before growth of *Candida* on culture and seem to be more sensitive in neonates

Figure 3: Fenton Preterm weight-for-age 22-50 weeks, boys.
Born at 26 weeks, a failure to thrive is setting in at the age of 4 weeks. At the age of 10 weeks Caspofungin was initiated, resulting in catch-up growth.



compared to adults, possibly caused by a higher fungal load during infection due to a poorly developed immune system (7). False positive BDG tests are possible in case of antibacterial treatment (mostly with amoxicillin-clavulanate and piperacillin-tazobactam), hemodialysis, intravenous treatment with immunoglobulins, albumin or coagulation factors. Two consecutive positive serum BDG tests have been associated with a high likelihood of invasive fungal infection (10). In our case broad-spectrum antibiotics (piperacillin-tazobactam) were given until 10 days before the first BDG test, a second positive test was performed 3 weeks later, both of which make a false positive result unlikely.

Risk factors for biliary tract candidiasis described in adults are immunosuppressive drugs or antibiotics and admission to an intensive care unit. The diagnosis is best achieved by direct culture of the bile post-ERCP (6). Both ERCP and cholecystectomy were considered in our case but judged not feasible. Low weight or age have been reported as a risk for ERCP failure (10). Moreover, the patient was clinically improving so an invasive procedure seemed redundant.

First line drug therapy is fluconazole, second line is caspofungin or amphotericin B. In our case we observed no improvement after two weeks of fluconazole treatment, assuming infection due to a fluconazole resistant *Candida* strain and therefore switched to caspofungin treatment with success.

Conclusion

A disseminated fungal infection should be considered in a preterm neonate with signs of sepsis with obstructive cholestasis and/or gallbladder stones, especially in the presence of other risk factors for invasive fungal disease, such as a central venous catheter or recent exposure to broad-spectrum antibiotics or steroids. A serum BDG test can help establish a presumptive diagnosis when microbiological cultures remain negative, even when patient is under fluconazole therapy. Empirical antifungal therapy is warranted in these cases, as early recognition and treatment are associated with decreased morbidity and mortality. In case of treatment failure with azoles, a switch to caspofungin to target fluconazole resistant *Candida* species should be considered (Figure 1).

Conflicts of interest

We know of no conflicts of interest associated with this publication, and there has been no financial support for this work that could have influenced its outcome.

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Tracheoesophageal fistula as a complication after ingestion of a button battery. Case report and literature review

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Keywords

Button battery, tracheoesophageal fistula, oesophageal perforation, foreign body, endoscopy

Abstract

Ingestion of a (button) battery is an increasing phenomenon in paediatrics and can have detrimental effects. We present a 15-month-old girl who ingested a button battery, which was removed 8 hours after ingestion. A week after removal, the girl was readmitted and a tracheoesophageal fistula was discovered. She was treated surgically.

Accidental button battery ingestion requires prompt recognition and removal, because of the risk of severe complications, which can already occur after 2 hours of oesophageal impaction. There is no consensus on treating tracheoesophageal fistulas. To reduce morbidity and mortality, a multidisciplinary team approach and follow-up are crucial.

Introduction

Children and toddlers frequently put objects in their mouth and unintentionally swallow foreign bodies. Ingestion of batteries is increasing as a result of the growing popularity of electronic devices. They can cause serious damage by electrochemical injury when they lodge in the oesophagus. Quick action to remove the battery is necessary to avoid complications. Perforation by impaction in the oesophagus can already arise after 2 hours. Even after relatively fast removal, serious complications can still occur and therefore a good follow-up is needed.

Case report

We encountered a previously healthy 15-month-old girl who had ingested a 20mm button battery (figure 1), which was removed several hours after ingestion in a local centre. The day after removal, she developed fever and a chest X-ray showed a left-sided pneumonia infrahilar in the left lower lobe. A chest computed tomography (CT) revealed no pneumomediastinum. Antibiotic treatment (amoxicillin-clavulanic acid) was initiated, and she left the hospital after 3 days. A week after removal, the girl started to vomit and drool without having fever. She was readmitted and

Figure 1: Chest X-ray shows the step-off sign on the lateral view and bilaminar structure: double-density or double-ring/halo shadow on the posterior-anterior view. Size: 20mm.

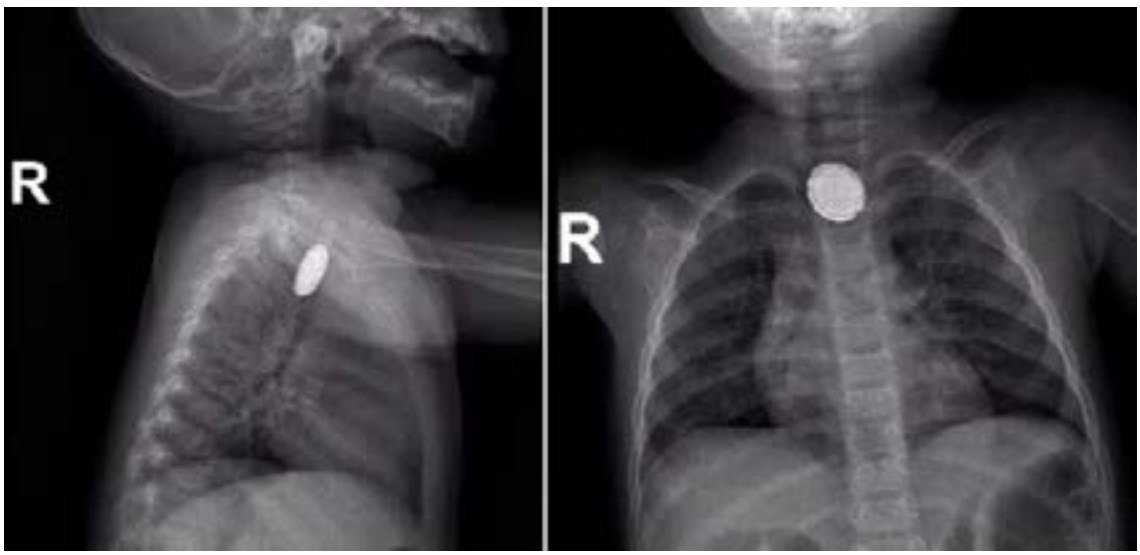


Figure 2: Images from gastro- and bronchoscopy.
A) Bronchoscopy image of the trachea showing the fistula between trachea and oesophagus, left lateral side of the trachea (±10mm).
B) Gastroscopy image demonstrating the large fistula with the cuffed tube in the trachea
C) Gastroscopy image after placing the endotracheal tube beyond the fistula to avoid ventilation problems.

