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het water bij uitstek voor wie borstvoeding geeft

Mama's die borstvoeding geven, moeten meer water drinken. Daarbij is het belangrijk dat ze een water kiezen dat past bij hun behoeften en die van hun baby. Een van nature zuiver, mineraalarm water dat een constante samenstelling heeft en strikt gecontroleerd wordt, zoals Spa® Reine, verdient dan aanbeveling.

HET BELANG VAN WATER VOOR DE BORSTVOEDENDE MAMA

*Borstvoeding geven lokt een dorstprikkel uit die de dagelijkse vochtinname met **12 tot 16%** doet toenemen. Borstvoedende mama's moeten de lactatie compenseren door meer te drinken. Aangezien moedermelk voor 85% uit water bestaat, zal het type water dat de moeder drinkt, een directe weerslag hebben op de kwaliteit van de hydratatie van de baby. Omdat de nieren nog niet volledig ontwikkeld zijn in de eerste twee levensjaren, moet elke overmatige inname (van minerale zouten, nitraat, natrium enz.) in deze periode voorkomen worden. De keuze van het water is dus van cruciaal belang.*

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UITDROGING TIJDENS DE LACTATIE VOORKOMEN

***54%** van de moeders die borstvoeding geven, haalt de aanbevolen dagelijkse waterinname niet.(1) Daarom is het belangrijk ze goed te informeren en zo nodig metingen te verrichten. Een mogelijkheid is de urine te controleren aan de hand van een kleurenschaal. Dat is iets wat de vrouwen thuis zelf kunnen doen. Aan de hand van de kleur van de urine kunnen ze nagaan of hun vochtinname volstaat dan wel of het nodig is meer te drinken. De resultaten zijn overtuigend: **83%** van de vrouwen die een urinekleurenschaal kregen, gebruikte die om hun waterinname te controleren.(2)*

***(1)** Bardosono et al. Pregnant & Breastfeeding Women: Drinking for two? Ann Nutr Metab 2017; 70 suppl 1) : 13-7. **(2)** Rigaud M et al Assessing a tool for self-monitoring hydratation using urine color in pregnant and breastfeeding women: a cross-sectionnal, online survey. Ann Nutr Metab 2017; 70 (suppl 1) : 23-9.*

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Editorial

The power of love

On May 1, 2023, a plane carrying seven passengers disappeared off radar in southern Colombia. On board were 4 children with their mother, a relative and the pilot. Two weeks later, on May 16, a search team found the plane in a thick patch of the Amazon rainforest and recovered the bodies of the three adults. This suggested that the children had escaped the wreckage and wandered into the jungle to find help. More than 100 soldiers accompanied by sniffer dogs and dozens of volunteers from Indigenous tribes launched the « Operation Esperance », a massive search in this large area of wild vegetation. Hopes of finding the children alive were strengthened by the discovery, a few days later, of a makeshift shelter with a few personal effects, a feeding bottle and some partly eaten fruits. Rescuers used helicopters to drop boxes of food into the jungle, and to broadcast a message recorded by the children grandmother telling them to stay in one place and and to trust the soldiers looking for them. On June 9, after 40 days by themselves in the jungle, Lesly (13 years), Soleiny (9 years), Tien Noriel (5 years) and Cristin (1 year) were found 5 km from the wreckage of the plane. They were weak and partially dehydrated. Apart from a few insect bites, they had not suffered any attack or injury. They were rapidly flown back to Bogotá, where they were reunited with their loved ones and could benefit from a progressive malnutrition program.

This story caught the attention of our editorial board. It bears witness to children's capacity for resistance, resilience and adaptability. As paediatricians, we regularly meet sick children who, at their level, demonstrate heroic courage and determination. In the face of what some are already describing as a miracle, we can wonder how these children from 1 to 13 year-old were able to survive in such a hostile environment. Friends and family insist that the children, members of an Indigenous tribe, had a deep knowledge and a particular connection to the jungle and its natural resources. After eating the flour and food carried on the plane, the youngsters fed on the fruits and roots of edible plants they could find in the jungle. They stayed close to a small stream to keep access to drinking water. Lesly, the eldest sister, showed leadership and an impressive sense of responsibility. She was an enormous moral support to her siblings as the two youngest children celebrated their 1st and 5th birthdays in the jungle. The rescuers also underline the importance of the will to live that they felt with the children. This feeling sustained them throughout the long weeks of the search. Antonio Sera, a Brazilian who also survived 36 days in the Amazon rainforest after his plane crashed in 2021, confirms that he has kept his confidence in life through the love of others, by knowing that he was expected and supported by his family and relatives. This was well understood by the children's mother. Before she died, she told them: « Y*ou guys are going to see the kind of man your dad is, and he is going to show you the same kind of great love that I have shown you…* ». These testimonials certainly have a special resonance for us, Belgian citizens, who witnessed the unfailing mobilization of a family and a community to support and help one of their own to get back in Belgium. The images of Oliver Vandecasteele and his family at their reunion at the Melsbroek airport on May 26, 2023 were such illustration of the power of love !

To invite you to enjoy the summer in a calm and peaceful environment, we are delighted to present the summer issue of the Begian Journal of Paediatrics. We publish a research article on medication discontinuation in children with epilepsy by E. Corthout and colleagues and the results of a survey made by L. Desmet and his team on first aid knowledge in Flemish youth movements. We also develop two review articles on traumatic pancreatic injury by P. Van der Speeten and colleagues and on the management of Helicobacter pylori infection in children by L. Toch and colleagues. Several informative clinical history are reported: recurrent oral aphtosis as presentation of Crohn disease, Aicardi Syndrome, Luc's abscess complicating otitis media, Cushing disease after topical application of corticosteroids, Behcet disease, side effect of risperdone, pneumoparotid and early recognition and treatment of atypical hemolytic uremic syndrome.

The made in Belgium section presents the thesis of R. Mbusa Kambale from UCLouvain about feeding practices and probiotic effects on nutritional recovery and morbidity in severely malnourished infants in Democratic Republic of Congo.

We hope this new issue and these happy-ending stories will inspire you this summer. As it was the case for us, they may help you to think on what is necessary for your life and what contributes to your fulfillment.

Christophe Chantrain and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

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Success rate of anti-seizure medication discontinuation in children with epilepsy

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Keywords

Epilepsy, pediatrics, withdrawal, anti-epileptic drugs, discontinuation

Abstract

Objectives. Epilepsy is a common condition in childhood. Anti-seizure medication (ASM) discontinuation can be considered after two years seizure-freedom. Predictive factors for the success of this withdrawal are needed to simplify the decision-making.

Methods. A literature search was performed to examine the most frequently used predictive variables for risk of recurrence. These 22 variables were then used in a retrospective data search and analysis of 3626 patient files. We focused on those patients seen in 2021 in the epilepsy clinic of the University Hospital of Leuven.

Results. 94 patients between 6 months and 18 years on monotherapy of ASM were included. 21% relapsed after a median of 4 months. Later age at onset of epilepsy, later age at discontinuation and male gender showed a significant effect on the risk of recurrence.

Interpretation. Relapse rate was similar as in existing literature with recurrence occurring more frequently in the first 6 months after discontinuation. Long-lasting epilepsies relapse more frequently. Epilepsy severity, cause and onset are other determinants of recurrence in literature. They were not statistically significant in this study. Further larger prospective studies are needed.

Introduction

Epilepsy is a common chronic neurological condition in childhood (1-4). In Belgium up to 0.4% of the children under the age of 18 years are affected (5). During life this prevalence increases up to 1% (2). Anti-seizure medication (ASM) is the main treatment option to control seizures. Around 70% of the patients with epilepsy achieve seizure freedom with ASM. (2-4,6-11) Many childhood epilepsy syndromes are self-limiting. Considering this, ASM discontinuation can be considered after a seizure-free period of 2 years to minimize the possible adverse effects of long term medication use (2,6,7,9,10,12,13). The complexity of the balance between benefits and risks of this discontinuation should always be carefully considered (1,2,6,7,11,14-18). Neurologists need to take account of multiple factors such as: epilepsy etiology, epilepsy syndrome, quality of life, (long term) negative side effects of the medication, the psychosocial and the economic/financial burden, the risk of recurrence, but also individual preferences (2-4,9-11,15-17). After a careful assessment before ASM discontinuation, 60-90% of the children who stop their medication remit with the highest risk of recurrence in the first 6 to 12 months after withdrawal (1,6,10,13,15,17). Several studies already attempted to determine the best timing and duration of withdrawal. As a general rule, ASM discontinuation is only begun after two-year seizure freedom, although some propose to consider earlier withdrawal in benign childhood epileptic syndromes (1,6,10,13,15,17). Some of them searched for predictive factors for success of withdrawal, such as epilepsy syndrome, cause of epilepsy, seizure type, the age at onset of epilepsy and the age at discontinuation of therapy, the gender of the patient, developmental delay, neurological deficit, history of status epilepticus or febrile seizures, length of the seizure-free period after treatment initiation,...(1,2,6,7,11,12,15,16,18-22). Still, unclarity and discussion on this topic remains. This single center study retrospectively examines the success rate of ASM discontinuation and the predictive factors in children with epilepsy who consulted a tertiary hospital in Belgium during 2021.

Materials and methods

Literature search

Data sources and searches

We performed a literature search in the Pubmed database from 2005 till 2020, using combinations of following Mesh Terms: children, anti-epileptic drugs, stop, withdrawal. Titles and abstracts of 481 articles were examined. We only included articles written in English, French or Dutch that investigated a pediatric non-oncological population. We excluded studies without accessible abstract or article, studies not containing withdrawal as one of the main topics and studies only examining withdrawal of ASM after epilepsy surgery. The reference lists of these articles were scanned for missing studies. 21 articles were withheld, of which 20 contained several predictive factors on risk of recurrence.

Outcome collection

We extracted the most frequently used predictive variables for risk of recurrence from the identified articles.

Data collection and analysis

In this single center study, we investigated the success rate of ASM discontinuation in children with epilepsy between the age of 6 months and 18 years, seen in the epilepsy unit in 2021. The medical records were gathered in the University Hospital of Leuven, a tertiary hospital in Belgium. As a secondary outcome, we examined which variables could be predictive of this success.

Medical records of 3626 patients were retrospectively reviewed and 94 patients, seen in the epilepsy clinic in 2021, could be included using the in- and exclusion criteria mentioned in table 1.

At 6 months post discontinuation and at the end of the follow up (last date July 1 2022), success of discontinuation was assessed.

The 24 predictive variables determined from the literature search were extracted from the medical records. Seizures were classified according to the classification of the international league against epilepsy (ILAE).

The patients were asked only to reconsult if relapsed. We assumed a good adherence to this question and marked the patients as in remission when they did not reconsult. Consultations in other hospitals were examined via the electronical medical record used by this university hospital and several other clinics in Flandres and via the eHealth Hub.

This study received the approval of the Ethische Commissie Onderzoek UZ/KU Leuven.

Table 1: In- and exclusion criteria for data collection.

Inclusion criteria	Exclusion criteria
Outpatient clinic/EEG lab in 2021	Undergone epilepsy surgery
Age between 6 months and 18 years • Older than 6 months at diagnosis • Younger than 18 years at ASM discontinuation	Oncological patients
Seizure free and on monotherapy at time of discontinuation	Follow-up less than 6 months

Statistical analysis

Our retrospective study will consist of a content analysis: we investigate the prevalence of recurrence and analyze the above mentioned predictive variables per patient. We examine how each predictive variable influences the risk of recurrence. The primary outcome is the risk of recurrence, which is a dichotomous variable. The secondary outcomes, the predictive factors, are partly categorical variables and partly continuous variables. In general the categorical variables are dichotomous (e.g. boy/girl) but we also examine some nominal variables like the epilepsy type and the epilepsy syndrome. We compared the data of those who relapse with the data of all the patients included in the study. When categorical variables Chi-Square statistics were used and when continuous variables a Mann Whitney U test.

Results

Literature search

We found 20 articles mentioning predictive factors for discontinuation of anti-seizure medication (ASM). We extracted 23 variables from these articles and counted the number of studies in which they were mentioned. The most elaborated paper on variables was the study of Olmez et al. with 20 variables listed. Tang and Zheng only used two variables on EEG. "Electroencephalography (EEG) pattern at the time of discontinuation" was the most mentioned predictive factor (16 articles), "History of status epilepticus" the least mentioned (2 articles). A variable was on average brought up in 8 articles. Due to low feasibility to extract from medical records, we suppressed "Seizure frequency before entering remission" from our variable list. The 22 variables listed in table 2 were used in further analysis, aware of the risk of overspecification bias caused by the large number of variables.

Data search in medical records

We examined a total of 3626 patient contacts and matching patient files. For the year 2021, 94 patients met the inclusion criteria, 58 boys and 36 girls. Mean age at ASM discontinuation was 9 years (min 1 year, max 17 years). The calculated median time of follow-up was 15 months (min 6 months, max 15 years).

Success rate of ASM discontinuation. Twenty of the 94 included patients re-experienced an epileptic seizure during or after withdrawal of anti-seizure medication. 79% remitted. The median time to relapse was 4 months. At a follow-up of 6 months 12 patients had relapsed. Thus, 60% (12/20) relapsed in the first 6 months after ASM discontinuation. At one year of follow-up this number increased up to 75% (15/20) (see figure 1).

In these 94 patients we examined which of the 22 predictive factors from our literature study were applicable in our small study population. The following factors showed significant differences between those who relapsed and those who did not: age at onset of epilepsy, age at discontinuation of ASM and gender.

Significant difference in age at onset of epilepsy. The median age at onset of the whole group was 4.6 years. In the analysis at last follow-up, the median epilepsy onset age of those with relapse is significantly higher (6.7 years old (p=0,04)). The median age of those with relapse was even higher in the analysis at follow-up of 6 months (7.3years (p=0,01)). They who were diagnosed between the age of 6 and 10 years had the highest percentages of recurrence (see figure 2).

Significant difference in patient's age at discontinuation of ASM. There was a nearly equal distribution of patient's age at discontinuation (see figure 3). Patients who re-experienced an epileptic seizure, had a higher median age at discontinuation of ASM than the control group. In the control group the median age was 9 years. At last follow-up the median age of those with recurrence was 12 years (p=0,04), after fixed follow-up of 6 months it was 13 years (p=0,03). Patients who stopped their medication when older than 9 years had the highest risk of recurrence (see figure 4).

Significant difference in gender. 36 of the included patients were girls (38%). Only 4 of these girls relapsed (11%), one before 6 months after discontinuation of ASM. 16 of the 58 boys had a recurrence of epilepsy (28%), 11 at a follow-up of 6 months. This difference between relapse in genders was significant, but only after a follow-up of six months (at last follow-up: p=0,06; 6 months follow-up: p=0,02).

No significant difference was found for the following predictive variables, although for some variables a trend was seen: epileptic syndrome, seizure type, developmental delay, history of status epilepticus, history of febrile seizures, duration of active epilepsy. No trend was seen in the following variables: etiology of epilepsy, neurological deficit, family history of epilepsy, number of seizures before start ASM, time between first epileptic seizures and start ASM, number and type of different anti-epileptic drugs, time to remission after start ASM, number of seizures before remission, length of seizure-free period after treatment initiation

Table 2: The 22 predictive variables used in further data analysis.

Predictive variables			
Epileptic syndrome	Epileptic etiology	Seizure type	Age at onset of epilepsy
Gender	Neurological deficit	Developmental delay	Family history of epilepsy
History of status epilepticus	History of febrile seizures	Number of seizures before start ASM	Time between first epileptic seizure and start ASM
Number of seizures before remission	Time to remission after start ASM	Length of the seizure-free period after treatment initiation	Duration of active epilepsy
Number of different AED taken before discontinuation	Type of AEDs taken at the time of discontinuation	Patient's age at discontinuation	Duration of tapering period
EEG pattern at the time of discontinuation			

Figure 1: Survival curve of patients in remission.

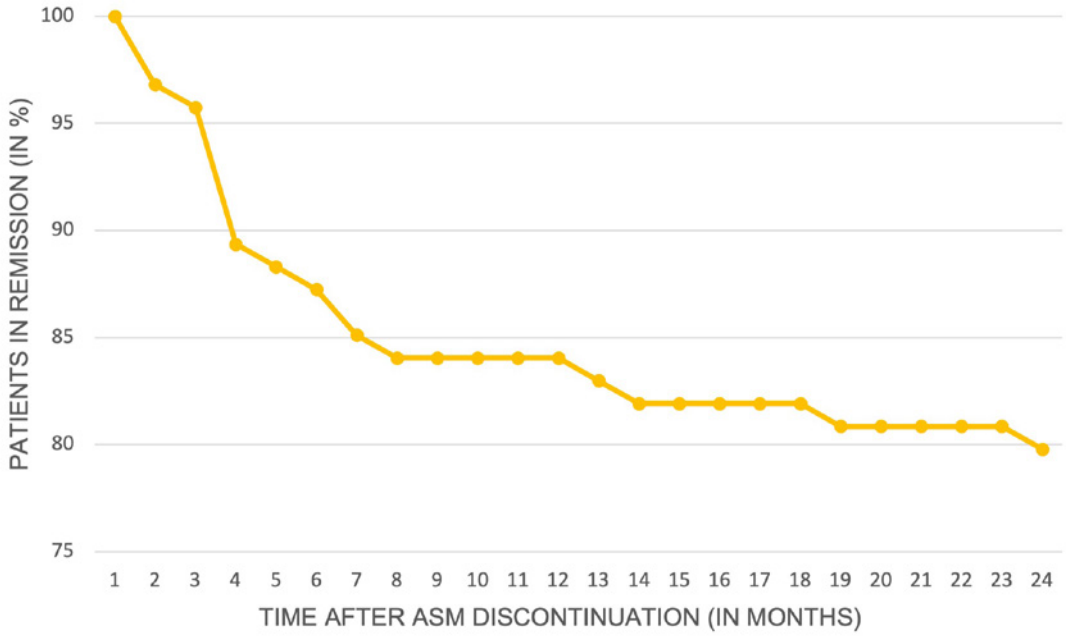
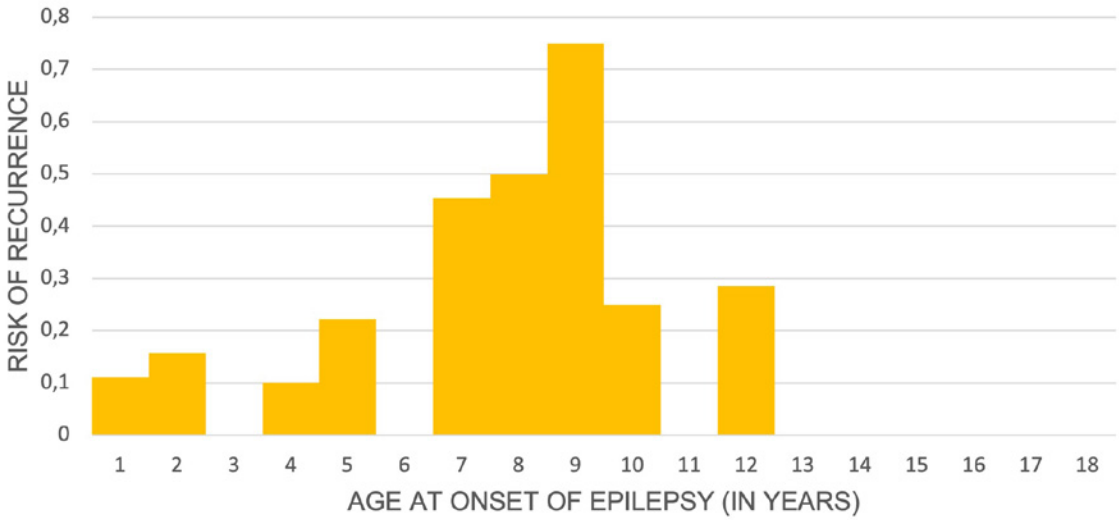


Figure 2: Risk of recurrence as a function of patient's age at onset of epilepsy.



and EEG pattern at the time of discontinuation. In the following sections we will detail some of these findings.