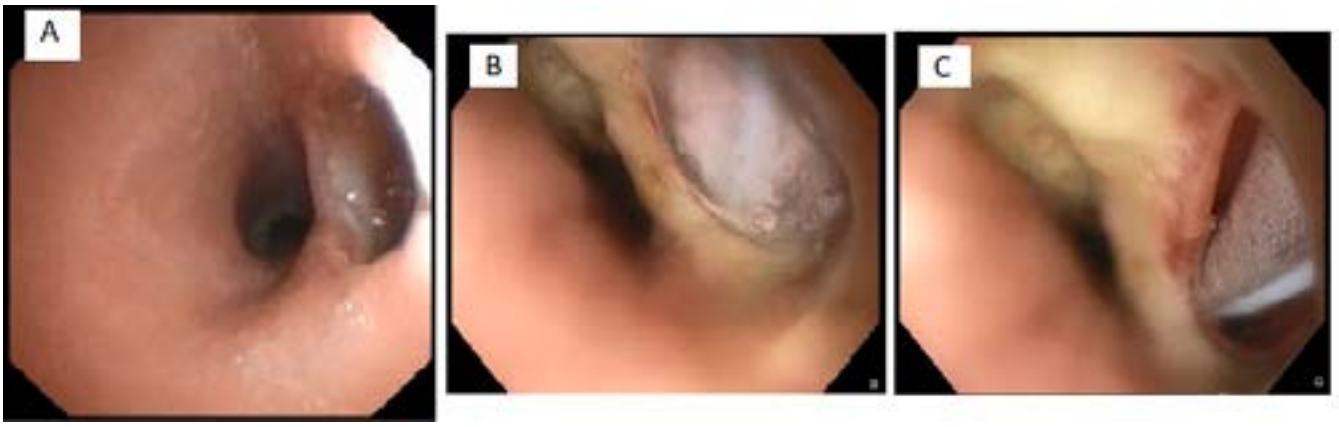
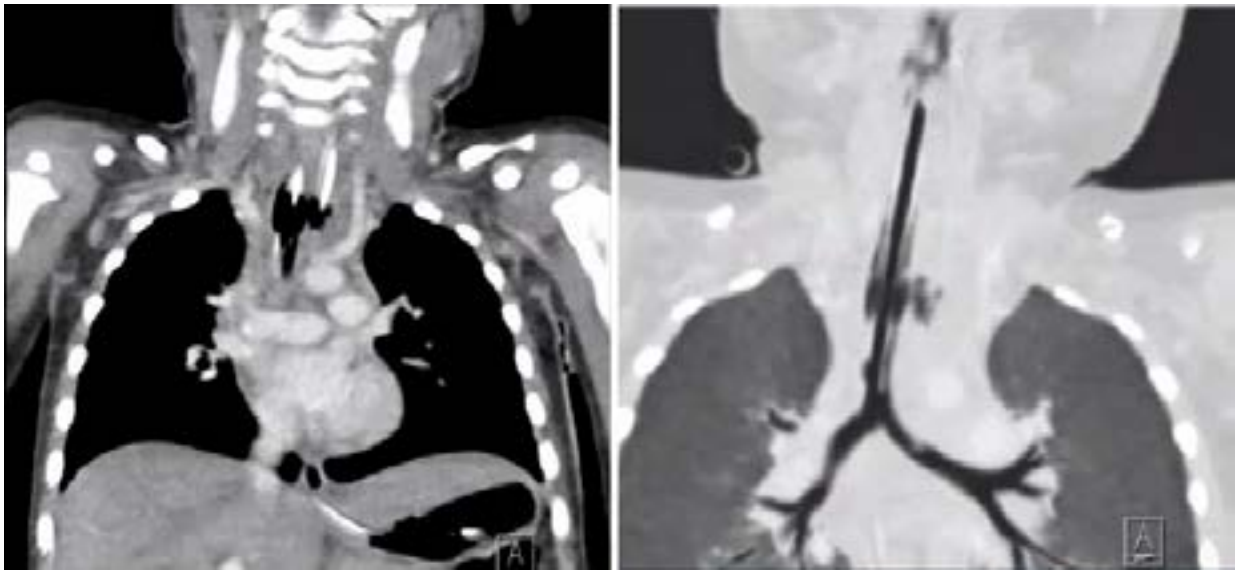


Figure 3: CT scan
Perforation presumably of the anterior wall of the oesophagus and the left wall of the trachea at level Th1-Th2 with limited air and fluid. Local enhancement around the perforation in the superior mediastinum may be associated with local mediastinitis.

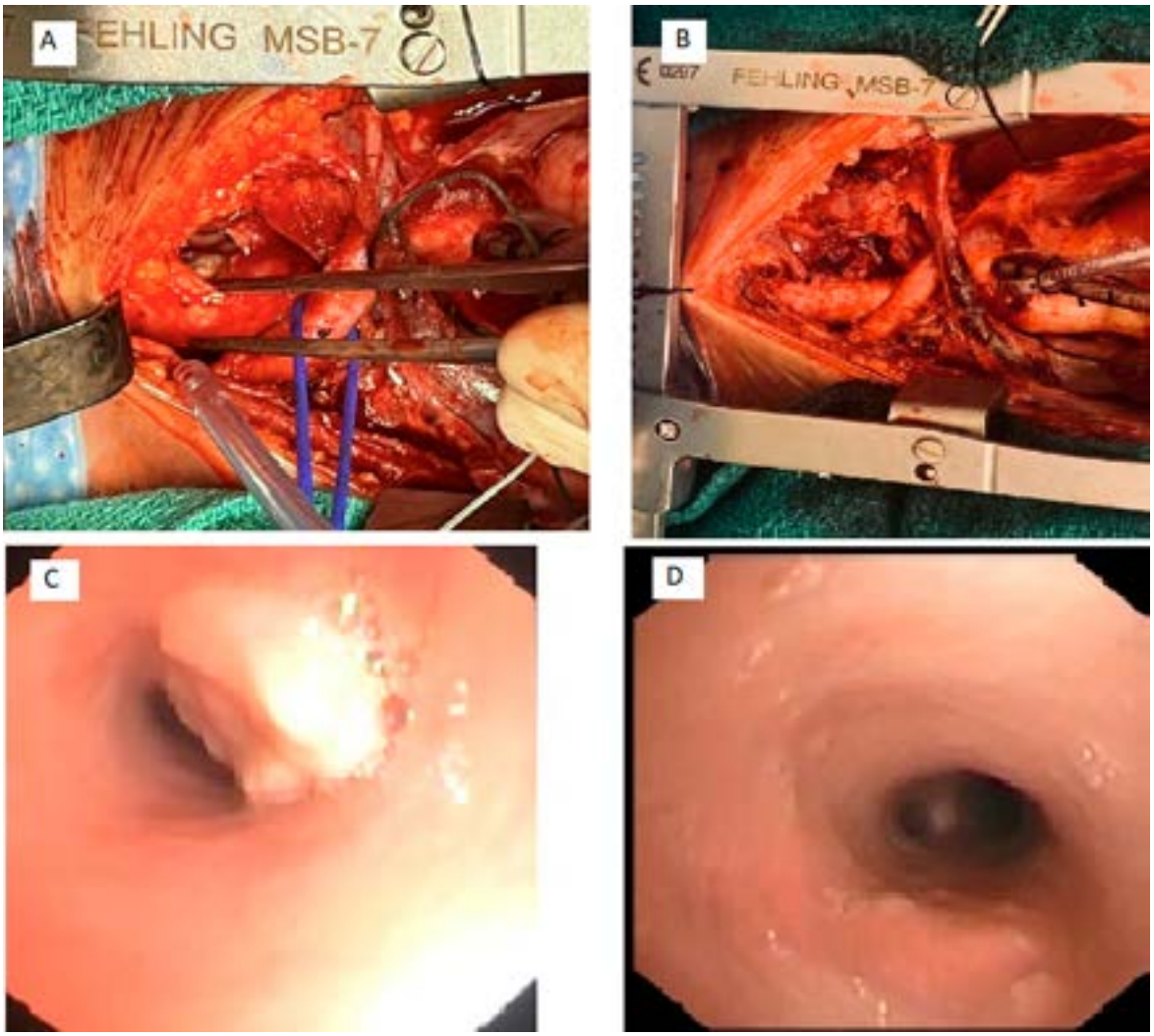


transferred to our university hospital. A large perforation of 15-20mm with fistulisation between oesophagus and trachea was discovered during gastro- and bronchoscopy (figure 2), and a repeated chest CT revealed mediastinitis (figure 3). A surgical approach through sternotomy was performed with the use of a cardiopulmonary bypass to maintain oxygenation during the reconstruction. A near transection of the mid-oesophagus and a large defect in the membranous part of the mid-trachea were identified. The necrotic part of the oesophagus was resected, followed by a primary repair of the oesophagus by end-to-end anastomosis. The tracheal defect was reconstructed with a pedicled sternocleidomastoid muscle flap (figure 4a+b). Perioperative bronchoscopy showed full coverage of the tracheal defect (figure 4c). She was extubated six days later. She suffered from transient unilateral vocal cord paralysis. Twelve days after surgery, a barium swallow X-ray was performed because of persistent coughing and choking during feeding, which initially did not show evidence of re-fistulisation. However, when reperforming this exam again on day 21 postoperatively, a small tracheoesophageal fistula was demonstrated. This was treated conservatively: diet with only solid food and thickened drinks with the improvement of complaints. Repeated barium swallow X-ray 51 days after surgery showed spontaneous resolution of the fistula. She recovered well but still needs repeated oesophageal dilatations because of recurrent stenosis. The girl has no tracheal or respiratory sequelae (figure 4d).

Discussion

Management of foreign body ingestion, especially button batteries, is challenging because of the serious and fatal complications, e.g. oesophageal perforation, spondylodiscitis, tracheoesophageal fistula, and oesophageal-aortic perforation (1). Larger disk batteries (20-23mm) have a tendency to result in higher morbidity, especially when they are impacted in the oesophagus (2,3). Additionally, age under 4 years is described as a risk factor for fistulisation (4). Injury can occur rapidly, within 2 hours after ingestion, and is caused by three different mechanisms: alkaline-induced liquefactive necrosis, low-voltage burns due to electrical discharge, and pressure necrosis (2, 3). Symptoms can be variable, non-specific, and differ according to the impaction site: drooling, vomiting, dysphagia, coughing, stridor, shortness of breath, irritability, and fever (5). To confirm the diagnosis (double ring/halo sign) and location of the button battery, a two-view (anterior-posterior and lateral) X-ray of the entire neck, chest, and abdomen is important (5). Imaging by contrasted computerized tomography (or MRI after battery removal)

Figure 4: Images taken during Tracheoplasty and images of Bronchoscopy after procedure
a) Situation before tracheoplasty with a near transection of the mid-oesophagus and large defect in the membranous part of the mid-trachea
b) Image taken after tracheoplasty with sternocleidomastoid muscle flap in situ.
c) Bronchoscopy right after tracheoplasty showing a sternocleidomastoid muscle flap situated at the former fistula opening
d) Bronchoscopy 3 months after tracheoplasty showing good healing of the trachea with muscle flap. The distal 1/3rd of the mucosa is discretely elevated and rough on the pars membranacea with normal color of the mucosa.



should be performed to identify complications: mediastinitis, fistulas, and spondylodiscitis, especially in patients with severe symptoms (haemorrhage, hemodynamic problems, respiratory problems, severe back pain, etc) or in case of severe mucosal damage after removal (5).