Epileptic syndrome. 57 patients could be classified into an epileptic syndrome/entity. 31 of them had a self-limited epilepsy (e.g. childhood absence epilepsy, childhood epilepsy with centro-temporal spikes, self-limited neonatal convulsions, temporal lobe epilepsy), the other 26 could be classified in West syndrome, epileptic encephalopathy with continuous spike-and-wave during sleep, juvenile myoclonic epilepsy, febrile seizures plus and other (like cerebral palsy). 23% of the patients with a self-limited epilepsy syndrome relapsed at some point, a difference with the 42% failing discontinuations in patients with these less benign epilepsy syndromes. This difference however was not significant (p=0,21). The analysis at 6 months did not show any significant difference either (13% when self-limiting versus 25% when less benign epilepsy syndromes (p=0,34)).

Etiology of epilepsy. The etiology of epilepsy was known in 35 of our study population despite standard diagnostic evaluations. 27 had a structural abnormality and 8 had a genetic cause for epilepsy. We did not notice a significant difference in risk of recurrence.

S*eizure type*. We did not notice a difference in relapse rates between patients with seizures with focal onset and with general onset. When comparing the patients with non-motor onset and motor onset, the first group seems to relapse more frequently than those with motor onset: 27% versus 21%, but this difference was not significant (last follow-up: p=0,63; 6 months follow-up: p=0,98).

Developmental delay. 44% of our included patients had a significant developmental delay. The risk of recurrence was higher in the group with developmental delay: 24% (10 of the 41) versus 19% (10 of the 53), although not significant (at last follow-up: p=0,52; 6 months follow-up: p=0,88).

History of status epilepticus. We did not notice a difference in recurrence between both groups when comparing at last follow-up (p=0,85). At a follow-up of 6 months having a history of status epilepticus seemed to raise the risk of recurrence (12% versus 24%) but this difference was not statistically significant (p=0,89). 22 of the identified patients had a history of status epilepticus.

Figure 3: Number of children per age at ASM discontinuation.

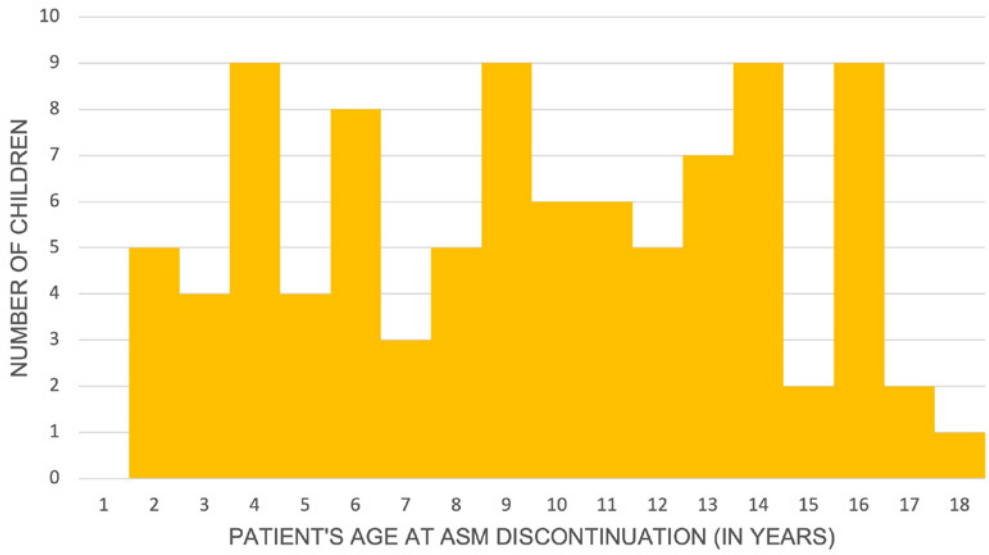
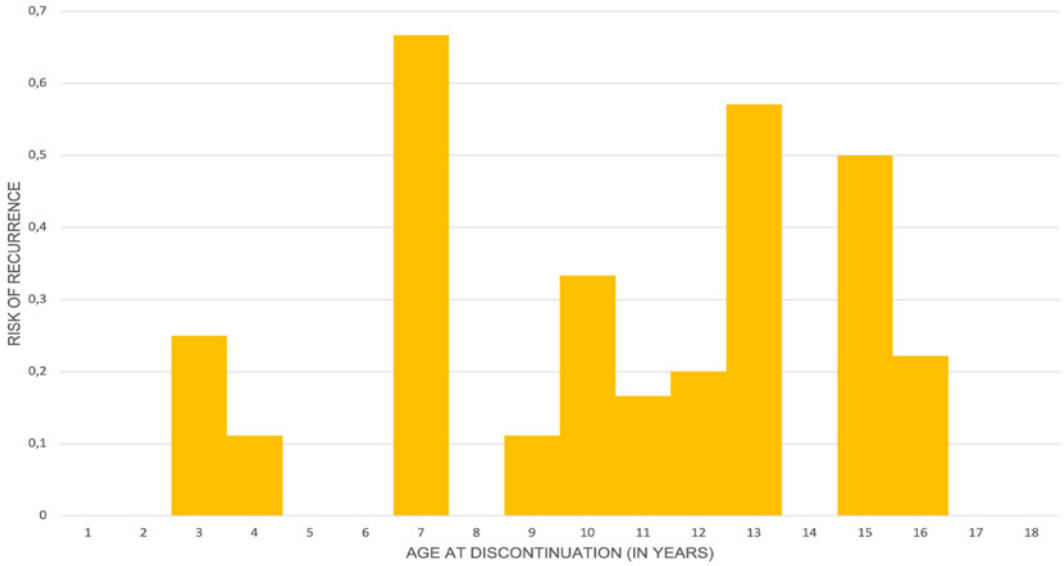


Figure 4: Risk of recurrence as a function of patient's age at ASM discontinuation.



History of febrile seizures. 25 patients had a history of febrile seizures. A trend was seen in the analysis at last follow-up that the overall relapse rate of patients with history of febrile seizures was less (16% vs 23%) than those without history. Statistically this was not significant (p=0,45), neither did the analysis at 6 months after ASM discontinuation find a difference (p=0,89).

Number of seizures before start ASM. The data on this parameter are not complete. In 29 of the 94 included patients the number of seizures before start ASM is not exactly known. This is mostly due to characteristics of the epilepsy syndrome (e.g. absence, ESES) or to unclarity and/or incompleteness in reporting. Of the remaining group of patients, only two patients had more than 5 epileptic seizures before start of medication, 27 patients had only one seizure before start ASM. No difference in risk of recurrence between the different groups was found.

Time between first epileptic seizure and start of anti-seizure medication. In the total group, the median duration of this period was 6 weeks. In those who relapsed at some point and before 6 months after ASM withdrawal, the median duration was 10 (p=0,37) and 12 weeks (p=0,31) respectively.

Time to remission after start ASM. 42 of the identified patients remitted immediately after start ASM. Therefore, 50 patients only used one anti-epileptic drug during the course of epilepsy. Included patients used maximum four anti-epileptic drugs before remission. In both analysis of recurrence at some point and in analysis after a 6 months of follow-up, no significant difference in median time to remission after start ASM was shown (p=0,69 and p=0,95 respectively).

Duration of active epilepsy. The median duration of active epilepsy in the whole group of identified patients was lower (11 months) than of those who ever relapsed (18months), but not significantly so (p=0,31). This difference was even less clear at follow-up of 6 months (p=0,87).

Number of seizures before remission. In 35% of the examined 94 medical records, there were missing data on this topic. The median number of identified seizures before remission is 2 in the whole group and 2,5 in those with recurrence of epilepsy at some point. In those with recurrence before 6 months of follow-up, the median number of identified seizures was 3.

Length of the seizure-free period after treatment initiation. The median duration was 25 months in the 94 included patients. No difference was seen when comparing with those who relapsed (at last follow-up: p=0,84; 6 months follow-up: p=0,62).

Electroencephalogram (EEG) pattern at the time of discontinuation. 43% of the included patients had an EEG before discontinuation of

their ASM. Only 6 of these 40 EEGs (15%) were abnormal. Only one of the 6 patients with abnormal EEG relapsed (after more than 6 months of follow-up). 28 of the 34 patients with an EEG within normal limits remitted. 80% of those without EEG pre-discontinuation remitted. Previous literature also examined the EEG pattern after discontinuation. In this study, only 15 of the 94 included patients had an EEG after discontinuation, of which 6 an abnormal EEG. A high number of those with an EEG performed after discontinuation relapsed (50%).

Table 3: Patient characteristics.

	Relapse	Remission	Sum	p
Number	12	82	94	
Male	11	47	58	
Age at onset of epilepsy (in years)	7,3	4,6		0,01
Age at discontinuation of ASM (in years)	13	9		0,03
Epileptic syndromes				0,34
Self-limited epileptic syndromes	4	27	31	
- Childhood absence epilepsy	2	13	15	
- Childhood epilepsy with centrotemporal spikes	2	8	10	
- Self-limited neonatal seizures	0	1	1	
- Temporal lobe epilepsy	0	6	6	
Other epileptic syndromes, less benign	3	23	26	
- Febrile seizures plus	3	13	16	
- Epileptic encephalopathy with continuous spike-and-wave during sleep	0	3	3	
- Juvenile myoclonic epilepsy	0	3	3	
- West syndrome	0	2	2	
- Other (Cerebral palsy)	0	2	2	
Not classified	5	32	37	
Etiology of epilepsy				
Structural abnormality	4	23	27	
Genetic cause	0	8	8	
Not identified	4	55	59	
Seizure type				
Focal onset	5	40	45	0,59
Generalized onset	7	40	47	
Motor onset	10	66	76	0,98
Non-Motor onset	2	13	15	
Developmental delay	5	36	41	0,88
History of status epilepticus	3	19	22	0,89
History of febrile seizures	3	22	25	0,89
Familial history of epilepsy	1	23	24	0,11

Discussion

94 patients between the age of 6 months and 18 years are included in this study. 21% of these patients relapsed. In literature a recurrence of epileptic seizures of 20-30% is usually reported (1,2,6,9,11,13,15,17,20,21). We conclude that the risk of recurrence in our study is rather low. Given the higher probability of severe epilepsy in a tertiary center, we could have presumed that the risk of recurrence would be higher than usually reported. The lower risk in our study is probably due to multiple factors, such as a pediatric population on monotherapy of ASM, exclusion of patients who have got epileptic surgery and a more conservative approach with a good preselection of candidates to discontinue their ASM.

Literature suggested that recurrence occurred more frequently in the first 6-12 months after ASM discontinuation (1,2,13,18,19). In our study too, the majority of those relapsing, relapsed in that period of time.

That leaves us with the discussion which factors are predictors for recurrence. We choose to examine 22 predictive factors after a literature research. However, this made the risk of overspecification bias larger, especially in combination with the smaller study population.

We identified the following factors which could be associated with a recurrence of epilepsy after ASM discontinuation: age at onset of epilepsy, age at discontinuation of ASM and gender. Gender was only a significant predictive variable at 6 months follow up.

The first two variables are not surprising. Most epilepsy syndromes are age-related (e.g. the most common age to develop childhood absence epilepsy is between 4 and 12 years of age). Etiology and type of epilepsy too are associated with age of onset of the epilepsy (6-9,16,17). Therefore, an older age at onset can reflect certain epileptic syndromes or types of epilepsy which aren't likely to remit. Our study showed a higher risk of recurrence when patients were older at onset and discontinuation (21). Long lasting epilepsies are thus less likely to remit, even after a period of seizure freedom.

Epilepsy syndrome and etiology are crucial factors in determining the severity of epilepsy (6-9,16,17). However in this study population, the difference between relapse of the patients with self-limiting epileptic syndromes and those with less benign epileptic syndromes was not significant (1,2,6,8,10,16,18,19). This is most likely due to the small sample size of our study. Furthermore, 4 of the identified 10 patients with childhood epilepsy with centro-temporal spikes relapse in our study. Given the self-limited characteristic of this epilepsy syndrome, we suggest that the decision of discontinuation was perhaps too early. Median seizure-free period before discontinuation of these patients is 2 years and 2 months. Discontinuation would be successful when performed after a new period of seizure freedom. Two patients with juvenile myoclonic epilepsy were included in this study. Literature suggests that this is generally a lifelong form of epilepsy (1,16,18,19). However, neither of these two patients relapsed after stopping the medication.

Reviewing the current evidence, ASM in epilepsy with either a genetic or an structural cause can almost never be discontinued (6). In our study, we did see some children in these etiological groups without recurrence. In seizures with focal onset, it can be expected that structural anomalities are the leading cause (6,10,21). The existing literature suggests that the rate of recurrence will be higher in focal epilepsy (2,6,7,10,16). This was also not observed in our study.

This retrospective review showed a difference in recurrence of epilepsy in boys and girls at 6 months follow-up. Boys more frequently relapsed in our study, although existing literature described either no difference between genders or a higher risk of relapse in girls (1,2,6,7,13,15,16,20). We do not have a clear explanation for the male predominance in our study.

Afshari et al. described the following factors to affect the rate of recurrence: age at onset of epilepsy, time between first epileptic seizure and start of anti-seizure medication, type and etiology of epilepsy, number of anti-epileptic drugs used before discontinuation, duration of tapering period of ASM and method of the tapering, EEG prior to beginning of therapy discontinuation (6). Beghi et al. states that an abnormal EEG at the time of treatment discontinuation, a documented etiology of seizures, seizures with focal onset and an older age at onset of epilepsy enhanced the risk of relapse (7). The Italian League against Epilepsy adviced to take neither the disease length or severity, nor the number and type of drugs into account (7). Geerts et al. found that age at onset of younger than 6 years, idiopathic epilepsy, absence epilepsy and having a normal EEG were predictive of staying in remission after ASM discontinuation (14). Karalok et al. did not find age at onset of epilepsy nor number of ASM a risk factor (1). Pavlovic et al. found an association of female gender, age at onset of seizures and at withdrawal of ASM, seizure types, EEG worsening during or after ASM withdrawal and age at discontinuation with relapse risk (19).

The study we performed could not confirm most of the findings above. Some of the abovementioned studies included more patients than ours. In some of them also adults were included.

To examine the effects of the parameters of mostly planned ASM discontinuation, only patients on one ASM at discontinuation were included. This inclusion criterion can cause some bias by selecting more benign epileptic syndromes and being not representative for the whole pediatric epileptic population.

In some of the variables there was quite some missing data, either because information was not recorded in the electronical medical record or because tests were not performed. In the clinical site where our study took place, an EEG study was not a standard examination to decide whether or not to discontinue ASM. Unclarity about the predictive value of EEGs still remains (1-3,6-9,13,15-17,19,21). Some studies investigated the effect of an abnormal EEG prior to therapy discontinuation, others the value of an EEG after therapy discontinuation (6,9,13,15,18,19).

Given the characteristics of our studied population, we could not totally exclude a preselection bias (20). We performed a retrospective study with preselection of our subjects by neurologists. The decision to stop or continue medication was not part of a standardized protocol but rather a case by case individual decision. There was not any pre-knowledge of this study. Also, some epilepsy syndromes and other characteristics are underrepresented.

Conclusion

In literature and in clinical practice, major discrepancies to decide on ASM discontinuation in childhood epilepsy remain, with a lack of evidence-based guidelines (18). We found a statistically significant effect of gender, age of epilepsy onset and age at discontinuation on the risk of recurrence. Given the sample size and the preselection bias, no hard conclusions could be made in our study, also not about the effect of epilepsy syndrome on the risk of relapse. Larger prospective studies are needed to further identify the predictive factors.

Conflict of interest

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

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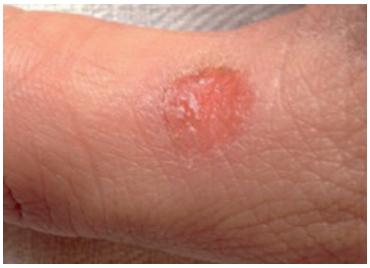

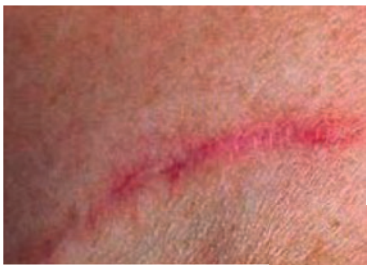

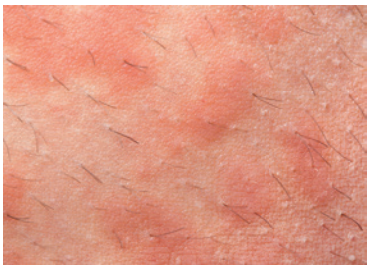

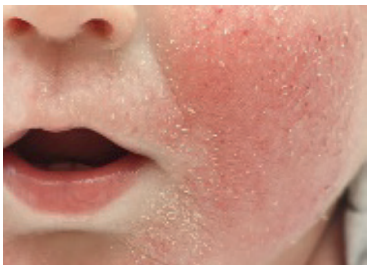

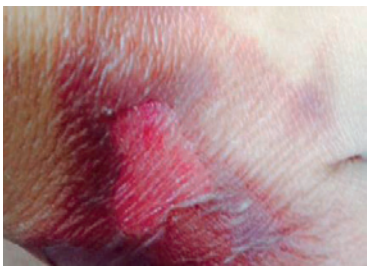

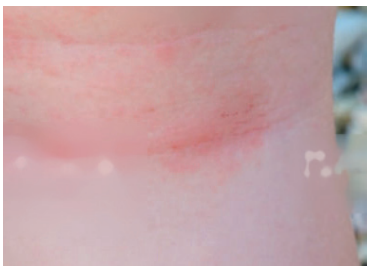

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A survey on first aid knowledge in members of Flemish youth movements

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Keywords

CPR, First Aid, Youth Movements

Abstract

Introduction: A significant proportion of childhood deaths is caused by unintentional injury. Every weekend and during summer holidays, approximately 267.000 Flemish children follow youth movement activities and camps. During these activities, injuries have to be managed by the responsible leaders. The aim of this study was to evaluate the first aid knowledge in leaders of a youth movement.

Methods: We conducted an online survey, consisting of 15 hypothetical scenarios, on first aid knowledge in Flemish youth movements. Every individual score was matched with following variables: having followed a first aid course, having a high self-assessment of first aid knowledge and having a health related job/study.

Results: Among the 2784 participants, 63% had attended a first aid course. The total score had a median of 8.0 and was significant higher ($p < 0.001$) if the participant had followed a first aid course (beta 0.39), had a health related job/study (beta 0.80) or had a high self-assessment of first aid knowledge (beta 0.73). The questions regarding Basic Life Support had a particularly high percentage of correct answers and scored significantly better in the group that attended a first aid course in the past.

Conclusion: Members of a youth movement have an appropriate knowledge of first aid. Many participants had followed a first aid course and scored significantly better. There is still room for improvement: a training in some very common scenarios could become part of the training course for youth movement leaders.

Introduction

It is well known that adequate first aid can save lives, can limit the consequences of an acute event and can avoid losing critical time while waiting for the emergency services to arrive (1). However, in fewer than 1 in 5 out-of-hospital cardiac arrests, bystander cardiopulmonary resuscitation (CPR) is administered (2). According to a recent study of the Red Cross Belgium 8 out of 10 Belgians claim to be able to act correctly in emergency situations. (3) However, when tested, it turns out that 35% misjudge their own capabilities. In the same study, 94% of Belgians believe that first aid training should become mandatory, ideally organized by schools or employers. In order to improve the successful application of basic CPR by lay people, a lot of secondary schools in Flanders implement first aid training and CPR as part of their educational goals (4,5). Initiating first aid training at an early age, from the age of 10, contributes to less anxiety about making mistakes and an increased willingness to offer help (6,7). First aid in the context of youth movements is especially valuable as unintentional injury represents the main cause of early morbidity and mortality among children and represents 40% of all childhood deaths (8). A considerable part of the Flemish youth goes to a youth movement. Every weekend approximately 267.000 Flemish children and adolescents between 5 and 18 years old don their uniforms to spend the afternoon with their peers. About 40,000 young leaders take care of them, both in weekends and during the annual summer camp (9). Weekend and camp activities are often associated with potential risk of injury. In the Healthy Camp study, which undertook a five-year surveillance study of injuries and illnesses during US summer camps, reference is made to the high-risk activities that take place during camp (10,11). To prevent further complications, making the difference between a minor injury or a more severe one is pivotal. Ensuring that there are trained first-aid providers within the youth movement will create a safer environment for the children and the leaders as well. Currently, obtaining a first aid certificate or attending a first aid course is not an obligation for youth movement leaders in Flanders. It is therefore possible that a youth movement will go on summer camp without a medically qualified person, even if there are children participating who have an underlying medical condition. When a youth movement wants to organize a basic CPR training, there are paid courses available, although not very cheap (12). Of course some individuals already followed a first-aid course at school or as part of their job/study. In this study we will map the knowledge regarding first aid among members of a Flemish youth movement using an online case-based survey.

Method

Design of the study

The survey consisted of an anonymous questionnaire with 26 questions, of which 11 were demographic in nature (age, gender, location, current education or job and self-assessment of first aid knowledge) and 15 consisted of hypothetical first aid scenarios. The KU Leuven university ethics committee approved the questionnaire and the study protocol (MP014140). The 15 questions assessing the first aid knowledge were a combination of multiple choice, open answer, image choice and ranking questions, divided into 6 main categories. The first category, named Basic Life Support (BLS), included the questions about CPR , an unconscious victim and choking. The second main category, named Bleeding, included nosebleed, abrasion with venous bleeding and arterial bleeding. The third, named Trauma, included bone fracture and dental avulsion. The fourth, named Medical Care, included questions about first aid kit, allergy and heatstroke. The fifth, named Wound Care, included the questions about burns and splinters. The sixth and last category, named Insect Bite, included the questions about a bee sting and tick bite. A total score was calculated for these questions, with one mark given for each correct answer. The maximum possible score was 15/15. The formation of the survey was based on the review of multiple-choice item-writing guidelines by Downing et al (13). The use of educational imagery and videos was included in the survey. After each answer, the participant was presented the right answer and an explanation. This format with a comprehensive explanation was chosen to make sure that the survey could also serve as an educational tool for the participants. At the end of the questionnaire participants were asked whether they had learned something about first aid from this survey.

At the beginning of the survey the participants were asked to assess their first aid knowledge by rating their knowledge on a Likert scale as 'very poor, poor, moderate, good or very good'. The respondents who assessed their own knowledge as 'good or very good' were included in a subpopulation 'high self-assessment of first aid knowledge'.

Because peer-review improves the quality of multiple-choice examinations, the survey was completed and thoroughly examined by at least 15 peers, both medical as non-medical (14). Adjustments were made based on their feedback. The only exclusion criterion of this study was not being an active member of a Flemish youth movement. In addition, incomplete surveys were also excluded from the statistical analysis.

Distribution

After the survey was designed, it was uploaded in Qualtrics, in order to convert it into a web-based survey. To reach as many members of Flemish youth movements as possible, the central authorities of 'Chirojeugd Vlaanderen', 'Scouts & Gidsen Vlaanderen', 'Katholieke Studenten Actie (KSA)', 'Vrouwelijke KatholiekeStuderende Jeugd (VKSJ)', 'Katholieke Landelijke Jeugd (KLJ)', 'FOS Open Scouting' and 'Jeugdbond voor Natuur en Milieu (JNM)' were contacted in October 2019 and asked if they could distribute the study at the national level by sending it to all of their members either using their newsletter, available e-mail lists and also their social media (Facebook groups). The study participants were not asked to list the manner in which they received the invitation for the survey.

Statistical analysis

Groups were made based on the following criteria: 'having followed a first aid course', 'studying or working in a health-related domain' (open question, dummy coded by the researchers) and 'having a high self-assessment of first aid knowledge'. Continuous variables were checked for normality and the difference between groups was tested with the t-test or Mann-Whitney U test. Categorical variables are expressed as frequency and proportions, and statistical differences were assessed with the Chi-squared test. Linear regression analysis was used to study the effect of the following pre-selected variables on the total test scores: 'age, gender, working, health-related job, first aid course, and first aid assessment score'. All tests were two-sided and a p-value less than 0.05 was deemed statistically significant. All analyses were performed using R Statistical Software (version 4.0.2 2020-06-22, Foundation for Statistical Computing, Vienna, Austria). Results are shown as mean and standard deviation (SD) when there is a normal distribution of data, if not, the results are presented as median and interquartile range (IQR).

Results

Survey responses

A total of 4405 surveys were collected with a subdivision of 1425 derived from 'Chirojeugd Vlaanderen', 1706 from 'Scouts & Gidsen Vlaanderen', 660 from 'KSA', 357 from 'KLJ', 63 from 'JNM', 67 from 'FOS Open Scouting', 38 from 'VKSJ' and 89 'others/not specified'. Out of 4405 surveys, 1621 (36.8%) were incomplete and therefore not eligible for statistical analysis, with a remaining 2784 surveys (63.2%) used for statistical analysis.

Participant demographics

Table 1 displays the demographics of the survey respondents. The median age of all respondents was 20 [19.0;22.0] years old and 70.5% were female. The largest proportion of survey respondents are a member of 'Scouts en Gidsen Vlaanderen' and 'Chiro Jeugd Vlaanderen'. The majority of respondents were students (88.8%, N=2471) and 17% (N=469) practised a health-related job or study. The largest proportion of this last group consisted of female participants (79,7%, p<0.001) and a significant percentage (74,4%, p<0.001) of them had already taken a first aid course. A notable result of the survey is that 63% (N=1758) of all participants attended a first aid course in the past. There is no significant difference in gender or youth movement compared to the respondents who did not attend a first aid course. Roughly 20% of this group followed a first aid course as part of his or her job/study. 43% (N=1197) of the study population was included in the subpopulation 'high self-assessment of first aid knowledge'. Of this group, more than 30% had a health-related job or study and 81% attended a first aid course in the past. The majority (77%, N= 169) of the respondents who have a health-related job or study estimated their first aid knowledge as 'good or very good'.

Results from the survey

Table 2 presents the main results from the case-based survey. The total score had a median of 8.00/15.00 with an interquartile range of [7.00;10.00]. The participants who followed a first aid course had a significantly higher total score (9.00 [7.00;10.00] with p <0.001) and scored significantly higher on all questions related to BLS (p <0.001). As for the other categories, those who followed a first aid course scored higher on most of the questions except for tick bite (p 0.333), arterial bleeding (p 0.139), abrasion with venous bleeding (p 0.153), dental avulsion (p 0.143) and heatstroke (p 0.081). Having a health-related job/study resulted in a significantly higher total score (9.00 [8.00;11.00] and p <0.001) and a significantly higher score on all questions regarding bleeding, wound care and trauma (all p <0.001). The questions with no significantly higher score were those about tick bite (p 0.193), heatstroke (p 0.128), first aid kit (p 0.145) and choking (p 0.021). Those participants with a high self-assessment of first aid scored significantly higher on the questions regarding insect bites (p<0.001), wound care (p <0.001), trauma (p<0.001), medical care (p <0.05) and basic life support (p < 0.001). Only one question regarding bleeding (i.e. abrasion with venous bleeding) was not significantly different (p 0.175). In addition, having a high self-

Table 1: Patient characteristics

Variable	Relapse	First Aid Course		Health-related study/job		High self-assessment of First Aid	
	Total (n=2,784)	n=1,758	P-value	n=469	P-value	n=1197	P-value
Age	20.0 [19.0;22.0]	20.0 [19.0;22.0]	<0.001	20.0 [19.0;21.0]	0.027	20.0 [19.0;22.0]	<0.001
Gender			0.533		<0.001		0.754
Male	813 (29.2%)	526 (29.9%)		95 (20.3%)		358 (29.9%)	
Female	1963 (70.5%)	1227 (69.8%)		373 (79.5%)		836 (69.8%)	
Other	8 (0.29%)	5 (0.28%)		1 (0.21%)		3 (0.25%)	
Youth movement			0.849		0.792	0.121	
Chiro	854 (30.7%)	528 (30.0%)		147 (31.3%)		358 (29.9%)	
Scouts	1193 (42.9%)	765 (43.5%)		206 (43.9%)		536 (44.8%)	
KLJ	222 (7.97%)	143 (8.13%)		37 (7.89%)		102 (8.52%)	
KSA	421 (15.1%)	263 (15.0%)		62 (13.2%)		160 (13.4%)	
Other	94 (3.38%)	59 (3.36%)		17 (3.62%)		41 (3.43%)	
Student	2471 (88.8%)	1514 (86.1%)	<0.001	432 (92.1%)	0.015	1028 (85.9%)	<0.001
Working	313 (11.2%)	244 (13.9%)	<0.001	37 (7.89%)	0.015	169 (14.1%)	<0.001
Health-related study/job	469 (16.8%)	349 (19.9%)	<0.001	—	—	361 (30.2%)	<0.001
First Aid course	1758 (63.1%)	—	—	349 (74,4%)	<0.001	970 (81.0%)	<0.001

Chiro: Chirojeugd Vlaanderen; Scouts: Scouts en Gidsen Vlaanderen; KSA: Katholieke Studenten Actie; KLJ: Katholieke Landelijke Jeugd;
Values are presented as median (IQR) or n (%). P<0.05 was considered significant.

Table 2: Results from the survey.

	Relapse	First Aid Course		Health-related study/job		High self-assessment of First Aid	
Item	Total (n=2,784)	n=1,758	P-val*	n=469	P-value*	n=1197	P-value*
CPR	2085 (74.9%)	1448 (82.4%)	<0.001	421 (89.8%)	<0.001	1034 (86.4%)	<0.001
Unconscious victim	2547 (91.5%)	1656 (94.2%)	<0.001	453 (96.6%)	<0.001	1148 (95.9%)	<0.001
Choking	2545 (91.4%)	1636 (93.1%)	<0.001	442 (94.2%)	0.021	1122 (93.7%)	<0.001
Nosebleed	1109 (39.8%)	768 (43.7%)	<0.001	242 (51.6%)	<0.001	588 (49.1%)	<0.001
Venous bleeding/Abrasion	1258 (45.2%)	813 (46.2%)	0.153	261 (55.7%)	<0.001	559 (46.7%)	0.175
Arterial bleeding	569 (20.4%)	375 (21.3%)	0.139	149 (31.8%)	<0.001	301 (25.1%)	<0.001
Bone fracture	1525 (54.8%)	1046 (59.5%)	<0.001	324 (69.1%)	<0.001	779 (65.1%)	<0.001
Dental avulsion	920 (33.0%)	599 (34.1%)	0.143	201 (42.9%)	<0.001	460 (38.4%)	<0.001
First Aid kit	1089 (39.1%)	760 (43.2%)	<0.001	198 (42.2%)	0.145	551 (46.0%)	<0.001
Heatstroke	2573 (92.4%)	1637 (93.1%)	0.081	425 (90.6%)	0.128	1122 (93.7%)	0.028
Allergy	2567 (92.2%)	1647 (93.7%)	<0.001	450 (95.9%)	<0.001	1135 (94.8%)	<0.001
Burn	1263 (45.4%)	845 (48.1%)	<0.001	259 (55.2%)	<0.001	615 (51.4%)	<0.001
Splinter	490 (17.6%)	349 (19.9%)	<0.001	119 (25.4%)	<0.001	271 (22.6%)	<0.001
Bee sting	450 (16.2%)	327 (18.6%)	<0.001	126 (26.9%)	<0.001	274 (22.9%)	<0.001
Tick bite	1824 (65.5%)	1164 (66.2%)	0.333	320 (68.2%)	0.193	830 (69.3%)	<0.001
Total score	8.00 [7.00;10.00]	9.00 [7.00;10.00]	<0.001	9.00 [8.00;11.00]	<0.001	8.00 [7.00;9.00]	<0.001

Values are presented as n (%) or median (IQR). P<0.05 was considered significant.
**Compared to complementary group (no First Aid Course / no Health-related study/job / no High self-assessment of First Aid)*

assessment of first aid resulted in a significant higher total score (8.00 [7.00;9.00] with p <0.001) compared to those who estimated their first aid knowledge less well (7.00 [5.00;8.00]).

2690 participants (96,7%) claimed to have learned something about first aid from this survey.

Linear regression models for total score

When looking at the different variables, age and work proved to be the only demographic data with a statistically significant correlation with the overall score. For each increase in age by 1 year, the total score improves with 0,15 (p <0.001) (Table 3).

Table 3: Linear regression models for total score.

	Univariable model			Multivariable model		
Variable	**Beta**	**95% CI**	**P-value**	**Beta**	**95% CI**	**P-value**
Age	0.15	0.12, 0.18	<0.001	0.11	0.08, 0.13	<0.001
Female gender	-0.05	-0.23, 0.13	0.6	—	—	—
Working	0.55	0.30, 0.81	<0.001	—	—	—
Health-related job	1.4	1.2, 1.6	<0.001	0.80	0.58, 1.00	<0.001
First Aid course	1.0	0.86, 1.2	<0.001	0.39	0.22, 0.56	<0.001
Self-assessment score	1.0	0.91, 1.1	<0.001	0.73	0.63, 0.84	<0.001

CI: confidence interval. P<0.05 was considered significant.

Having a health-related job, having followed a first aid course and the self-assessment score are all significantly correlated (p<0.0001) with the total score. This significance remains after multivariate analysis with respective beta values of 0.80 (95% CI [0.58, 1.00] p < 0.001), 0.39 (95% CI [0.22, 0.56] p < 0.001) and 0.73 (95% CI [0.63, 0.84] p < 0.001).

With a beta of 0.55, being employed also has a significant impact (95% CI [0.30, 0.81] p<0.001) on the total score. However, after multivariate analysis, this correlation disappeared.

Discussion

We conducted a case-based online survey in Flemish youth movements to assess the level of first aid knowledge among their leaders. We managed to reach 4405 members of a youth movement, most of whom are members of one of the main youth movements in Flanders (Chiro Jeugd Vlaanderen, Scouts en Gidsen Vlaanderen, KSA and KLJ). A total of 2784 participants fully completed the survey and were used in the statistical analysis. The average percentage of participation is lower than for studies where a survey among the youth movement leaders was organized by the organization itself (24% in a Chiro survey) (15). We also noted that the participation rate was higher for females, which is in line with other voluntary surveys in young adults (16).

During youth movement activities, various accidents can occur. In addition, the circulation of infectious diseases is not uncommon in youth camps. Several studies have shown that outbreaks of diarrhoea during summer camps are common as well as medical problems caused by heat waves (17-19). Little data is available on the incidence of medical interventions during youth movement activities. The Healthy Camp Study is to date the only example of a long-term illness and injury surveillance study conducted with a representative sample of US summer camps (10,11). The overall injury rate was low: 0.47 injuries per 1000 camp days for resident camps and 0.42 injuries per 1000 camp days for day camps.