Both the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) advocate for an imminent removal of a button battery from the oesophagus under general anaesthesia (5,6). During the transport and waiting time, honey (5-10mL) or sucralfate 500 mg can be administered, to mitigate the button battery-induced injury, if the ingestion was less than 12 hours ago, the child is stable without signs of perforation, able to swallow, and older than 1 year of age. This should however not delay the transport to the hospital nor the endoscopic procedure (5).

After endoscopic removal, the caustic burn and inflammation may continue to evolve, causing mucosal injury and eventually fistulisation, posing difficulties with airway management or vascular involvement (1,7). All patients should be admitted and monitored, and suspicion of complications should be evaluated using imaging techniques (5). The presence of respiratory symptoms may indicate tracheal complications and/or vocal cord problems (8). When mucosal injury is present after removal, a second endoscopic exam 2 to 4 days later may be considered (5). Before starting enteral feeding, a barium swallow X-ray can reveal a perforation, and treatment of a fistula is discussed later in this article (5). The extent and location of oesophageal injury determine the long-term follow-up with contrast oesophagograms and/or repeated endoscopies to detect the formation of strictures and to dilatate them (5). The follow-up is individualized for each patient.

Ingestion of button batteries can also cause laryngeal nerve paralysis, which affects the vocal cords, as present in our case. Although the precise mechanism is unclear, there are a few assumptions. Firstly, the button battery may directly cause pressure on the laryngeal nerve, or the nerve may be damaged as a consequence of infiltration of corrodent (9,10). Secondly, the laryngeal nerve may be impaired following the release of the trachea during surgery (9,10). Bilateral vocal cord paralysis is more common when the impaction was close to the hypopharynx (10). The time to recover from paralysis is not clear and needs further investigation (10).

In the second part of the discussion, we would like to pay attention to the treatment of one of the delayed complications; the tracheoesoph-

Table 1: Literature review of clinical course/management and complications of oesophageal perforations after button battery ingestion

Case	Age (year)	Time to presentation (hours)	Clinical course/management	Complications/Outcome	Ref.
1	1,4	588	Thoracotomy, ECMO, oesophagostomy, gastrostomy, mechanical ventilation, resuscitation, re-thoracotomy twice, aortic stent, jejunostomy, second gastrostomy, oesophageal drain	Full left lung atelectasis, aortic bleeding, arteria spinalis anterior syndrome with paralysis both legs	(2)
2	1,4	2,5	Gastroscopy and rigid bronchoscopy, conservative approach	-	(2)
3	1,0	72	Gastroscopy, conservative approach, swallowing problems for 2 months	-	(2)
4	4,5	5	Gastroscopy, conservative approach	-	(2)
5	1,1	?	Gastroscopy, bronchoscopy, nasogastric tube, IV antibiotics, tracheal and oesophageal reconstruction: partial median sternotomy with tracheal end-to-end re-anastomosis, primary repair of oesophageal perforation + local strap muscle interposition	Intermittent croup 3,5y after injury, tracheal granulation tissue without stridor	(3)
6	2	2	Gastroscopy, conservative approach, nasogastric tube 25 days		(6)
7	1,3	24	Resuscitation (3x cardiac arrest), open laparotomy	Death due to hypovolemic shock : ulceration of midoesophagus and haemorrhage from large arterial source	(6)
8	6	2,5	Gastroscopy, conservative approach, parental feeding, IV antibiotics	Oesophageal fluid collection	(6)
9	0,9	27	Gastroscopy, conservative approach, nasojejunal tube, repeat oesophagram, gastrostomy	Vocal cord paralysis with normal trachea	(6)
10	1,7	10,5	Gastroscopy, bronchoscopy, nasogastric tube, mechanical ventilation, repeat endoscopy, IV antibiotics, surgical correction of proximal oesophagus to an cervical oesophagostomy (spit fistula) and temporary closure of distal oesophagus, gastrostomy	Vocal cord paralysis, mediastinitis, stricture at the cervical oesophagostomy	(6)
11	3	36	Mechanical ventilation, nasogastric tube, surgical repair by combined right cervical incision and complete median sternotomy with segmental resection of trachea and oesophagus followed by primary anastomosis and right sternohyoid muscle interposition.	Oesophageal fluid collection	(7)
12	2	72	Gastroscopy, bronchoscopy, mechanical ventilation, nasogastric tube, primary tracheoesophageal repair and inferiorly based sternocleidomastoid muscle flap between trachea and oesophagus	Aspiration pneumonitis	(9)

(Abbreviations: ECMO = extracorporeal membrane oxygenation, IV = intravenous, ref. = reference)

ageal fistula. There is no consensus on how to treat tracheoesophageal fistulas caused by a button battery. In literature, one can find a conservative approach as well as different surgical techniques using autologous cartilage, pericardial patch, or muscle flap. This is based on retrospective reports. A recent systematic review by Poupore et al. which included 79 studies with 105 patients suggested a period of observation of 8 weeks if clinical status permits and in small fistula (smaller than 10mm) and this because of potential morbidity/mortality of surgery (recurrency, oesophageal stricture, recurrent laryngeal nerve damage, tracheomalacia) (4). Conservative approach with total rest of the oesophagus by nasogastric or jejunostomy tube feeding can result in spontaneous healing in a small tracheoesophageal fistula, but the time to closure is difficult to predict (7,10). These children may be at risk for mediastinitis, aspiration pneumonia, or respiratory problems that needs placement of a tracheostomy, and will be deprived of oral feeding during a prolonged period of time which also causes significant morbidity (7,11). Surgical repair should be considered for larger fistulas and important respiratory problems, but not immediately after removal because of the ongoing inflammation (12,13). A tracheal defect of up to 2 tracheal rings may allow primary anastomosis (12). In the past, multistage surgical interventions were considered because of the affected surrounding tissue (13). The interposition of tissue between the two suture lines is important to prevent re-fistulisation (11). For this purpose, different tissues have been used for instance sternal periosteum or vascularized tissue such as pericardium, pleura, or veins (14). Ripudaman et al described an anterior cervical approach to access the fistula. They performed an interposition of the sternocleidomastoid muscle to avoid recurrent fistulisation (13). In 1998 Holland et al also reported the use of a pedicled sternocleidomastoid muscle flap in a one-stage procedure in the management of recurrent fistula in a girl with oesophageal atresia (14). In this case, we also used the same approach. There was a small re-fistulisation after surgery, which was managed conservatively with success. More experience is needed to confirm the best technique to avoid re-fistulisation. This may however be influenced by the size and location of the fistula as well as the degree of inflammation and local tissue damage.