To our knowledge, no data exist on the incidence of accidents in youth movements in Flanders. In personal communication, KSA and KLJ confirm that respectively 354 and 274 accidents were declared to insurance companies in 2019-2020, which are presumably underestimated figures given that infections or mild traumata might not have been reported.

In this study we investigated the first aid knowledge of members of a Flemish youth movement using 15 different medical situations. We noted that 63% of all participants (N=1758) had already attended a first aid course in the past. This percentage is similar compared to reports from Sweden, USA, Australia and New Zealand (rates of 45-79%) and a survey conducted in Belgian primary school teachers (68% in the age group 21–30 years) (20-25). No prior studies have investigated first aid knowledge in youth leaders and most have only examined CPR training. Therefore these cannot be compared directly.

In this survey, we looked more closely at some important medical topics which were divided in 6 main categories as mentioned before.

The total score of the 15 survey questions assessing the first aid knowledge was not normally distributed with a median of 8.00 [7.00;10.00]. None of the participants achieved a perfect score of 15 out of 15. 7/15 was the score achieve by 20% of the participants, while 43% (N= 1195) scored 8/15 or higher. The total score was significantly higher when a first-aid course was followed, when the participant had a health-related job/study or when the participant had a high self-assessment regarding first aid.

Performing a health-related job/study has the most impact. We believe that this is due to the fact that these people are more frequently confronted with healthcare situations. Also, 74,4% of the respondents with a job or study in healthcare had followed a first aid course. The finding of a higher overall score in medically trained people is comparable to other studies (26). The variables 'First Aid assessment score' and 'having followed a first aid course' remain, after multivariate analysis, significant for a higher total score. These results are in line with the international literature (20, 27, 28). A survey amongst primary school teachers in Belgium concluded that attending a CPR course in the past had a positive effect on knowledge and also increased self-confidence (20). The results from a study from New Zealand with 494 students between 16 and 17 years old showed that the students who had received a first aid course showed greater first aid knowledge and in addition that having a positive attitude towards CPR and first aid training contributes to a higher score and more willingness to administer CPR to a stranger (28).

In our survey we divided the different questions in separate categories. One of these is BLS, where we notice that the vast majority of participants gave the correct answer (CPR N=2085 (74.9%), unconscious victim N=2547 (91.5%) and choking N=2545 (91.4%)). As one would anticipate, participants who followed a first aid course scored significantly higher on each question related to BLS than those who did not follow a first aid course. The question regarding heat stroke is the one that was answered most often correctly (N= 2573 (92.4%)). This indicates that the vast majority of participants, educated in first aid or not, know what to do in such circumstances, which is a reassuring finding as heath strokes are common during summer camps.

Several questions had a consistent low score. Among these are the questions about the bee sting (N = 450 (16.2%)), splinter removal (N = 490 (17.6%)) and arterial bleeding (N = 569 (20.4%)). The first two are very common occurrences during youth movement activities, and the correct intervention in these cases may thus need more attention in further training or youth movement leaders. The question about arterial bleeding was not significantly answered more correctly if the participant had followed a first aid course. This is worrying because this is a potentially life-threatening situation. This is certainly a working point for future first aid courses that are organized among youth movement leaders in Flanders.

Strengths and limitations of the study

The large study population of 2784 respondents who completed the survey was considered as a strength of this study. We were able to reach many Flemish youth leaders from various youth movements and districts.

Furthermore, the survey used in this study was not only a tool for acquiring information but also an educational tool.

Concerning the limitations of the study, we have to take into account possible bias. There may be a selection/participation bias as people with an interest in this topic and with good access to the digital channels that were used will be more likely to complete the survey. Those who have already taken a course or are engaged in a health-related profession or study may be more willing to test their first aid knowledge.

In addition, observational studies such as surveys are often limited in flexibility and depth. We are bound by a predesigned questionnaire which contained only one question per category. Within this questionnaire it was not possible to nuance an issue or learn more about how respondents seem to understand the question. The conclusions deduced might not be correlating if a more detailed assessment would be done.

It is worth a thought that answers provided through a digital questionnaire might not be correlating with real-life scenarios.

Regarding the statistical analysis, the statistical testing on the different topics was not subjected to correction for multiple testing. More extensive statistical comparisons might exclude some incidentally positive results.

Conclusion

From the data of our survey, we provide evidence for appropriate knowledge of first aid in the majority of youth movement leaders in Flanders, with higher scores in those that followed first aid courses in the past or are professionally involved or being educated as a student in health care. We identify knowledge gaps in common scenarios that, with the support of coordinating organizations with expertise in this field, can be addressed in order to improve first aid training for youth movements in Flanders.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest to declare with regards to the conduction and reporting of the case presented in this manuscript, in line with the editorial policy of the Belgian Journal of Paediatrics.

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Traumatic pancreatic injury after blunt abdominal trauma among children

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Keywords

Blunt abdominal trauma, traumatic pancreatic injury, practical guideline, management

Abstract

Traumatic pancreatic injuries or traumatic pancreatitis are rare among children and difficult to diagnose because of the nonspecific symptoms. A review of the literature from the last 20 years on the diagnostic approaches and management of blunt pancreatic injury in children was performed and practical guidelines are proposed.

A high index of suspicion for pancreatic injuries is needed for all pediatric patients with blunt abdominal injuries. Diagnosis is made based on a combination of laboratory findings and radiological imaging (ultrasound, or more preferably in the acute setting, computed tomography of the abdomen). Early surgical treatment may benefit patients with main pancreatic duct injuries, while other types of pancreatic injuries can be treated non-operatively. Although, randomized controlled trials are lacking to justify the most appropriated approach. The most common short-term complication after pancreatic injury is the development of pseudocysts and can be treated conservatively if asymptomatic. The risk of development of diabetes mellitus or exocrine pancreatic insufficiency as long-term complication in children remains unknown. More prospective trials and research initiatives are required.

Introduction

Pancreatic injuries and associated traumatic pancreatitis are rare among children. The incidence of acute pancreatitis among children is 12,3 per 100 000, of which 10-40% are caused by trauma (1).

Blunt abdominal trauma is the most frequent cause of abdominal injury among children, while among adults, penetrating abdominal traumas are more common (2). According to data of National Trauma Data Bank of America, blunt pancreatic injuries occur among 0,6% of pediatric patients with abdominal injuries and comprises 0,3% of all traumas (2). An observational cohort study based on a trauma register in Norway, identified a total of 14 patients with pancreatic injury over a 15-year period. Nine of these patients were children, representing 1% (9/869) of all injured children in the registry and 11,4% (9/79) of the children with documented abdominal injuries (3).

Pancreatic injury is the fourth most common solid organ injury, following injuries of the spleen, liver, and kidney (4). Blunt pancreatic injury among children has a high morbidity and mortality rate of respectively 26.5% and 5% (2).

Acceleration- deceleration injuries and direct compression force in the epigastrium (for example caused by the force of a seat belt in a motor vehicle accident or bicycle handlebar injuries) are most likely responsible for pancreatic injury. The pancreas is crushed against the lumbar vertebrae resulting in compression and contusion of the pancreatic tissue and sometimes even tearing of the pancreatic duct resulting in a broad range or injuries from traumatic pancreatitis to complete gland transection (5). In addition, the pancreas is closely related to the duodenum, the stomach, the common bile duct, the spleen and the major upper abdominal vessels and therefore, associated intra-abdominal injuries are common (2).

Injury to the pancreas may be difficult to diagnose, especially among children. This is due to the retroperitoneal positioning of the pancreas. Therefore, onset of abdominal symptoms is delayed and the signs and symptoms are often vague and nonspecific. Epigastric pain is the most common complaint of pediatric pancreatic injury, followed by abdominal distension and nausea (6). It is recommended to keep a high index of suspicion for possible pancreatic injury in trauma patients based on the mechanism of injury (7). Among adults, delayed diagnosis is associated with higher complication rate that contributes to morbidity and mortality (8). However, data on this topic in children are scarce.

The aim of this literature review is to investigate the diagnostic approach and management of blunt pancreatic injury in children and to propose a practical guideline.

Method

A literature search was performed according to the PRISMA guidelines in PubMed/Medline using the Medical Subject Heading (MeSH) terms: ((“Abdominal Injuries”[Mesh]) OR “Wounds, Nonpenetrating”[Mesh])) AND “Pancreas”[Mesh] AND “Child”[Mesh]. Only articles published in English between 2001 and January 2022 were selected. Case reports with less than five patients were excluded. An exception was made for a case report describing long-term complications after pancreatic injury. In addition, the reference list of all selected articles was manually searched for relevant articles.

Results

Diagnosis

Pancreatic injury among children is diagnosed based on a combination of laboratory findings and radiological imaging, in combination with a high index of suspicion after blunt abdominal trauma. In case of pancreatitis at least two of the following criteria should be presented according to the INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In Search for a CuRE) criteria: 1) abdominal pain (epigastric or right upper quadrant with or without radiation to the back), 2) serum amylase and/or lipase values 3 or more times

upper limits of normal (ULN), 3) imaging findings consistent with inflammation of pancreas (9).

Biochemical diagnosis

Elevated serum levels of pancreatic enzymes (and especially amylase) are not specific for pancreatic injury, because high levels have also appeared in case of craniofacial injuries or other intra-abdominal conditions (8). A recent prospective cohort study among 164 adult patients with blunt abdominal trauma showed a specificity of 100% and sensitivity of 85% of combined serum amylase and lipase levels (> 2 times ULN) for predicting pancreatic injury (10). No separate data are available for children and therefore, the predictive value in pediatric patients remains unclear.

To avoid false negative results, these pancreatic enzymes should be determined at least six hours after the injury. Since serum lipase and amylase will increase gradually over time with a significant dose-time response association. Measuring the levels before that timepoint will have no diagnostic value in both adults as children (10,11). A retrospective multicenter study showed no correlation between initial or peak amylase/lipase level and grade of pancreatic injury in 131 children. However, a maximal amylase level greater than 1100 U/L (> 10 times ULN) was predictive for development of a pancreatic pseudocyst among pediatric patients in this study (12).

Radiological imaging

Imaging plays an important role shortly after the trauma in determining the localization and severity of the pancreatic injury and the treatment options. The most commonly used grading system for pancreatic injury was developed by the American Association for the Surgery of Trauma (AAST) and is illustrated in table 1 and figure 1 (13). The scale contains 5 grades determined by ductal integrity and anatomic location of the injury and is used for both adults and children. Sutherland et al. suggested to add grade 0 stage that contains children with clinical and biochemical signs of acute pancreatitis after blunt abdominal trauma without large radiological abnormalities (14).

Ultrasound (US), known as extended Focused Assessment with Sonography in Trauma care setting (eFAST), is a screening tool for detecting acute life-threatening conditions. It can detect the existence of free fluid and large damage to abdominal organs. The most important limitation of the US is the difficulty in identifying pancreatic injury because of the retroperitoneal location of the pancreas (15). In case of high suspicion (depending on the trauma mechanism and the force of impact) a computed tomography (CT) of the abdomen with intravenous contrast should be performed with a low threshold.

CT of the abdomen is a rapid, easily available test and the primary imaging modality of choice for evaluating pediatric patients with high impact blunt abdominal trauma. Assessing the integrity of pancreatic duct is important for deciding the treatment options of the pancreatic injury (surgical or conservative). The sensitivity of CT for the accurate determination of the grade of pancreatic injury shows a large heterogeneity, ranging from 60-80% among reported studies in adults (16,17,18). No data are available for children. A negative CT within the first 24 hours after the accident does not rule out a pancreatic

Figure 1.

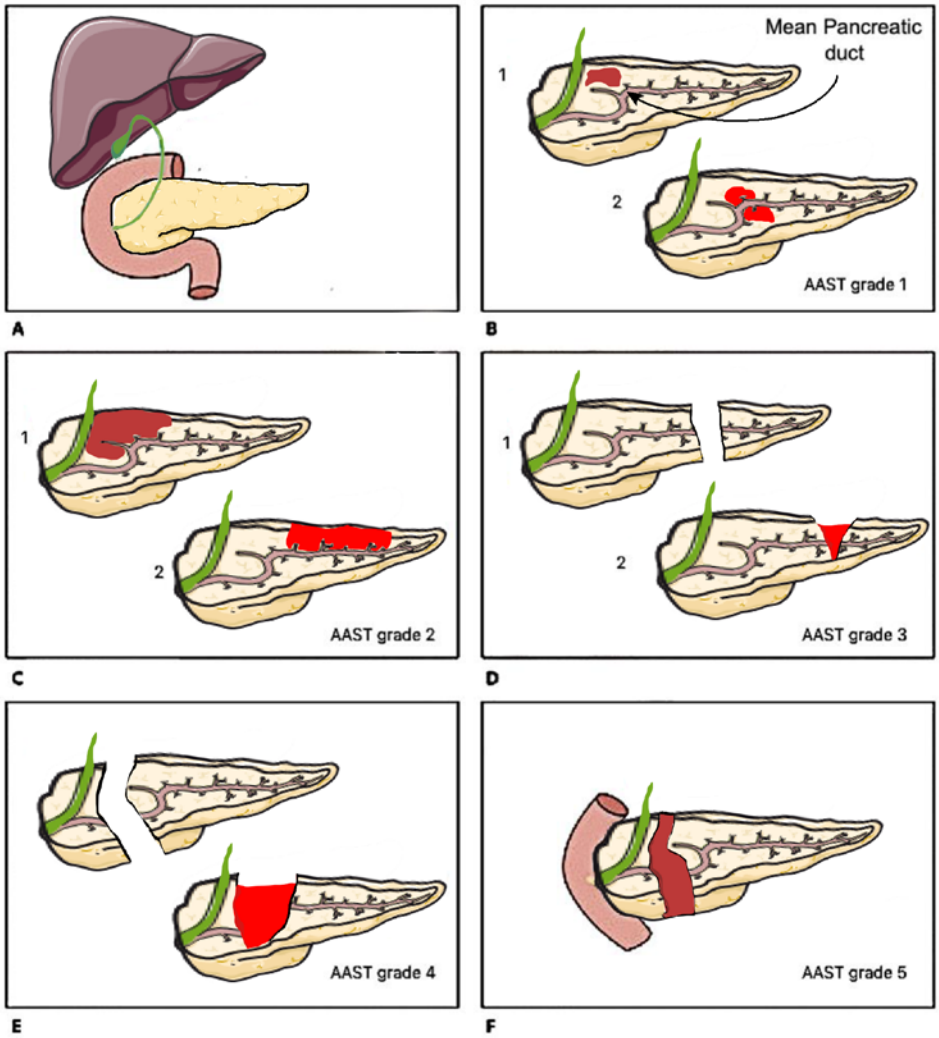


Table 1: Organ Injury scoring scale for pancreatic injury according to AAST

	Day 0	Reference value
1	Hematoma	Minor contusion without duct injury
	Laceration	Superficial laceration without duct injury
2	Hematoma	Major contusion without duct injury or tissue loss
	Laceration	Major laceration without duct injury or tissue loss
3	Laceration	Distal transection or parenchymal injury with duct injury
4	Laceration	Proximal transection or parenchymal injury involving ampulla
5	Laceration	Massive disruption of pancreatic head

injury since the lack of direct or indirect signs of pancreatic trauma shorty after blunt abdominal trauma. A repeat CT more than 24 hours after the injury can be useful in case of high index of suspicion of pancreatic trauma, however the cumulative dose of radiation in case of repeated CT scans must be considered (19). Therefore, a contrast enhanced ultrasound (CEUS) can be used as a safer alternative. Since this is an ionizing-radiation-free technique that can detect in highly sensitive way intra-abdominal injury in children, but only when performed by trained radiologist (20).

During the acute assessment of blunt pancreatic injuries, the role of magnetic resonance cholangiopancreatography (MRCP) is limited due to its restricted availability and longer scanning time in comparison to CT. However, in case that the status of the pancreatic duct is unclear on CT, MRCP can be useful to assess secondary changes in pancreatic parenchyma and the pancreatic duct (19,21). A retrospective multilevel study in 21 children with pancreatic injury by Rosenfeld et al. showed that MRCP is more useful than CT for identifying the pancreatic duct but is non-superior to confirm the integrity of the duct (19).

Endoscopic retrograde cholangiopancreatography (ERCP) can accurately diagnose pancreatic duct disruption in children. However, this invasive procedure will only be performed if therapeutic options, such as stent placement, are available (22).

Treatment options

Depending on the severity and grade of the injury of the pancreas or other organs, treatment could be conservative, interventional, or surgical. When the patient is hemodynamically unstable or shows signs of peritonitis, it is necessary to proceed with an urgent surgical exploration by laparotomy or laparoscopy (3).

Treatment of low-grade pancreatic injuries

For minor pancreatic injuries without pancreatic duct involvement (AAST grade 0-2), non-operative management (conservative and if applicable interventional with ERCP) is recommended, which has widely been accepted as the treatment of choice (23).

In a retrospective study by Rosenfeld et al., ERCP was used in 26 children with pancreatic injury (mostly AAST grade III or IV) in the diagnostic evaluation of pancreatic duct integrity, early management of pancreatic duct leak and the treatment of late complications like duct stricture, pseudocysts, or pancreatic fistulas. No clinical benefit of early ERCP intervention on the length of the hospital stay could be detected, although prospective studies are required to confirm this finding (24).

The non-operative management of blunt pancreatic trauma and associated traumatic pancreatitis consists of supportive care with cardiorespiratory monitoring, preserving effective circulating volume with intravenous fluid and pain medication. In case of signs of acute pancreatitis, early aggressive fluid resuscitation with 1,5-2 times the maintenance rate is recommended (25). Optimal pain management for children with acute pancreatitis should be strived (1). No evidence exists that morphine causes adverse effects on the sphincter of Oddi, and opioids can be administered safely (1).

The use of prophylactic antibiotics for acute pancreatitis or pancreatic injuries is not recommended by the North American Society for Pediatric Gastroenterology, Hepatology and nutrition (NASPGHAN) (26). There are no data on the benefits of somatostatin for the treatment of pancreatic injuries. The early use of parenteral nutrition (PN) has no clinical benefit in the non-operative management of blunt pancreatic trauma and should be avoided unless prolonged oral feeding intolerance (> 7 days) occurs (27). This is supported by a retrospective cohort study of 554 children with blunt pancreatic injury (28). Therefore, NASPGHAN recommends early enteral nutrition in cases of mild pancreatitis and states that a combination of enteral nutrition and PN is superior to PN alone (26).

Treatment of high-grade pancreatic injuries

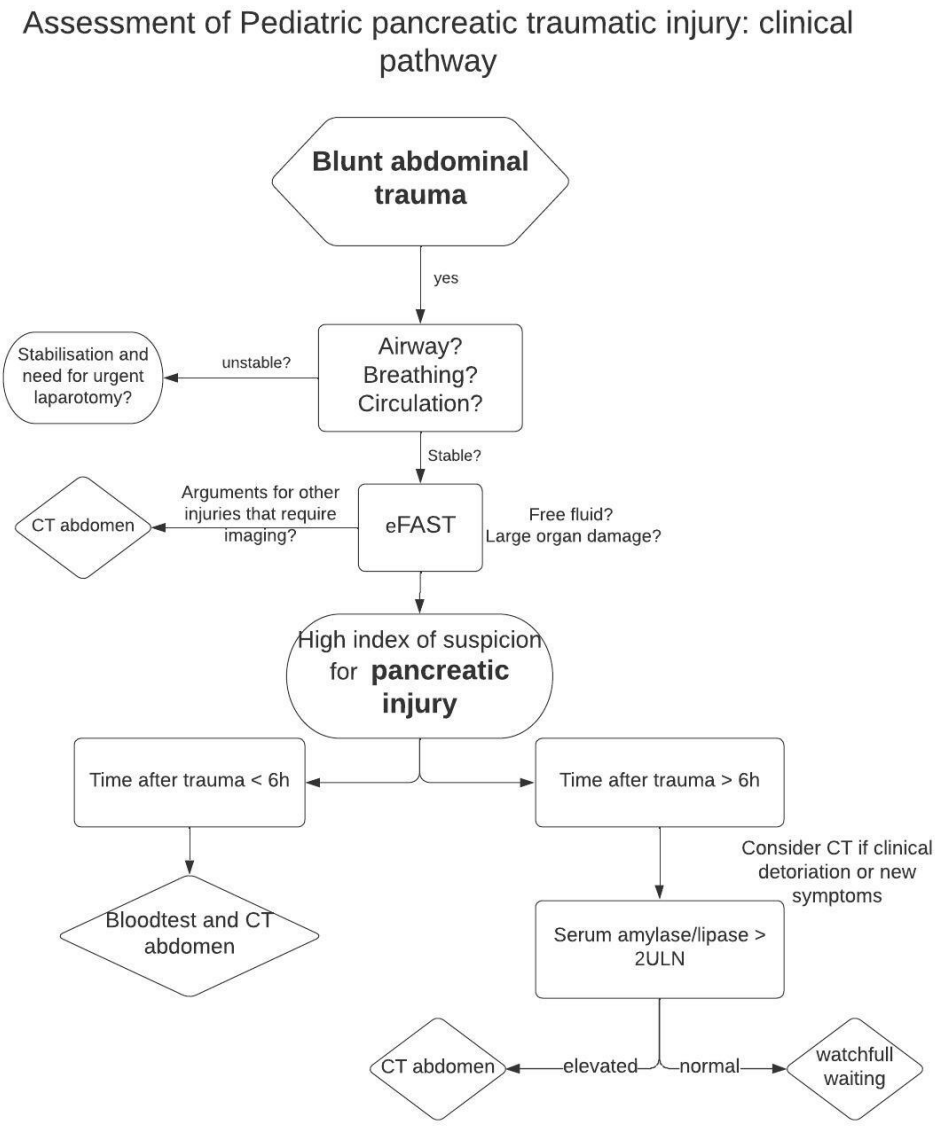
Treatment options of children with major pancreatic injuries of AAST grade 3-5 (meaning pancreatic duct involvement) remain controversial. A Cochrane review in 2014 showed the absence of randomized clinical trials investigating the optimal treatment strategy in this type of injury (29). A recent systematic review and meta-analysis by Kopljar et al., demonstrated that there is no difference in mortality between an initial non-operative management versus initial operative management of pancreatic injuries (30). However, pediatric patients who are initially treated non-operatively developed more frequently pseudocysts than patients treated operatively. Nevertheless, there was no difference in the length of hospital stay between operative or non-operative management for pancreatic injuries or the risk of rehospitalization (30,31). Evidence based selection criteria for patients with pancreatic injury who benefit the most from operative management are urgently needed.

The surgical approach depends on the grade of injury and includes distal pancreatectomy with splenic preservation for grade 3 injuries, spleen-sparing proximal pancreatic resection, and Roux-en-Y drainage of the distal pancreas for grade 4 injuries and lastly, the pylorus-preserving pancreaticoduodenectomy (Whipple operation) for pancreatic head transection (grade 5 injuries) (32).

Complications

Short term complications following pancreatic trauma arise within 30 days after the injury and include inter alia pancreatic pseudocysts and infection. On the long term, formation of ductal stricture and development of exocrine and endocrine pancreas insufficiency can be witnessed (6).

Figure 2.



Short term complications

A pancreatic pseudocyst can be defined as an organized fluid collection in the pancreas. High initial serum levels of amylase and persistent elevated serum amylase levels 10 days after the trauma are associated with the development of pancreatic pseudocysts (12,33).

The majority of these pseudocysts require drainage because of persistent symptoms or the presence of complications (infection, gastric outlet obstruction, bleeding) (34). Three different strategies for the draining of pancreatic pseudocysts are available: endoscopic drainage, percutaneous drainage, or open surgery. The assessment of pancreatic ductal anatomy is useful for the selection of patients requiring percutaneous drainage. Since there is a higher risk of complications (like pancreatic fistula formation) in adults when performing percutaneous drainage in case of cyst-duct communication (35).

Asymptomatic pseudocysts can be safely followed up with US, irrespective of the size and duration of the collection (36). A retrospective study showed a spontaneous disappearing of these pseudocysts in nine of the eleven asymptomatic children within 1-15 months after the episode of acute pancreatitis, with a median pseudocyst size of 6.4 cm (34).

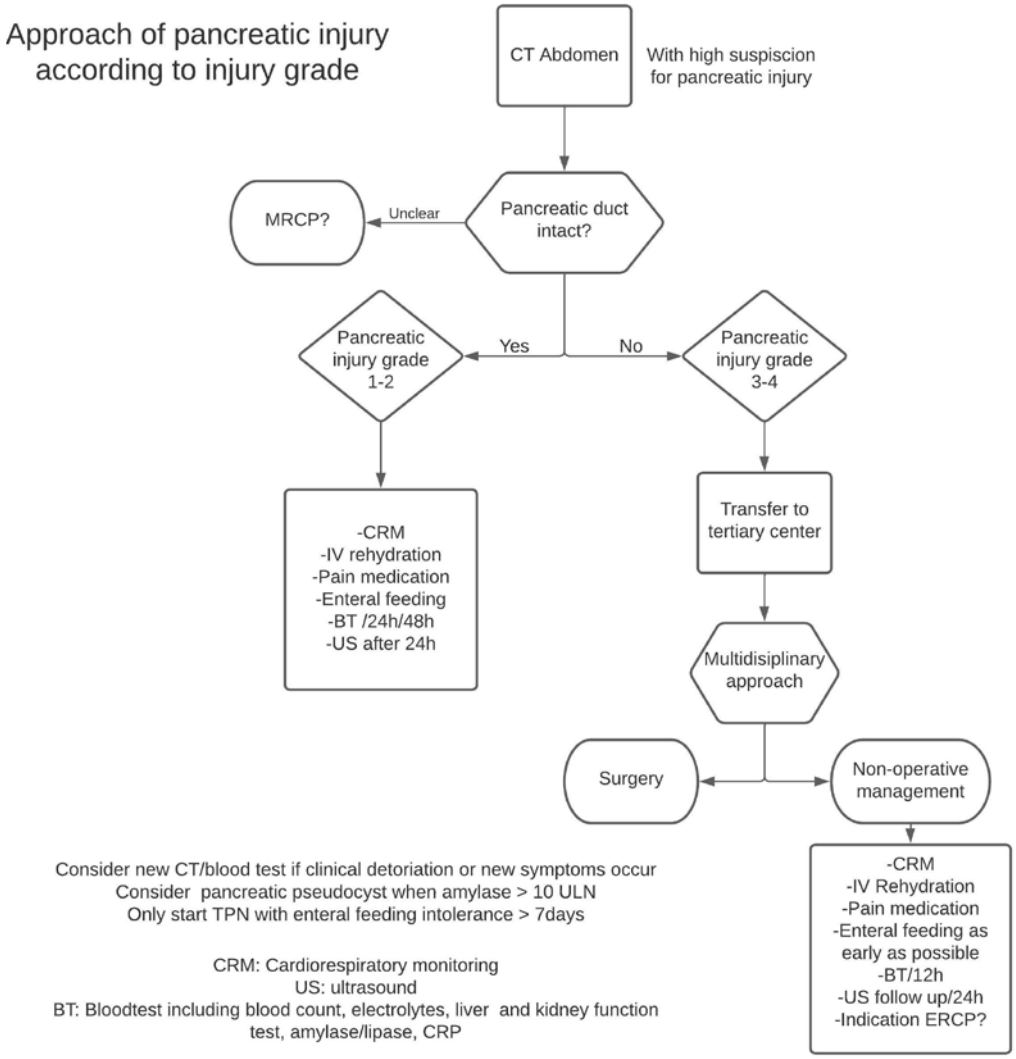
Long term complications

Ravindranath et al. described long term sequelae of pancreatic trauma in 13 of the 36 studied children on follow up imaging, such as signs of chronic pancreatitis with atrophy of the pancreatic body and tail. Only 46% of the studied patients with radiological changes developed symptoms of chronic pancreatitis such as recurrent epigastric pain (7). The clinical relevance of these radiological changes after traumatic pancreas injury without symptoms remains unclear. Further research and follow up is therefore needed.

Data on the prevalence of endocrine or exocrine insufficiency after pancreatic trauma in children is limited by only three studies. A case cohort study describing the long term outcome of non-operative management of complete pancreatic transection in nine pediatric patients revealed no exocrine or endocrine insufficiency after a median follow up of 47 months (37). Ravindranath et al. followed 13 children with radiological evidence of long term sequelae of pancreatic trauma and found that two pediatric patients developed prediabetes (based on HbA1C) and three exocrine pancreatic insufficiency (7). One additional patient of eight years developed diabetes mellitus and pancreatic atrophy three years after a blunt pancreatic injury (38). Of note, this patient had a genetically susceptibility to develop type 1 diabetes based on the human leucocyte antigen genotype (38).

Therefore, the underlying pathogenesis of this glucose intolerance in children after blunt pancreatic injury remains unclear and could be due to loss of beta cell mass, genetic susceptibility, or environmental

Figure 3.



factors. In adults, impaired glucose tolerance was seen after a loss of 65% of beta cell mass of the pancreas after pancreatic surgery for both tumors or trauma (39). The exact timing of development of these long term complications after pancreatic injury in children is unclear because of the lack of long term data.

Discussion and conclusion

The accurate and timely diagnosis of pancreatic injury or traumatic pancreatitis after blunt abdominal injury is important to determine the best treatment options. A high index of suspicion for pancreatic injuries is needed for all pediatric patients with blunt abdominal injuries, such as handlebar injuries or motor vehicle accidents. Diagnosis is made based on a combination of laboratory findings and radiological imaging. Serum amylase and lipase should be measured more than 6 hours after the injury to be representative. Normal levels after that timeframe have a high specificity. Ultrasound is a good screening tool in the work up of a trauma patient but, most of the time, not diagnostic for pancreatic injury. CT scan of the abdomen with intravenous contrast is a rapid, easily available test and the primary imaging modality of choice for evaluating pediatric patients with blunt abdominal trauma that can also assess the integrity of the pancreatic duct. Keeping in mind that within 24 hours after the injury, these results could be false negative. When duct integrity is unclear after CT scan, MRCP should be considered.

The optimal strategy for the diagnosis and management of pancreatic trauma among children continues to be a source of controversy due to absence of randomized controlled trials. In addition, a large variation in management strategies exists, making it difficult to compare outcomes and adverse events between operative management or non-operative management.

Based on the available evidence, we can propose recommendations for practical use in a pediatric care setting (figure 2 and 3). Pancreatic injuries grade 1 or 2 can be treated conservatively, while injuries grade 3 to 5 should be referred to a specialized pancreatic surgeon and pediatric gastroenterologist for a multidisciplinary approach.

Non-operative management consist of cardiorespiratory monitoring, rehydration with intravenous fluid and pain medication. The early use of PN has no benefit in the non-operative management of blunt pancreatic trauma and should be avoided unless prolonged oral feeding intolerance (> 7 days) occurs.

Early surgical treatment is recommended for hemodynamic unstable patients. However, evidence-based selection criteria for patients with pancreatic injury that benefit most from operative management are lacking. This choice will often depend on the expertise of the treatment center with pancreatic surgery or endoscopic techniques.

Only symptomatic pseudocyst require treatment and asymptomatic pseudocysts can be safely followed up with ultrasound, irrespective of the size and duration of the collection.

The long-term outcome of pancreatic injuries in children regarding the risk of development of diabetes mellitus or exocrine pancreatic insufficiency remains unknown. More prospective trials and research initiatives are required. Until more data becomes available, we propose a high index of suspicion in the follow up of these patients with check up every two months with ultrasound and blood test until pseudocyst disappears and every two year thereafter with closely follow-up of biometrics of the patients and measurement of HbA1C and fecal elastase every two year or sooner in case of complaints.

Conflict of interest

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

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

who will?

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

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

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

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep 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, ATC code: 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. coli*cellen door recombinantDNAtechnologie [2]Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3]NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **THERAPEUTISCHE INDICATIES** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **DOSERING EN WIJZE VAN TOEDIENING** Dosering **Tabel 1. Samenvatting van de dosering Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden [a] Primaire immunisatie:** Drie doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c] • **Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden [a] Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c] • **Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c] • **Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c] • **Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar: Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] • **Leeftijd bij eerste dosis: Adolescenten (11 jaar of ouder) en volwassenen*: Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] [a]De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b]In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c]Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d]Zie rubriek 5.1 van de volledige SPK. *Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **CONTRAINDICATIES** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **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 immunosuppressieve 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 vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Bloed- en lymfestelselaandoeningen Niet bekend: lymfadenopathie Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (vanaf 11 jaar en ouder) en volwassenen** Bloed- en lymfestelselaandoeningen Niet bekend: lymfadenopathie Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen Zeer vaak: misselijkheid Huid en onderhuidaandoeningen Niet bekend: huiduitslag Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten Afdeling Vigilantie Postbus 97 1000 Brussel Madou Website: **www.eenbijwerkingmelden.be** e-mail: **adr@fagg.be** **Luxembourg** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé Site internet : **www.guichet.lu/pharmacovigilance** **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** 09/2022 (v14) **AFLEVERINGSWIJZE** Op medisch voorschrift. **References: 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. 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Diagnosis and management of Helicobacter pylori infection in children

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Keywords

Helicobacter pylori; child; diagnosis; treatment.

Abstract

The prevalence of infections with Helicobacter pylori is declining in industrialized countries, yet a significant percentage of children still test positive. Although infection usually occurs in childhood, H. Pylori infection in children differs significantly from infection in adults with respect to clinical presentation, treatment strategy and antibiotic resistance. Because of all these differences, guidelines also differ substantially between children and adults.

Based on the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/ NASPGHAN) guidelines, this article aims to guide the pediatrician when and how to test for H. pylori infection and discusses treatment options.

Given the lack of symptomatic improvement after treating H. pylori in the absence of gastric erosions and ulcers and the rising rate of antibiotic resistance worldwide, the joint European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines were updated in 2017. The society states that the primary goal of testing for H. pylori in children is to find the underlying cause of abdominal symptoms and that eradication therapy is only recommended in patients with confirmed peptic ulcer disease. Furthermore, anti-H. pylori therapy should be tailored accordingly after antimicrobial susceptibility testing and the outcome of the treatment should be assessed at least 4 weeks after completion, using non-invasive tests such as the 13C-breath test or the fecal antigen test.

Introduction

Helicobacter pylori is a gram-negative spiral bacterium with several characteristics that allow it to colonize and survive the acidic conditions of the human stomach (1). Although the gastric mucosa is well protected against most bacterial infections, *H. pylori* is able to enter into the mucus, attach to epithelial cells and evade the immune response, which makes it suited for persistent living in this harsh gastric environment (2, 3). Infection is acquired by oral ingestion of the organism, mainly transmitted within families in early childhood by saliva, vomitus or feces (4).

The clinical outcomes of infection are highly variable, resulting from a combination of bacterial characteristics, host genetics and environment (5, 6). Many patients do not experience any symptoms, but damage to the gastric mucosa caused by *H. pylori* can lead to chronic gastritis which can eventually evolve into peptic ulcer disease (PUD) (2, 3, 6).

The World Health Organization has classified *H. pylori* as a group 1 carcinogen as large epidemiologic data suggest a strong association between the bacterium on the one hand and gastric adenocarcinoma on the other hand (3, 7, 8, 9, 10). Another neoplastic disease due to chronic infection with *H. pylori* is gastric mucosa-associated lymphoid tissue (MALT) lymphoma, though this condition is much less common than PUD or gastric carcinoma (2). Finally there are some extra-intestinal conditions that have also been associated with *H. pylori* infection such as refractory iron deficiency anemia (rIDA) and chronic immune thrombocytopenia (cITP) (5, 8, 11).

Children and adolescents develop these complications much less frequently compared to adults (1, 12). A different immune response to the infection may be a possible explanation. Compared with *H. pylori*-infected adults, studies in infected children show an increased number of local immunosuppressive T regulatory (Treg) cells and anti-inflammatory IL-10, along with a reduced gastric pathology , suggesting that these Treg cells cause a decrease of inflammation and ulceration induced by *H. pylori* (13, 14).

Epidemiology

Over recent decades, the rate of acquisition of *H. pylori* has significantly decreased in developed countries (3, 10, 15). While the overall global prevalence of *H. pylori* infection in children is still estimated at 32.3% (16, 17), epidemiology varies greatly among countries and even among population groups within the same country (3, 15).