A poster is created by ESPGHAN to alert parents about the dangers of button batteries (https://espghan.info/files/EM012199_ESPGHAN_Button_Battery_Parental_Advice_Guide_211117_V0-6_SMB.pdf).

Conclusion

We present a case of a large tracheoesophageal fistula that was successfully repaired in a single-stage procedure with a sternocleidomastoid muscle flap interposition, after button battery ingestion. The likelihood of re-fistulisation can be reduced by using this alternative method. Because tracheoesophageal fistulas in children are life-threatening and uncommon, a multidisciplinary team approach in a specialized centre is required. This case highlights the challenges in terms of prompt diagnosis, surgery, airway management, the high risk of complications, and the follow-up of patients. Raising awareness about the risks of button battery ingestion and the importance of early intervention and also follow-up after removal is of utmost importance to prevent serious morbidity or death.

Conflict of interest statement

The authors of this case report declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this case report.

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The role of fetal brain magnetic resonance imaging in current fetal medicine

PhD thesis presented on June 2nd, 2022 at KU Leuven, Leuven, Belgium

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In this thesis the role of advanced fetal imaging in current fetal medicine was investigated. This discussion will follow the different pathologies that have come across in this manuscript: spina bifida aperta, congenital diaphragmatic hernia, cytomegalovirus infection and complicated monochorionic diamniotic pregnancies.

We investigated the use fetal magnetic resonance imaging (MRI) in patients being assessed for fetal surgery for spina bifida by, first, evaluating the reliability of MR based posterior fossa measurements around the time of spina bifida repair, second, by describing the prevalence of supratentorial anomalies and, third, by using new post-processing techniques to document brain development in the third trimester, and eventually use these to document brain changes following fetal repair. Eventually the latter techniques were used to develop a spatiotemporal atlas of the developing fetal brain in fetuses with spinal dysraphism.

First, we demonstrated that the majority of measurements that are used on postnatal MR images cannot be reliably made around the time of fetal surgery (1). These measurements include brain stem measurements (mamillopontine distance, pontine thickness, pontine length, foramen magnum diameter, level of brain stem kinking, medullar length), and foramen magnum diameter, tentorial length and cisterna magna width. Conversely, assessment of the posterior fossa dimensions and the level of cerebellar herniation were shown reproducible. The latter has been used as a secondary outcome measure in the landmark study on fetal surgery for spina bifida, i.e. the Management of Myelomeningocele Study (MOMS) study, i.e. before and after fetal surgery.

In the same study we demonstrated that already early (within 7 days) in the majority of fetuses, there is re-appearance of fluid cisterns in the posterior fossa in the vast majority of cases. Earlier studies also reported such changes between 3 and 6 weeks after the surgery in all fetuses where this was measured. The re-accumulation of intracranial cerebrospinal fluid can be an interesting proxy of the efficacy of spinal closure.

Second we described the nature and occurrence of supratentorial abnormalities in fetuses with spina bifida. Proper assessment is important for counselling women about fetal surgery and may also be relevant to parents not choosing for fetal surgery. Brain assessment is currently being used to predict the need for postnatal shunting, based on the degree of ventriculomegaly at the time of surgery. When using MRI in fetuses meeting the criteria for fetal surgery on ultrasound findings, half of them were found to have corpus callosum abnormalities and/or ventricular wall (2). This number is in line with findings in a recent systematic review by our group. Whether MRI is essential for this, hence adds information to US, has to our knowledge not been proven.

Third, we used a new 3D SVR algorithm and an automated segmentation method to document perioperative changes in fetal brain development in fetuses with spina bifida as compared to fetuses without the conditions (3, 4). Documenting in utero changes following surgery is important, as increasingly fetal surgery is being practiced, and it is expected that more of these operations will be done when minimally invasive methods will be widely implemented.

In our cohort we did not find any difference in cerebellar volume with that of controls, but demonstrated that the cerebellar shape changed importantly after fetal surgery, eventually becoming more comparable to that of controls (5). In a prior study, we have found that posterior fossa dimensions in spina bifida prior to 26 weeks, were very variable (1).

We also evaluated the white matter in our fetal surgery population, and, again, no differences in volume or shape were found compared to normal controls. These fetuses however had a variable degree of ventriculomegaly prior to fetal surgery; after the operation the ventricular width continued to increase, in concordance with the observations of others (1, 5, 6). To us, it remains unclear how the white matter volume evolves during the remainder of the pregnancy and in postnatal life in this subset of patients.