A study of 509 Belgian, asymptomatic schoolchildren between the age of 12 and 25 years old in 2010-2011 confirms the latter. By means of a 13C-breath test, the authors showed a very diverse distribution of *H. pylori* infection in our country. The general prevalence is 11%, but in children born in Belgium with Belgian born parents prevalence was only 3,2%. This is in contrast with infection rates rising up to 30% if one or two parents originated from high prevalence countries (prevalence is highest in Africa (70,1%), South America (69,4%) and Western Asia (66,6%)) and even increasing to 60% in children who migrated after birth from a high prevalence country (18).

Further *H. pylori* prevalence studies are needed in the subgroup of symptomatic Belgian children with dyspepsia who have parents originating from a high prevalence country.

In addition to country of parental origin, other associated risk factors are lower socioeconomic status, household crowding, lower parental

education, mental disability, living in a rural area with poor hygiene and sanitation, lack of running water etc. (4, 15, 16).

Diagnosis

Routine testing for *H. pylori* infection is not considered appropriate since the vast majority of pediatric patients are asymptomatic and do not have any related clinical disease, except for some microscopic gastric inflammation (7, 9, 12, 16).

In general, treatment to eliminate *H. pylori* infection outside the context of confirmed PUD, is not expected to improve abdominal symptoms in children. This results in the current European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN/ NASPGHAN) guidelines recommending to only undertake (invasive) diagnostic testing for *H. pylori* if peptic lesions are clinically suspected (e.g. epigastric pain during/short after the meal, nocturnal abdominal pain, refractory iron deficiency anemia) or identified by endoscopy (12). An overview of the indications for screening for *H. pylori* (and treatment in confirmed cases) is shown in Table 1.

Table 1: Indications for testing for *H. pylori* infection, according to ESPGHAN/NASPGHAN Guidelines.

Diagnosis of gastric or duodenal erosions/ulcer
Suspicion of PUD in case of dyspeptic complaints (epigastric pain related to meals) and/or nocturnal pain Following extra-intestinal conditions:
• **Diagnosis of gastric or duodenal erosions/ulcer** - Refractory iron deficiency anemia - Chronic immune thrombocytopenic purpura
• **Testing not indicated in the following indications:** - Asymptomatic patients - Chronic (functional) abdominal pain - Gastro-esophageal reflux - First-degree relative with gastric cancer

The threshold for suspicion and testing is lower for immigrant children with one or more parents originating from high prevalence countries.

There are different possibilities to test for the presence of *H. pylori* in children:

13C-breath test

For children older than 6 years, the 13C-breath test can be used to demonstrate the presence of *H. pylori* in the gastric mucosa, relying on the bacteria's high urease activity (an enzyme needed to colonize the acidic environment of the stomach) (12). The test involves drinking 13C-labeled urea which is hydrolyzed to ammonia and bicarbonate. After absorption and diffusion into the blood, the labeled bicarbonate is excreted as CO2 via the lungs and can be measured in the expired breath sample and compared with a baseline value. The 13C-breath test has an excellent sensitivity and specificity for detecting the presence of *H. pylori* in older children, both exceeding 95% (1, 4, 8). Moreover, it is simple to execute and has an excellent safety profile (6).

Fecal antigen test

The lower specificity of the breath test in children younger than 6 years, makes the test not preferable for this age group. A fecal antigen test can be considered as a reliable and simple alternative. The test measures stool excreted *H. pylori* antigen with an enzyme-linked immunosorbent assay (ELISA). A mixture of monoclonal antibodies against *H. pylori* is added to the feces sample, whereafter all the non-binding antibodies are washed away. In the presence of antigen-antibody complexes a chemical reaction will identify the presence of *H. pylori* (8, 9, 12). The fecal antigen test also has a sensitivity and specificity of more than 92% (8,12) and its low cost, ease of use and sample collection at home have made this method increasingly widespread (6).

Endoscopy

Although the non-invasive 13C-breath test and fecal antigen test are commonly used to detect *H. pylori* infection, the gold standard for the diagnosis of *H. pylori* remains the gastroscopy.

In line with the above fact that *H. pylori* infection is not expected to give rise to symptoms in the absence of PUD an upper endoscopy rather than noninvasive testing for *H. pylori* should be performed to determine the underlying cause of the symptoms (12, 16).

Initial diagnosis of the infection is based on culture or histopathology along with one other positive biopsy-based test. During the gastroscopy at least six biopsies should be taken: four biopsies should be obtained from the antrum (two for the histopathological evaluation, one for culture (if available) and at least one for any additional diagnostic tests (e.g. rapid-urease or molecular-based assays)) and three biopsies from the corpus (two for the histopathological evaluation and one for culture (if available)) (12). Complications of this gastroscopy with biopsies are rare and generally reversible, but reaction to anesthesia, hypoxia, perforation or bleeding cannot be ruled out and should be discussed with patients and parents before obtaining informed consent for endoscopy (2).

Importantly, although they are not effective antimicrobial agents, proton pump inhibitors (PPIs) have suppressive effects on *H. pylori* and may give rise to false-negative results. Therefore PPIs should ideally be discontinued two weeks before testing for infection, while antibiotics should be stopped four weeks before testing (9, 12).

Other

Guidelines recommend against serologic testing for *H. pylori* (in serum, whole blood, saliva and urine) in the clinical setting as these tests do not distinguish between past or ongoing infection with *H. pylori*, neither to determine whether the eradication was successful (4, 8, 9, 12, 16).

Management

Because of increasing antimicrobial resistance worldwide, treatment following confirmation of symptomatic *H. pylori* infection should be tailored according to antibiotic resistance profiles (table 2) (11, 12, 16). Moreover, doctors should discuss therapy-related adverse effects (mostly minor, but still relatively frequent), set realistic expectations for clinical symptomatic improvement and emphasize the importance of strict adherence to the anti *H. pylori* therapy which is critical for a successful eradication of the infection (2, 12).

Various drug regimens can be used to eradicate *H. pylori*. Most are based on two antibiotics plus a proton pump inhibitor or a bismuth preparation, always for a duration of 14 days. In patients with a penicillin allergy, metronidazole should be used instead of amoxicillin, if the strain is susceptible to clarithromycin and to metronidazole. In case of clarithromycin resistance however, bismuth-based therapy with tetracycline in place of amoxicillin can be an alternative in children above the age of 8 years (12, 16).

A shorter duration than recommended or the use of a single antibiotic reduces the effectiveness of eradication therapy (2).

Adding supplemental probiotic therapy to the treatment with the aim of reducing adverse effects, which in turn could lead to increased adherence is still under debate and additional pediatric studies are needed to develop more reliable conclusions (12).

Table 2: Standard treatment and dosing regimens – 14 days.

Drug	Bodyweight range	Morning dose, mg	Evening dose, mg
Susceptible to clarithromycin			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	500	500
	25-34 kg	750	750
	≥35 kg	1000	1000
Clarithromycin	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500
Resistant to clarithromycin, susceptible to metronidazole			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	500	500
	25-34 kg	750	750
	≥35 kg	1000	1000
Metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500
Unknown susceptibility or resistant to clarithromycin and metronidazole[2]			
PPI[1]	15-24 kg	20	20
	25-34 kg	30	30
	≥35 kg	40	40
Amoxicillin	15-24 kg	750	750
	25-34 kg	1000	1000
	≥35 kg	1500	1500
Metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	≥35 kg	500	500

1. Doses are based on omeprazole and esomeprazole. Doses of different PPIs are not equivalent.

2. Alternative bismuth-based therapy:

For children younger than 8 years: bismuth plus standard triple therapy (PPI, amoxicillin, metronidazole);
in children older than 8 years: bismuth plus PPI, metronidazole and tetracycline.
Dosing of Bismuth subsalicylate: if younger than 10 years, 262 mg 4 times a day; if 10 years or older, 542 mg 4 times a day.

Based on 'Helicobacter pylori in Pediatric Patients' (Korotkaya et al. 2020)

The treatment necessity, in case of incidental histopathologic finding of *H. pylori*-associated gastritis during an endoscopy performed for unrelated indications such as the diagnosis of celiac disease or inflammatory bowel disease, without the presence of PUD, is less clear. The patient and family should be explained that *H. pylori* gastritis without PUD rarely causes symptoms nor progresses to more serious disease complications during childhood. The benefits and risks of treatment and the adverse effects (generally abdominal pain, nausea, diarrhea and antibiotic resistance) should also be discussed in order to come to a treatment decision together (2, 12).

Follow-up

Since the relief of symptoms is not an indicator for successful treatment, confirmation of eradication should be performed in all children treated for *H. pylori* with a reliable (noninvasive) test (5, 12), being either the 13C-breath test or the fecal antigen test (see diagnosis).

Gastric acid suppressing medication or antibiotic treatment will increase the false-negative results of both the breath test and the fecal antigen test (8). Therefore, testing for eradication should be performed at least four weeks after completion of the eradication therapy with PPI and antibiotics (12).

Finally, there is no evidence to infer that testing (and treating) family members of *H. pylori*-infected children reduces the risk of reinfection (4, 12).

Conflict of interest

There is no conflict of interest to disclose.

Flowchart

See figure.

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Recurrent oral aphthosis as the solitary clinical manifestation of Crohn's disease in children: a case report

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Keywords

Aphthosis; Crohn's disease; intermittent abdominal pain; calprotectin.

Abstract

Crohn's disease is a chronic inflammatory bowel disease that affects the digestive tract, where the clinical presentation highly depends on disease localisation. The majority of patients typically present with (bloody) diarrhoea, abdominal pain, weight loss and growth impairment. We describe an atypical case of a nine-year-old boy with chronic aphthosis for more than one year as sole manifestation of Crohn's disease, without other gastrointestinal symptoms, beside intermittent abdominal pain. Even in the absence of biochemical signs of inflammation and negative calprotectin, further investigations are warrant if oral lesions are persistent, deep with a more atypical

Introduction

Crohn's disease (CD) is a chronic, inflammatory, panenteric gastrointestinal disorder (1). It has a prevalence of 0.3% in Europe, with an expected increase over the next decades (1). CD is primarily diagnosed in young adults, but up to 25% of patients developed symptoms in childhood (1). Patients typically present with gastrointestinal complaints, such as abdominal pain, chronic diarrhoea with or without bloody stools, and weight loss (1). Since CD is a panenteric disease, patients can also present with upper gastrointestinal symptoms including oral lesions (1). Oral manifestations of CD are prevalent (7-40%) and comprise a spectrum of different types of lesions (2, 3). Some oral manifestations have typical clinical and/or histologic characteristics related to CD, such as cobblestoning of the mucosa, granulomatous cheilitis, mucogingivitis, linear ulcerations or mucosal tags (2-4). Whereas aphthous stomatitis (2), the most prevalent oral manifestation of CD in children, is related to a variety of disorders and thus not specific to CD (2, 6). Diagnosing CD can prove challenging when children present with oral lesions without gastrointestinal symptoms, leading to physicians' delay in treating CD and subsequent patient burden.

We present a case of a nine-year-old boy diagnosed with oral lesions as the sole clinical manifestation of CD.

Case

A nine-year-old boy initially presented at a secondary care centre with recurrent oral aphthosis and mucosal swelling resulting in anorexia for several weeks (figure 1,2). Occasionally there were complaints of abdominal pain, nonetheless, this was not a source of significant discomfort. His bowel movement pattern was normal with a tendency to constipation. There were no other gastrointestinal symptoms, nor extraintestinal manifestations (fever, joint pain, uveitis, skin lesion). Clinical examination revealed deep and linear aphthous stomatitis of the tongue, soft palate, and buccal mucosa (figure 1). There were no other clinical abnormalities with a height between the 50-75 percentile (131.5cm) and a weight between the 25-50 percentile (24.5kg). He had no known medical history or recent medical therapy and his familial history for chronic diseases was negative. Biochemical evaluation was performed and revealed no haematological abnormalities or signs of inflammation (normal white blood cell count of 9.0 x103/uL, neutrophil count (58%)), C-reactive protein of 3mg/L [N < 5mg/L]and slightly elevated sedimentation (34mm/h [N <20 mm/h]). There was a low iron status with a ferritin of 50ug/L [N ≥30 - ≤400µg/L] and a transferrin saturation of 14% [N ≥16 - ≤45%] (transferrin 2.3g/L [N ≥2.00 - ≤3.60g/L]), without other signs of nutritional deficiencies (including zinc). Both IgM and IgG for herpes simplex and cytomegalovirus were negative. Antinuclear and anti-neutrophil cytoplasmic antibodies testing were negative. IgA anti-tissue transglutaminase was negative and faecal calprotectin was within the normal range (41 µg/g). There was no occult blood in the faeces sample and stool cultures were negative.

Since the patient had no obvious evidence of underlying infection, gastrointestinal disease, or auto-immune disorder, he was referred for further stomatological evaluation with the advice to continue local therapy and to start iron suppletion. Despite seeking medical treatment in several centra for more than one year the lesions persisted and were even more severe than initial, resulting in weight loss. Eventually, a biopsy of an ulcerative lesion of the tongue was taken. Histology showed severe acute on chronic inflammation with deep granulomatous ulceration. Since histological findings could be associated with oral CD, he was referred to a tertiary centre. At that time, he had continuous severe oral pain which led to anorexia and weight loss, where the weight dropped to the 10th percentile and height to the 50th percentile.

The patient was admitted for further evaluation. Clinical examination shows oral aphthosis on the tongue and the lower lip. Further clinical examination was completely normal without abdominal tenderness, peri-anal disease or skin lesions. Ultrasound of the abdomen showed wall thickening in the terminal ileum and proximal third of the colon ascendens. Upper gastrointestinal endoscopy showed haemorrhagic gastritis with small aphthous ulcers without oesophageal or duodenal abnormalities. Colonoscopy revealed inflammation of the caecum

Table 1: Differential diagnosis oral aphthosis.

Differential diagnosis oral aphthosis	
Recurrent aphthous stomatitis	Superficial, small, white aphthosis. Duration +/- 2 weeks (5,6)
Infections	Herpes simplex virus, varicella zoster virus, coxsackie virus human immunodeficiency virus, Treponema pallidum, Mycobacterium tuberculosis, Yersinia enterocolitica, Helicobacter pylori, leishmaniasis (7,8)
Deficiencies	Zinc, iron, folic acid, vitamin deficiency (6)
Drugs	Nonsteroidal anti-inflammatory drugs, beta-blockers, immunosuppressive drugs, or chemotherapy Stevens-Johnson syndrome or toxic epidermal necrolysis (6)
Periodic fever syndromes	Periodic fever with aphthous stomatitis, pharyngitis, and adenitis syndrome (6,7)
	Cyclic neutropenia (6,7)
	Mouth and genital ulcers with inflamed cartilage syndrome (6,7)
Auto-immune disorders	Systemic lupus erythematosus (hard palate) (6,7)
	Behçet syndrome (6,7)
	Lichen planus (tongue) (6,7)
	Mucous membrane pemphigoid, pemphigus vulgaris, bullous pemphigoid (6,7)
Gastro-intestinal disorders	Inflammatory bowel diseases (2,3)
	Coeliac disease (6)

with deep ulcerations, including the ileocecal valve, confirming the diagnosis of CD. He received induction therapy with corticosteroids, and azathioprine was given as maintenance therapy. Rapid response was seen, however, lesions reoccurred one week after stopping corticosteroid therapy. Step-up therapy with infliximab, an anti-tumour-necrosis-factor-alfa (anti-TNF-α), was associated and the patient again achieved clinical remission. After six months of anti-TNF-α therapy, upper and lower endoscopy showed no macroscopic abnormalities with normal random biopsies of the gastrointestinal tract. Anti-TNF-alfa monotherapy was continued effectively without any flares for four years. This work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent of patient and legal guardians were obtained.

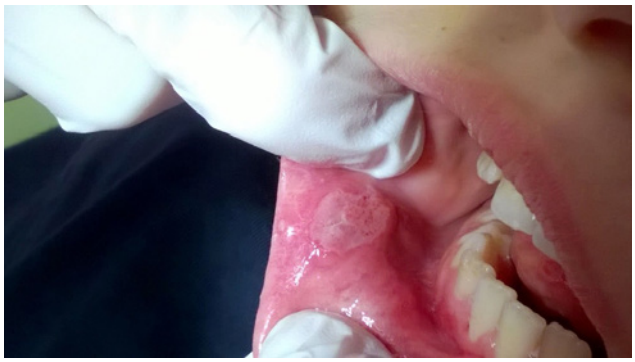
Discussion

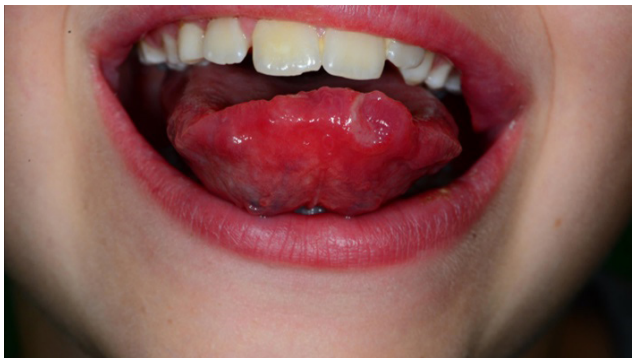
Aphthous stomatitis is a clinically prevalent yet unspecific symptom of multiple diseases, therefore, identifying the potential underlying condition can prove challenging in clinical practice (5). In this report, we presented the case of a nine-year-old boy with recurrent oral aphthous stomatitis with underlying CD without gastrointestinal symptoms or biochemical abnormalities associated with CD.

Recurrent ulcerative aphthous stomatitis is associated with several diseases (see table 1), medication use or trauma / dental appliances. Most common drugs inducing oral aphthosis are nonsteroidal anti-inflammatory drugs, beta-blockers and immunosuppressive drugs (2,3,6-8). Ulcerative lesions can be of infectious origin, wherein herpes simplex, varicella zoster, Epstein-Barr virus, coxsackie virus or cytomegalovirus infection are the most prevalent in children (7, 8). However, in immunocompetent children, they are self-limiting (7). Nutritional deficiencies, being vitamin deficiencies (B1, B2, B6 and B12) or iron, zinc and folic acid deficiencies are associated with oral aphthosis (6). Yet, nutritional deficiencies themselves can also be an expression of underlying diseases related to aphthosis, such as coeliac disease (6). Aphthosis can also present with recurrent fever, such as in cyclic neutropenia, MAGIC (mouth and genital ulcers with inflamed cartilage) or PFAPA (periodic fever with aphthous stomatitis, pharyngitis and adenitis) syndrome or other auto-immune disorders (systemic lupus erythematosus, lichen planus, or Bechet syndrome) (6, 7). However, when patients present with oral aphthosis related to aforementioned conditions, this is frequently accompanied by systemic symptoms (6).

Aphthosis is a relatively common finding in patients with CD, but often clinically underestimated. The prevalence of oral aphthosis varies

Figure 1 & 2: oral aphthosis on buccal mucosa and tongue in our patient





significantly across different cohorts, namely between 3-42% (3). In CD oral ulcerations are often larger, deeper, and more irregularly or linearly shaped than benign aphthous ulcers, which are typically round or oval-shaped (9-11). Oral lesions in CD also appear more often on the gums, lips, tongue, or palate, while benign aphthous ulcers usually occur on the inside of the cheeks or lips. In addition, these lesions tend to persist longer than benign aphthous ulcers, which usually heal within a week or two. Nevertheless, they can be difficult to differentiate clinically with other causes of aphthous stomatitis (10). Histologically aphthous ulcers associated with CD differ primarily from other causes of aphthosis based on the presence of granulomatosis (6). Therefore, a biopsy should be considered in patients with recurrent ulcerative aphthous stomatitis of unknown origin (12). If granulomatous aphthosis is diagnosed, gastrointestinal endoscopy should always be performed, even when patients present without other clinical symptoms or biochemical evidence of CD. Combining topical and systemic treatments is warranted for effectively treating these oral CD lesions.

These oral lesions are part of a broader upper gastrointestinal manifestation of CD. Upper gastrointestinal manifestations are more prevalent in paediatric than in adult CD patients with a male sex predominance (ratio of 1.2:1) and has been described in up to 9% of patients as the sole manifestation of CD (2). Upper gastrointestinal involvement can precede intestinal symptoms, be present at diagnosis or may develop during the disease course (6). Diagnosis could be more difficult as faecal calprotectin can remain strictly negative (1). Nevertheless, the upper gastrointestinal involvement of CD should not be overlooked, as it can result in serious complications such as gastric outlet obstruction depending on the localisation.

Conclusion

To enable early diagnosis and improve the quality of life for patients, paediatricians and dentists must seriously consider that the presence of oral manifestations may precede or follow intestinal symptoms of CD. Persistent aphthous stomatitis should always warrant further investigation, especially if the lesions are deep and atypical. Endoscopy with biopsies should be considered if its cause remains unknown to diagnose or dismiss CD despite negative biochemical evaluation, even in the absence of other gastrointestinal symptoms.

Conflict of interest

Authors declare no conflict of interest.

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Aicardi Syndrome, a case report

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Keywords

Aicardi syndrome ; epileptic spasms ; case report.

Abstract

Aicardi syndrome is a very rare neurological condition caused by an unknown de novo mutation on the X-chromosome. The diagnostic triad is composed of infantile spasms, agenesis of the corpus callosum and chorioretinal lacunae but it can present with more additional neurological and physical manifestations. Epileptic spasms are often the first clinical presentation of a girl with Aicardi syndrome. Due to a wide range of aetiologies in epileptic spasms, identifying a rare cause is not always easy. This case report describes the clinical and imaging characteristics of an uncommon presentation of infantile spasms, Aicardi syndrome.

Case report

A four-month-old girl presented to the emergency department with sudden onset of focal motor seizures. One day before, her mother had noted frequent twitches of the left corner of the mouth and eye deviation to the left. Pregnancy and birth were unremarkable, she had a normal neurological development so far and family history was negative for any neurological disorder. Initial clinical examination was unremarkable, so she was admitted to the hospital for observation. During admission there was an increase in seizure frequency with the occurrence of focal seizures with posturing of the right arm and brief eye deviation to the left. After one day a new seizure type was observed with clusters of brief bilateral arm extensions, consistent with epileptic spasms.

As she developed fever during admission an extensive workup was performed to rule out infection. Blood analysis, urine analysis and lumbar puncture were normal. In addition, a metabolic screening on urine and blood was negative. A short electroencephalogram (EEG) taken the day after admission showed rare isolated centrotemporal spikes on the left side without any evidence of hypsarrhythmia. There were no epileptic seizures during the registration. Magnetic resonance imaging (MRI) of the brain showed an agenesis of the corpus callosum with interhemispheric cysts, grey matter heterotopias, abnormal white matter myelination (figure 1) and a nonspecific cyst in the right cerebellar tonsil. Screening for infection with toxoplasmosis or cytomegalovirus was negative.

Levetiracetam was started and progressively increased because of increasing focal seizure frequency. Unfortunately, there was no clinical improvement and phenobarbital was given once intravenously. As the seizures evolved to flexor spasms, vigabatrin was associated as a third antiepileptic drug.

Given the increasing seizure frequency despite therapy, the patient was referred to a university hospital for further investigation and treatment.

Repeated EEGs showed multifocal spikes with evolution to hypsarrhythmia, and a permanent asymmetry in the background. The left hemisphere showed a burst-suppression pattern and the right hemisphere multifocal epileptic activity maximally posterior temporal with slow onset (figure 2).

Figure 1: A. Agenesis corpus callosum; B. Heterotopia of the grey matter; C. Interhemispheric cysts; D. Abnormal white matter myelination.

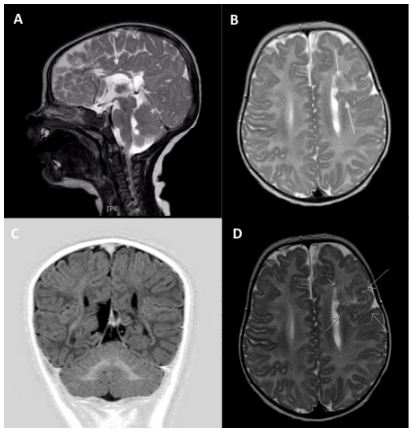
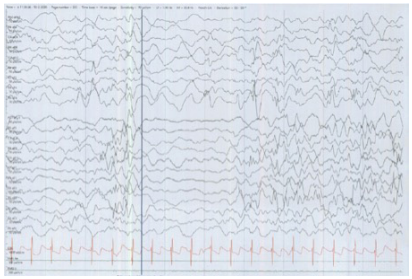
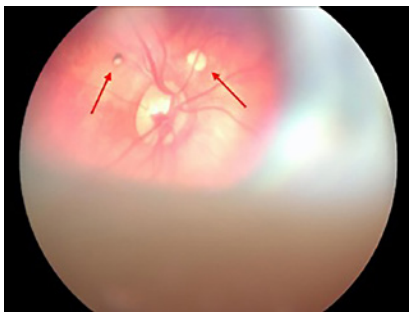


Figure 2: The right hemisphere is represented by the first nine leads, showing rather a multifocal appearance of epileptic activity and slow firing temporally. The left hemisphere is represented by the lower leads, showing rather a burst-suppression pattern (indicated by the vertical line).



There was a high suspicion of Aicardi syndrome, given the female sex, infantile spasms and agenesis of the corpus callosum. In addition, fundoscopy revealed multiple chorioretinal lacunae with peripapillary pigmentation on the right side (figure 3). This pathognomonic sign confirmed the tentative diagnosis of Aicardi syndrome. An X-ray of the dorsal spine was normal.

Figure 3: Fundoscopy of the right eye shows chorioretinal lacunae (arrows).



Consequently, levetiracetam and vigabatrin were increased, and prednisolone was associated. Unfortunately, this was without any improvement and levetiracetam was changed to topiramate for a better seizure control.

Micro-array was negative and a genetic panel for cortical dysplasia showed that the girl was heterozygous for a variant of unknown significance in the *COL18A1* gene, located at chromosome 21. This variant follows an autosomal recessive inheritance pattern. No second variant could be observed in this gene. Consequently, the presence of this variant is probably a coincidental finding.

Discussion

Aicardi syndrome is a rare neurodevelopmental disorder and often presents with epileptic spasms.

It occurs almost exclusively in girls. The presentation is characterised by a typical triad of corpus callosum agenesis, central chorioretinal lacunae and infantile spasms. As more affected individuals have been identified, it has become clear that other neurological and systemic anomalies are also possible. This syndrome occurs in 1 in 100,000 newborns in the US and 1 in 93,000 newborns in the Netherlands. Unfortunately, Belgian numbers are lacking. The prognosis of children with Aicardi is poor and they often have a severe global development delay with refractory epilepsy (1–3).

Children with Aicardi syndrome can present with characteristic facial features such as a prominent premaxilla, tip-tilted nose, small angle of the nose bridge and sparse lateral eyebrows (1,4). Nonetheless, Jean Aicardi stated that dysmorphism was unusual and did not occur in his patients (5).

In the initial phase of the disorder, infantile spasms may pass unnoticed and might be overlooked by parents (4). The average age for presentation in girls with Aicardi Syndrome is 3-4 months. But, as well in this case report, the spasms associated with Aicardi syndrome can be asymmetrical or unilateral, and focal seizures could be seen. Eventually, refractory epilepsy with a variety of seizure types develops over time (1,3,5).

The typical EEG pattern in West syndrome is hypsarrhythmia. But in patient with Aicardi syndrome it is often asymmetrical or absent (5). Another presentation on EEG is a split-brain with a suppression-burst pattern independently arising from the different hemispheres as seen in this case (figure 2). Evolution to a spike-wave pattern and Lennox-Gastaut syndrome is rarely seen due to the lack of certain brain structures for organisation and bilateral spread of paroxysms (1,4–6).

MRI imaging may show an agenesis of the corpus callosum and polymicrogyria as result of the reduced axonal pull on the gyri. It often presents with asymmetry of the cerebral hemispheres and intracranial cysts, of which more than half is located in the choroid plexus. In addition, other brain abnormalities are also possible, such as cortical dysplasia, heterotopia of the grey matter, anomalies of the vermis, and sometimes choroid plexus papillomas. The MRI findings can be wrongly attributed to a toxoplasmosis or cytomegalovirus infection (5,7,8).

Chorioretinal lacunae are a pathognomonic sign for Aicardi syndrome and a fundoscopy is obligatory for diagnosis. The ophthalmic findings associated with Aicardi syndrome are mostly bilateral and do not change with exception of the pigmentation, which is often located in the periphery of the lacunae and may increase with age. Other frequent ophthalmologic findings include microphthalmia and coloboma of the optic disk, also presenting with surrounding pigmentation and resembling the 'morning glory disk'. These features can lead to blindness but barely change over time (2,5). Additionally, girls with Aicardi syndrome have an increased risk of scoliosis, missing ribs and vertebral anomalies and further investigation for co-morbidities is necessary (4,5).

Genetic testing has become increasingly important in the diagnostic evaluation of children with epilepsy. However, the genetic aetiology of Aicardi syndrome is still unknown. It is hypothesised to be caused by a de novo pathogenic mutation on the X-chromosome, lethal to XY males, as most case reports involve females or XXY males (1). Recent case reports have also described male patients (46, XY karyotype) with Aicardi syndrome and one study has shown the possibility of genetic heterogeneity (9). Another recent study described a case of Aicardi syndrome with a duplication event on the X-chromosome (Xp22.33 including SHOX), which could have led to abnormal neural tissue development, but it could also be an incidental finding (10). Other studies have suggested inactivation of the X chromosome because of the variable severity and asymmetry of the phenotype, but the studies are not all consistent (11). Further research is definitely needed to better understand the underlying pathogenic mechanisms in this syndrome.

The diagnosis of Aicardi syndrome is based on the presence of the three classic symptoms. In 2005, Sutton et al. proposed modified criteria for the diagnosis Aicardi syndrome (8). The presence of two symptoms of the classic triad plus at least two other major symptoms (cortical malformations, periventricular and subcortical heterotopia, cysts around third cerebral ventricle and/or choroid plexus, or optic disc/nerve coloboma or hypoplasia) or supporting features (vertebral and rib abnormalities, microphthalmia, "split-brain" EEG, gross cerebral hemispheric asymmetry, vascular malformations or vascular malignancy) is strongly suggestive of the diagnosis of Aicardi syndrome.

Just like the diagnosis, treatment also requires a multidisciplinary management. The survival rate of patients with Aicardi is highly variable and depends on seizure control. The goal of therapy should include resolution or at least modification of hypsarrhythmia as soon as possible. Hormonal therapies and vigabatrin have the most evidence to support their use in infantile spasms. However, epilepsy is difficult to control in Aicardi syndrome and often become refractory. Kroner et al. described a survival rate of 62% at 27 years of age (2). They have often developmental delay with limited language skills and will benefit from physiotherapy with orthopaedic interventions (3,5,8).

In **conclusion**, Aicardi syndrome is a rare genetic disorder that primarily affects newborn girls, due to an unknown de novo mutation on the X-chromosome. It is characterized by the typical triad of infantile spasms, agenesis of the corpus callosum and the pathognomonic

sign of chorioretinal lacunae. Other symptoms may include different seizure types, refractory epilepsy, atypical facial features, skeletal abnormalities, developmental delay and intellectual disability. It requires a multidisciplinary approach to diagnosis and while there is no cure, treatment is focused on managing symptoms and supporting developmental and physical needs. With this case we highlight the awareness of a more infrequent presentation of epileptic spasms, Aicardi syndrome.

Disclosure of potential conflicts of interest

There were no potential conflicts of interest.

Informed consent

Informed consent was given by the mother of this patient.

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Luc's abscess as a rare complication of otitis media: a case report

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Keywords

Luc's abscess ; otitis media ; mastoiditis ; complication ; case report.

Abstract

Luc's abscess, a subperiosteal pus collection beneath the temporal muscle, is an extracranial complication of otitis media. Treatment including antibiotic therapy and abscess drainage often results in clinical improvement. Awareness of this rare complication is needed to get a prompt diagnosis and early treatment.

We describe a case of a 5-year-old boy with fever, otorrhea and a left-sided preauricular swelling. Temporal CT revealed a bilateral opacification of the mastoid bones and Luc's abscess. Unlike other case reports, abscess drainage was unsuccessful. Treatment with intravenous antibiotics and myringotomy with grummet insertion resulted in full recovery.

Case presentation

A 5-year-old boy presented to the pediatric department with fever for 2 weeks, otalgia for 1 week and a preauricular facial swelling since several hours. The maximum temperature was 39,0°C. Because of fever and cough, his general practitioner prescribed amoxicillin (50 mg/kg/d) for 4 days. One week later, left-sided otalgia developed. This was diagnosed as a left-sided acute otitis media, which was treated symptomatically by his primary care physician with analgesics and antipyretics. On the day of presentation in the pediatric department, his parents noticed a preauricular and temporal facial swelling. There was no history of trauma. His past medical history was unremarkable and his immunization status was up to date.

Physical examination revealed pharyngeal inflammation, left-sided otitis media, painful swelling in the left temporo-zygomatic region with mild erythema, left auricular protrusion and lymphadenopathy in the posterior cervical triangle (Figure 1). Facial nerve function was intact.

Figure 1: Our patient on the day of admission. Note the left preauricular and temporal swelling (red arrow).

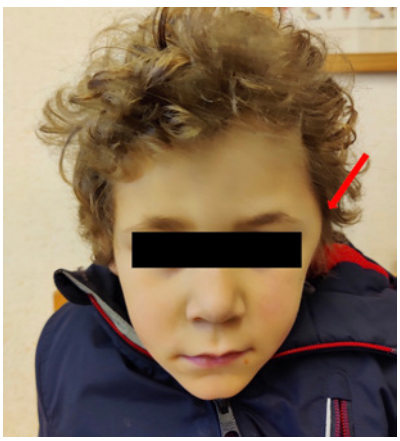
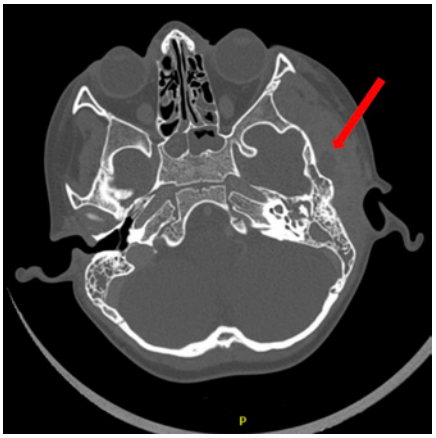


Figure 2: The Luc's abscess is seen as an extracranially purulent collection of 2 cm lateral to the left temporal bone (red arrow). There are no signs of bone destruction. Note the severe edema of the surrounding tissue.

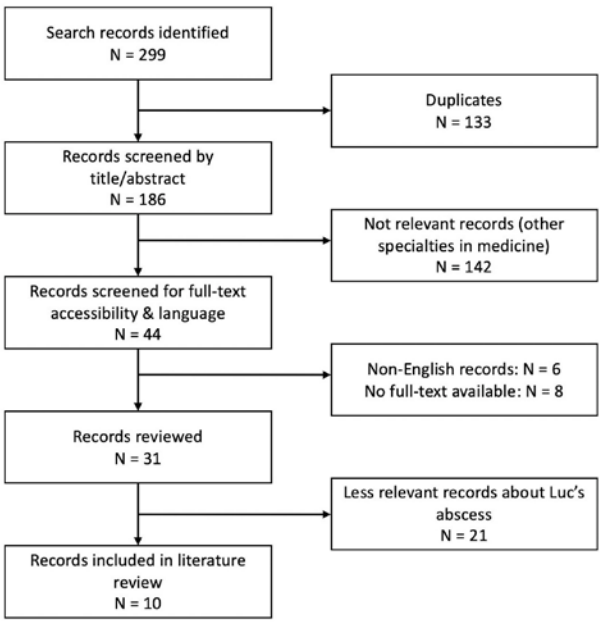


Laboratory data showed an elevated C-reactive protein of 67 mg/L (normal value: < 10 mg/L) without leukocytosis. A throat swab was taken for pharyngitis and was positive for *Streptococcus pyogenes*. Blood cultures were negative after 5 days.

Computed tomography (CT) of the brain and temporal bones showed a bilateral mastoid opacification, consistent with bilateral mastoiditis. There was no radiologic evidence of bone destruction. An extracranial purulent collection of 2 cm was noted lateral to the left temporal bone. There was a diffuse inflammatory process of the surrounding tissues in the supra-auricular region (Figure 2).

After initial laboratory and imaging studies, a diagnosis of a *Streptococcus pyogenes* pharyngitis and bilateral mastoid opacification complicated by Luc's abscess was made. After admission, the otorhinolaryngologist was consulted. Later that day, the patient underwent a bilateral myringotomy with grommet insertion. Surgical drainage of the extracranial temporal abscess was unsuccessful due to severe inflammation and edema of the surrounding soft tissues.