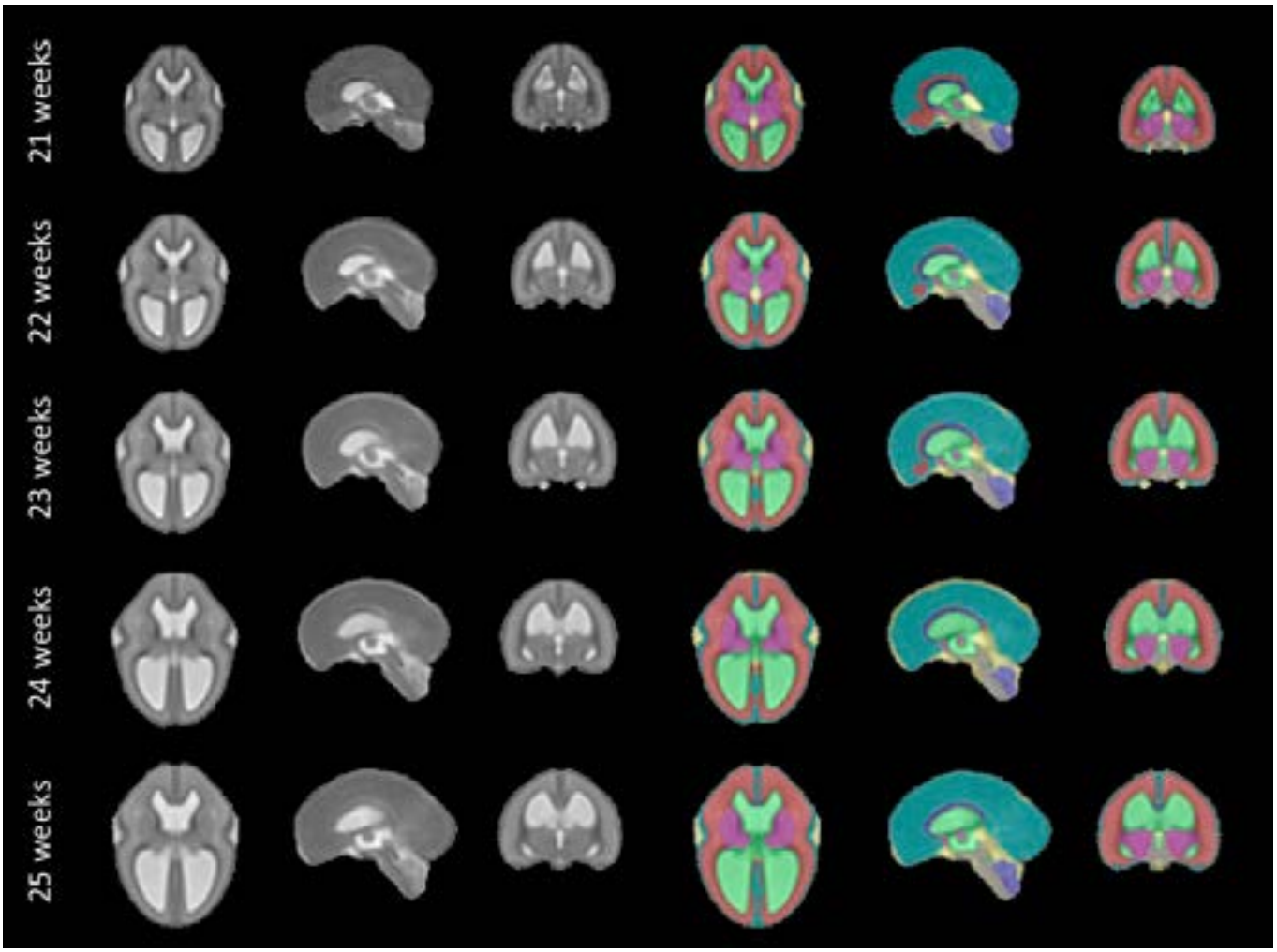
In the same study, we used spectral matching to document cortical folding. We demonstrated an increased shape index prior to fetal surgery, and a decreased shape index 7 days after fetal surgery, both compared to the index in normal controls. This is, to our knowledge, the first study specifically documenting cortical development in fetuses before and after fetal surgery (5).

Fourth, we applied the new 3D SVR algorithm to create the first spatio-temporal atlas of the fetal brain in spina bifida aperta (3, 7) (Figure 1). The application of our atlas for automated segmentation of fetal brain MRIs with open spinal dysraphism did result in a more accurate segmentation compared to those based on other atlases that used normal fetal brains.

Congenital diaphragmatic hernia (CDH) is another congenital malformation for which fetal surgery has been shown to be beneficial in given circumstances. We reported on a significant delay in brain development in fetuses with isolated CDH at 28 weeks of gestation, and to a lesser extent at 33 weeks of gestation. This is in line with earlier observations by ultrasound and the first MRI-data demonstrating an altered brain development in utero in CDH fetuses. Others have not found such differences and those looking only at postnatal data, hypothesized that postnatal events (NICU, ECMO, …) may eventually cause altered brain development.

In fetuses infected with cytomegalovirus (CMV) in the first trimester there is an increased risk of sensorineural hearing loss and impaired cognitive development. Neurosonography is the most important modality in the follow-up of fetuses with confirmed first trimester CMV-infection (8). We found an added value of fetal MRI in the third trimester in fetuses with proven first trimester CMV infection. We evaluated the routine application of diffusion weighted imaging (DWI) in fetuses with proven first trimester congenital cytomegalovirus infection (cCMV). Despite a failure rate of >10%, DWI should be implemented in routine fetal MRI for CMV. In addition, we found a significant higher apparent diffusion coefficient (ADC) value in the brain of cCMV infected fetuses compared to controls and our findings suggested a correlation with the severity of abnormalities found on anatomical sequences (9). The higher ADC is in line with a postnatal study comparing cCMV with periventricular leukomalacia in children. Moreover, they found similar findings on magnetic resonance spectroscopy, suggesting that damage and loss of oligodendrocytes are crucial factors in white matter abnormalities in cCMV infected children. This further encourages the development of a new imaging based scoring system

Figure 1: Overview of the pre-operative fetal brain in spina bifida aperta between 21 and 25 weeks of gestation with the segmentation overview. (yellow: extra-axial fluid, turquoise: cortex, red: white matter, green: intra-axial fluid, dark blue: corpus callosum, blue: cerebellum; purple: deep grey matter, grey: brain stem)



including DWI to stratify the outcome risk of fetuses after first trimester CMV infection.

In twin pregnancies, there is an increased risk of abnormal postnatal neurological development in fetuses surviving twin-twin transfusion syndrome (TTTS). Others showed a benefit of fetal brain MRI for the detection brain abnormalities in TTTS. The ISUOG practice guidelines on the role of ultrasound in twin pregnancy do not encourage fetal brain MRI at 30 weeks in survivors after laser ablation in TTTS. Nonetheless, we offer our patients a routine fetal brain MRI in the third trimester. In our retrospective study, compared to ultrasound, we found MRI is able to detect an additional brain lesion in 6% (4/69) (10). Although the number of abnormalities in our study, as in other studies, was rather small, their consequences however were very important. Of 4 such pregnancies the only one that was continued showed cerebral palsy of the affected twin postnatally. The abnormalities only detected on MRI were disorders of cortical development, known to be often missed on US and detected more easily on MRI. Our results suggest routine third trimester MRI in survivors of TTTS after laser ablation seems justified. We do feel a large prospective trial, likely multicentric, will be able to provide a complete risk assessment of these fetuses and their detected brain abnormalities.

Although we have demonstrated the added value of fetal brain MRI in several fetal conditions, it remains a challenging technique that needs to be performed upon proven indications and in centers with the necessary expertise in fetal imaging. Not only will this allow to maximize the exposure in these specialized centers, this will also permit to interpret the findings on fetal imaging (neurosonography and fetal MRI) all together in a multidisciplinary setting (including fetal specialist, radiologist, pediatric neurologist, geneticist, pathologist) as recommended.

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In collaboration with Cebam, Cochrane Belgium
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Splinting for the non-operative management of dysplasia of the hip in children under six months

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Question

How effective is splinting and which splinting strategies are best for the non-operative management of developmental dysplasia of the hip in children under six months of age?

Context

Developmental dysplasia of the hip (DDH) covers a spectrum of hip abnormalities in babies ranging from completely dislocated hips to immature hips which show a delayed physiological development but are stable within the socket throughout examination. DDH is associated with premature osteoarthritis and is the cause of 10% of all hip replacements. In western countries, DDH is a common condition which occurs in about 10 per 1000 live births, with one per 1000 being completely dislocated.

Treatment of DDH depends on its severity and the baby's age. In babies under six months of age, abduction splints are often used to guide the hips into the socket. Dynamic splints, such as the Pavlik harness, still give the legs some freedom to move whereas static splints, such as the fixed abduction brace, fix the legs in position. Occasionally, double diapers which gently push the legs apart are used to act as a splint. However, there is no consensus on which severity of DDH mandates treatment and on when to start splinting, which splints to use, the duration of splinting, weaning versus cessation and the long-term follow-up. Hence, treatment varies by country, hospital and even between practitioners in the same hospital. Moreover, splinting can cause complications such as avascular necrosis and parents remain concerned about its effects on bonding between parents and baby and on gross motor skill development because of the decreased tummy time.

This Cochrane review aimed to assess how successful splinting is and which strategy would be best.

Criteria for study selection

The review included studies comparing dynamic splinting, static splinting or double diapers with no splinting or delayed splinting (usually by 5- 6 weeks). The participating babies were under six months of age with DDH of any severity. The main outcomes were acetabular index, need for operative intervention after splinting and complications including avascular necrosis and femoral nerve palsy. The acetabular index, the angle between the Hilgenreiner line and the acetabular roof as determined by radiographs, is a proxy for hip health as it is a known predictor of osteoarthritis long-term. Usually, an acetabular index angle below 30 degrees is considered normal in babies aged over six months, and below 25 degrees is considered normal at 24 months.

Summary of the results

The authors identified six randomized controlled trials (RCTs) which included 576 babies and 16 non-randomized studies which included 8237 babies. The review authors chose to only draw conclusions supported by randomized study data due the bias associated with the included non-randomized studies.

Immediate dynamic splinting versus delayed splinting or no splinting

Four RCTs and nine non-RCTs compared immediate dynamic splinting to delayed dynamic splinting or no splinting. Two RCTs looked at stable hips, one at unstable (dislocatable) hips and one considered both conditions.

Two randomized studies (256 babies) found there may be no evidence of an effect of splinting stable hips at first diagnosis versus active surveillance on acetabular index at one year, but the certainty of the evidence is very low. Similarly, two RCTs (181 babies) reported there may be no evidence of a difference in acetabular index at two years. There were no studies who reported the effect on acetabular index at five years. Four RCTs reported on the need for surgery after splinting (434 babies, very low-certainty evidence). In three of these studies, no surgical interventions occurred in either treatment group and in the fourth study two babies in the immediate dynamic splinting group were treated surgically. Three RCTs looked at complications and reported no cases of avascular necrosis or femoral nerve palsy (390 babies, very low-certainty evidence).

Dynamic splinting versus static splinting

One RCT and five non-RCTs compared dynamic with static splinting. The RCT reported no cases of avascular necrosis with either treatment (118 hips, very low-certainty evidence), but did not report on any other outcomes of interest.

Other comparisons

One study compared double nappies with delayed or no splinting, but did not report any outcomes of interest. No randomized studies compared immediate static splinting with delayed static splinting or no splinting, double diapers with single diapers or immediate removal of the splint after treatment with weaning.

Results from the non-randomized studies aligned with the findings from the randomized studies and did not provide additional clarity.

Conclusion

Although splinting is a very common treatment for the non-operative management of DDH, there is a clear lack of evidence that supports its effectiveness.

For babies with stable hips, splinting may make little or no difference at any timepoint compared to delayed or no splinting. For babies with unstable hips, delaying splinting up to 6 weeks may have little or no effect on the acetabular index or the need for surgery at one year. Current evidence for all primary outcomes is of very low certainty meaning that we are very uncertain of the effects of splinting.

Implications for practice

Whilst consensus guidelines may assist with decreasing the unnecessary variation in treatment strategies at the moment, it is clear that more well-conducted randomized studies and a robust evidence base are needed to inform the evidence-based treatment of DDH.

REFERENCE:

Dwan K, Kirkham J, Paton RW, Morley E, Newton AW, Perry DC. Splinting for the non-operative management of developmental dysplasia of the hip (DDH) in children under six months of age.

Cochrane Database of Systematic Reviews 2022, Issue 10. Art. No.: CD012717. DOI: 10.1002/14651858.CD012717.pub2.

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SPA® REINE is een uiterst zuiver natuurlijk mineraalwater dat door iedereen gedronken kan worden, op elk moment van de dag en zonder enige beperking. Het geheim van de legendarische zuiverheid? De uiterst strenge bescherming van de omgeving en de jarenlange reis die het water maakt door de unieke ondergrond van de Venen.

Geschikt voor de bereiding van babyvoeding.

Naam van het geneesmiddel: mama natura gastro tabletten. Kwalitatieve en kwantitatieve samenstelling: per tablet (100 mg): 20 mg Croton tiglium D6, 20 mg Okoubaka aubrevillei D4, 20 mg Veratrum album D12. Hulpstof met bekend effect: lactose. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1. Farmaceutische vorm: tablet. Klinische gegevens: therapeutische indicaties: mama natura gastro is een homeopathisch geneesmiddel met bestanddelen die traditioneel gebruikt worden ter verlichting van misselijkheid en een verstoorde spijsvertering. Dosering en wijze van toediening: kinderen van 0 tot 1 jaar: bij de eerste verschijnselen elk uur 1 tablet, maximaal 6 tabletten per dag. Daarna, 4 maal daags 1 tablet. Kinderen van 1 tot 6 jaar: bij de eerste verschijnselen elk uur 2 tabletten, maximaal 12 tabletten per dag. Daarna, 4 maal daags 2 tabletten. Oraal gebruik. Druk de tablet fijn tussen twee schone lepeltjes of los de tablet op in een lepel water. Bij aanhoudende, onverklaarbare of nieuw optredende klachten is het aan te raden een arts te raadplegen. Contra-indicaties: overgevoeligheid voor de werkzame stoffen of voor een van de in rubriek 6.1 vermelde hulpstoffen. Bijzondere waarschuwingen en voorzorgen bij gebruik: patiënten met zeldzame erfelijke aandoeningen als galactose-intolerantie, algehele lactasedeficiëntie of glucose-galactose malabsorptie, dienen dit geneesmiddel niet te gebruiken. Interacties met andere geneesmiddelen en andere vormen van interactie: er zijn geen interacties met andere geneesmiddelen bekend. Vruchtbaarheid, zwangerschap en borstvoeding: niet van toepassing. Beïnvloeding van de rijvaardigheid en het vermogen om machines te bedienen: niet van toepassing. Bijwerkingen: er zijn van mama natura gastro geen bijwerkingen bekend. 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: Federaal agentschap voor geneesmiddelen en gezondheidsproducten, Afdeling Vigilantie, Postbus 97, 1000 Brussel Madou, Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg.be. Overdosering: volgens de homeopathie is het effect gerelateerd aan de verdunningsgraad en niet zozeer aan de dosering. Wanneer men een dubbele dosis zou gebruiken, zal het effect daardoor niet sterker zijn. Er is tot nu toe geen geval van overdosering gerapporteerd. Farmacologische eigenschappen: farmacodynamische eigenschappen: het gebruik van dit geneesmiddel berust op het traditioneel gebruik van zijn bestanddelen. Farmacokinetische eigenschappen: niet van toepassing. Gegevens uit het preklinisch veiligheidsonderzoek: er zijn geen additionele niet-klinische gegevens van belang voor de voorschrijver, buiten deze die reeds elders in deze SKP vermeld zijn. Farmaceutische gegevens: lijst van hulpstoffen: microkristallijne cellulose (E460), lactosemonohydraat, magnesiumstearaat (E572), talk (E553b). Gevallen van onverenigbaarheid: er zijn geen onverenigbaarheden bekend. Houdbaarheid: dit homeopathisch geneesmiddel is in een goed gesloten verpakking 5 jaar houdbaar. Na opening is mama natura gastro 12 maanden houdbaar. Speciale voorzorgsmaatregelen bij bewaren: voor dit geneesmiddel zijn er geen speciale bewaarcondities. Aard en inhoud van de verpakking: de primaire verpakking bestaat uit een bruinglazen tabletflesje van 120 stuks, voorzien van een plastieken dop met aluminium inlage. Speciale voorzorgsmaatregelen voor het verwijderen: geen bijzondere vereisten. Houder van de vergunning voor het in de handel brengen: Schwabe Pharma Belgium, Prins Boudewijnlaan 7D bus 0301, B-2550 Kontich, telefoonnummer: +32 (0)3 4508160; e-mail: info@schwabe.be. Nummer van de vergunning voor het in de handel brengen: HO-BE511484. Datum van eerste verlening van de vergunning/verlenging van de vergunning: Datum van eerste verlening van de vergunning: 09/06/2017. Datum van verlenging van de vergunning: 11/02/2022. Datum van herziening van de tekst: Datum van goedkeuring: 02/2022.

VERPAKKING	PP (incl. BTW)
120 tabletjes	€ 10,95

mama natura® gastro

Misselijkheid & verstoorde spijsvertering [1]

Brede werking: spijsverteringsorganen

Veratrum album D12 [2]
Diarree, verstoorde spijsvertering, krampen

Okoubaka aubrevillei D4 [3]
Krachtige ontgifter bij voedselvergiftiging

Croton tiglium D6 [4]
Diarree, brandende pijn

+0

- Vanaf de geboorte (0-6 j.)
- Geen suiker
- Geen toegevoegde kleur- of smaakstoffen

Adviseer in alle veiligheid het volledige gamma van mama natura® vanaf de geboorte!

www.mamanatura.be

Referenties: 1. SPC mama natura gastro®; 2. Boericke, W. Boericke's New Manual of Homeopathic Materia Medica. 2000 (3e druk): 585-586. B.Jain Publishers (P) LTD. ; 3. Phylak Sachsen (2007). Okoubaka Aubrevillei. Lichamelijk aspect. Seminar Spagyriek Phylak. http://www.spagyrics.nl/wp-content/uploads/53.-Okoubaka-aubrevillei-juni-2007.pdf ; 4. Boericke, W. Boericke's New Manual of Homeopathic Materia Medica. 2000 (3e druk): 213-214. B.Jain Publishers (P) LTD.

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