Figure 3: Flow chart of record screening for the literature review.



After the procedure, intravenous amoxicillin/clavulanic acid was started at a dose of 100 mg/kg per day for 7 days. Topical ciprofloxacin otic drops were given for 10 days.

Clinical improvement was noted after initiation of therapy. No fever was documented since the beginning of the hospitalization. The left temporal facial swelling slowly decreased. An audiogram revealed no hearing loss.

Repeat laboratory testing after 3 days of hospitalization showed a decrease in C-reactive protein from 67 mg/L to 40 mg/L.

After 7 days of intravenous antibiotic therapy, the patient was discharged with good clinical and biochemical improvement. Only mild preauricular swelling remained. A high dose of amoxicillin/clavulanic acid (80 mg/kg per day) was continued orally for another 3 weeks.

The child was seen for follow-up 1 week after discharge and after completion of antibiotic treatment. The preauricular swelling had significantly decreased and he no longer complained of otalgia. Because of this positive clinical evolution, imaging was not repeated.

Methods literature review

A literature search on Luc's abscess was performed using PubMed, Scopus and Cochrane Library. The following search terms were used: Luc abscess; zygomatic abscess; temporozygomatic abscess. A flow chart showing the steps of record screening is shown in Figure 3. All included records are case reports with (systematic) literature reviews.

Discussion

Otitis media is a very common disease in the pediatric population. The incidence of complications of otitis media has decreased over the years due to the widespread use of antibiotics (1, 2). However, clinicians should be aware of possible life-threatening intra- and extracranial complications. Intracranial complications include epidural abscess, subdural empyema, meningitis, encephalitis, cerebral abscess, lateral sinus thrombosis and petrous apicitis. Extracranial complications include mastoiditis, facial nerve palsy, labyrinthitis and subperiosteal abscesses, such as Luc's abscess, Bezold's abscess (a rare deep neck abscess), and zygomatic abscess (1, 3).

In 1913, Henri Luc described a subperiosteal collection under the temporal muscle of otic origin without intraosseous suppuration. Associated characteristic symptoms were transient otorrhea, supra-auricular and temporal swelling, mastoid tenderness and low-grade fever. In his article, he described a case of a 9-year-old girl with a subperiosteal abscess in whom he performed an abscess drainage and mastoidectomy. Unfortunately, he did not find any pus after opening the mastoid antrum. To raise awareness of this entity and to avoid unnecessary mastoidectomies in the future, he suggested that mastoidectomy should not be performed in the absence of clinical signs of mastoiditis, such as persistent otorrhea, retroauricular swelling, mastoid tenderness region and high fever (4).

The spread of microorganisms is thought to follow preexisting anatomical pathways. Microorganisms spread from the middle ear to the subperiosteal plane of the superior wall of the auditory meatus and to the lateral subperiosteal plane of the temporal bone to form a subperiosteal pus collection and accumulate deep beneath the temporal muscle (1, 4, 5). Since the literature suggests that most patients also have radiologic signs of mastoiditis, another possible route is through the cortex of the mastoid bone to the zygomatic root area (3, 6).

80.9% of reported cases of Luc's abscess have been in the pediatric population (3). Luc's abscess has also been reported in older people with underlying risk factors, such as drug use, diabetes, cholesteatoma and inappropriate use of antibiotics (1, 3, 7). In most cases, no risk factors have been identified (1-3).

In the original article, Henri Luc described that the subperiosteal temporal abscess was not associated with mastoid involvement (4). Since then, several case reports of patients with Luc's abscess associated with mastoiditis have been published (3, 5). A systematic review of Luc's abscess reported that almost all patients (95,2%; 20/21) had signs of mastoiditis on CT scan, with 42,8% (9/21) having clear evidence of bone erosion (3). In our patient bilateral opacification of the mastoid bones was diagnosed on CT scan, suggesting the presence of bilateral mastoiditis, but no bone destruction was seen.

Because Luc's abscess is relatively unknown, its diagnosis is often delayed. However, a timely diagnosis is necessary to initiate early treatment and to prevent the development of other complications (8).

The characteristic symptoms of Luc's abscess can help to raise the suspicion of the diagnosis (1, 3). Clinical features of Luc's abscess include otalgia, fever, temporo-zygomatic swelling, external auditory meatus swelling, facial swelling (anterior, superior or posterior to the auricle), malaise and ipsilateral cervical lymphadenopathy. Other clinical findings may include trismus, mastoiditis, septic arthritis of the temporomandibular joint or cholesteatoma (1-3, 5). In our case, the atypical preauricular swelling raised suspicion of a Luc's abscess,, which prompted a CT-scan.

A temporal CT scan is necessary to confirm the diagnosis, assess the extent of the abscess and mastoid involvement, and to exclude other intra- and extracranial complications of otitis media (9). Radiologic evaluation helps in determining the management of the disease (10). In our case, the CT scan revealed a bilateral mastoid bone opacification and a Luc's abscess with diffuse edema of the surrounding soft tissues (Figure 2). This led to a myringotomy with grummet insertion and an attempt to drain the abscess. Because of the diffuse edema of the surrounding tissues seen on the CT scan, only a limited number of attempts were made to drain the abscess.

Both aerobic and anaerobic bacteria have been found in cultures of Luc's abscesses, most commonly *Streptococcus pyogenes*, *Fusobacterium necrophorum*, *Klebsiella ozaenae*, and *Streptococcus constellatus*. Because of the wide variety of microorganisms, broad-spectrum antibiotics should be used until the causative organism is known from culture. In some cases, the causative microorganism remains unknown (5, 8). Because no culture was taken during myringotomy and abscess drainage in our case, the causative

organism of the Luc's abscess in our patient is unknown. Therefore, treatment with broad-spectrum antibiotics (amoxicillin/clavulanic acid) was warranted in our case.

In general, subperiosteal abscesses are most commonly treated with antibiotics, drainage of the subperiosteal abscess and grommet insertion. This less invasive treatment is found to be an effective alternative to mastoidectomy (3). Mastoidectomy should be considered when the radiological diagnosis of mastoiditis is in doubt, when there is damage to the mastoid bone, and when there is no clinical resolution after 48 hours of conservative treatment (9). In our patient, treatment consisted only of antibiotics and myringotomy with grummet insertion. Because of a good clinical and biochemical improvement, subsequent surgery was not necessary. Further research is needed to evaluate the benefits and risks of not draining the subperiosteal abscess.

Conclusion

Luc's abscess is a rare extracranial complication of otitis media. Its typical clinical features should raise suspicion. Diagnosis is made radiologically with a temporal CT. Conservative treatment with antibiotics, abscess drainage and myringotomy with grummet insertion is often successful. Physician awareness is necessary for early diagnosis and prompt treatment to prevent the development of other complications.

Conflict of interest

The authors have no conflict of interest to declare.

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Informed consent

Parental written informed consent was obtained. Any identifying information of the patient was removed from the manuscript.

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Cow's milk protein allergy (CMPA): why it is important to rebalance the gut microbiota

A child's immune system develops during the first 1,000 days of life. The gut microbiota plays an important role in this development. An adequate composition of the microbiota and its maintenance during this maturation is of paramount importance for the good health of the child [1].

Breast milk is the nutrition that best meets the requirements of the infant's overall health and the proper development of the immune system. It contains among other things beneficial bacteria (lactobacilli and bifidobacteria), prebiotic oligosaccharides, protein, fat and lactose. Prebiotics are substrates selectively used by microorganisms that confer health benefits on the host [2]. Probiotics are live microorganisms that, when administered in adequate amounts, offer a health benefit [3]. All of these components are present in quantities suitable for the child's general development, for the development of a properly composed microbiota (eubiosis) and for the development of a normal immune system.

CMPA affects 1.9-4.9% of European children in their first year of life [4]. It occurs in the early years. A child who is allergic to cow's milk protein has a different gut microbiota from that of a healthy child. Fewer favourable bacteria are present and more potentially pathogenic germs, especially clostridium and eubacterium species. Such a disbalance of microbiota is called dysbiosis [5]. It leads to an increased risk of impaired immune system function, inflammation and infection [6]. The main manifestations of CMPA are gastrointestinal, skin (atopic dermatitis) and respiratory (asthma-like) disorders [7].

Rebalancing the microbiota, reducing infections

It is therefore very important to re-establish or promote the development of a balanced microbiota, especially in children suffering from CMPA because they are significantly more at risk of contracting infections. Sorensen et al. [8] have shown this in a population of nearly 7,000 British children with an average age of four years (Table I). Other studies had already shown this. For example, Woicka-Kolewja et al. [9] estimated in 2016 in a study of Polish children up to 10 years of age that the odd ratio for recurrent respiratory infections was almost four times higher in those who were allergic to β-lactoglobulin than in those who were not.

Table 1:
Frequency of infection (%) in the presence or absence of CMPA

Infection	CMPA (+)	CMPA (-)	p-value
Gastro-intest.	8.1	4.6	< 0.001
Skin	54	45	< 0.001
Respiratory	89	82	< 0,001
Ears	25	19	< 0,001

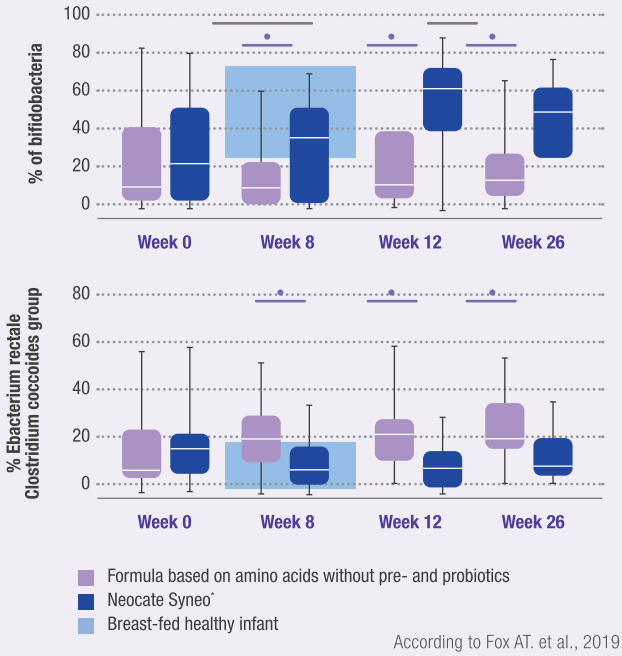
According to Sorensen et al., 2022.

After breastfeeding or if breastfeeding is not possible, it may be advisable to choose an amino acid-based formula with a composition closer to that of breast milk and which has positive effects on the development of the intestinal microbiota.

The Syneo® engine is a synbiotic. Synbiotics are combinations of pre- and probiotics [10]. The probiotic contained in Syneo® is *Bifidobacterium breve* M-16V. Bifidobacteria are among the most represented bacterial species in breast milk [11]. The prebiotics contained in Syneo® are short-chain galacto-oligosacchardides: long-chain fructo-oligosaccharides or short chain fructo-oligosaccharides: long-chain fructo-oligosaccharides. They have been added to the formula to mimic the structure (90% short chain & 10% long chain) and the complexity (>100 structures) of the oligosaccharides found in breast milk.

Fox et al. [12] conducted a study in 71 children with non-IgE-mediated CMPA and 51 healthy breastfed children as a reference group. These children were fed a free amino acid formula for 8 weeks. In one group (n=36), which served as a control, this formula did not contain any pre- or probiotics. In the other group (n=35), the test group, synbiotics (Syneo®) were added to the formula. After 8 weeks, the microbiota of the children who had received Syneo® had come closer to that of breastfed children: an increase in bifidobacteria and a decrease in potentially pathogenic germs (Figure 1). This effect was still present after 26 weeks.

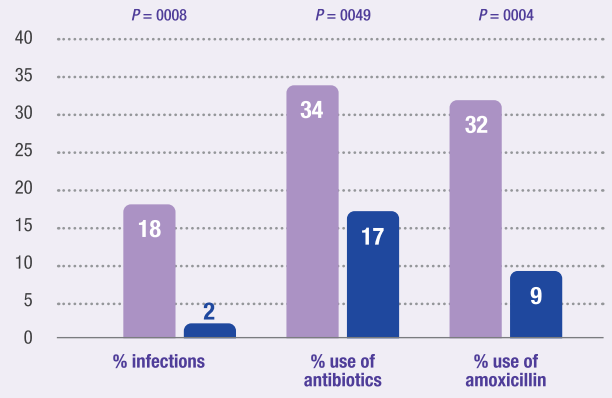
Figure 1:
Changes in the intestinal microbiota of children allergic to cow's milk proteins fed with Syneo®



According to Fox AT. et al., 2019.

In a randomized clinical trial [13] of infants with CMPA, 54 infants were fed a free amino acid diet with a synbiotic (Syneo®) and 56 infants were fed the same formula without the synbiotic. These children were followed for 16 weeks. During this period, they contracted significantly fewer infections and took fewer antibiotics than the children who did not receive Syneo®. (Figure 2)

Figure 2:
Effect of Syneo® on the frequency of infectious episodes and antibiotic use in infants with CMPA



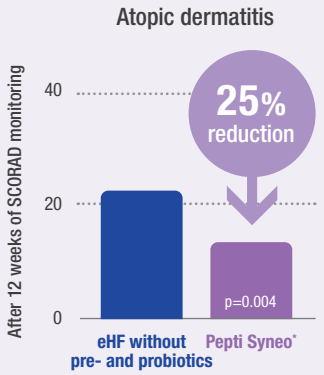
According to Fox AT. et al., 2019.

Improving skin, respiratory and digestive symptoms

The synbiotic blend also has a favourable effect on the manifestations of CMPA. A multicentre, randomized, double-blind, placebo-controlled study [14] showed this in atopic dermatitis. Infants less than 7 months old suffering from atopic dermatitis were randomized into two intervention groups for 12 weeks.

The first group (control, n=44) received an extensively hydrolyzed whey formula (eHF), the other group (n=46) received the same formula with the synbiotic. Infants with IgE-associated atopic dermatitis who received the formula with synbiotic showed a significant improvement in the SCORAD score after 12 weeks compared to those who did not receive the synbiotic (Figure 3).

Figure 3:
Effect of Syneo* on the severity score of atopic dermatitis in infants allergic to cow's milk protein

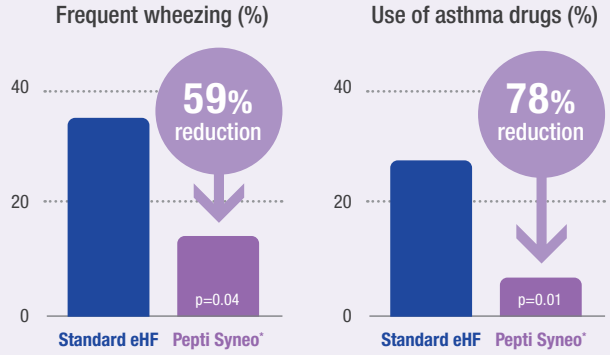


(*) IgE positive infants

According to Van der Aa et al., 2010.

Synbiotics also play a role in preventing asthma-like symptoms in infants with atopic dermatitis. In a multicentre, randomized, double-blind, placebo-controlled study [15], infants with atopic dermatitis were randomized into a control group (n=39) and a test group (n=36). For 12 weeks, the control group received an extensively hydrolyzed whey formula. The test group received the same formula with the addition of Syneo*. After a one-year follow-up, the prevalence of asthma-like symptoms (e.g. wheezing) and the use of asthma drugs were significantly lower in the study group than in the placebo group (Figure 4).

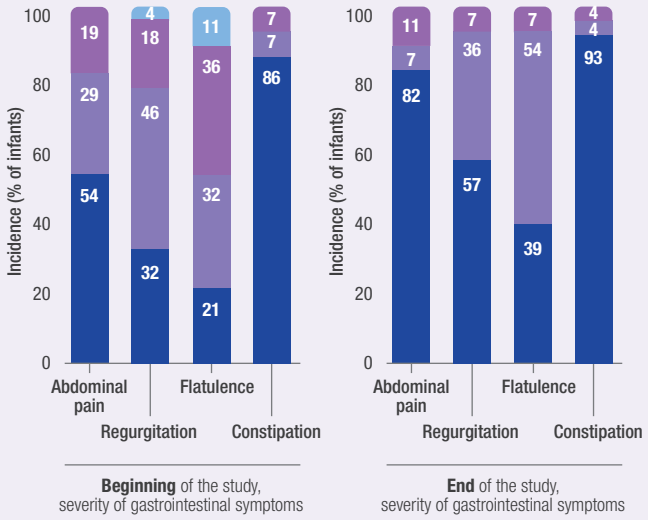
Figure 4:
Effect of Syneo* on wheezing and use of anti-asthma drugs in infants with atopic dermatitis



According to Van der Aa et al., 2010.

Finally, synbiotics in extensively hydrolyzed formulas reduce the severity of gastrointestinal symptoms in infants with CMPA. This was shown in the Hubbard et al. [16] study, a single-arm, 31-day pilot study of 29 infants with CMPA. Significant improvements ($p<0.05$) in the severity of abdominal pain (in 57%), regurgitation (in 46%), flatulence (in 79%) and constipation (in 14%) were observed over time (Figure 5).

Figure 5:
Evolution of gastrointestinal symptoms between the beginning and the end of the study (31 days) under the effect of Syneo* in infants allergic to cow's milk proteins



According to GP et al., 2022.

Conclusions

Extensively hydrolysed formulas and Amino acid-based formulas with Syneo* are the only formulas to which prebiotics and probiotics have been added. Syneo* helps to rebalance the intestinal microbiota in infants with a CMPA.

This rebalancing of the intestinal microbiota with Syneo* has been shown to have a positive effect on asthma-like symptoms, gastrointestinal disorders and atopic dermatitis. In addition to this, Syneo* leads to a reduction in reported infections and antibiotic use. Syneo* also promoted a reduction in reported intestinal infections leading to hospitalization [17].

Important note
Breastfeeding is best. Neocate Syneo* and Nutrilon Pepti Syneo* are foods for special medical purposes. To be used under medical supervision, after full consideration of the feeding options available including breastfeeding. This information is exclusively intended for health care professionals.

* Pepti Syneo*: for the dietary management of CMPA.

* Neocate Syneo*: for the dietary management of CMPA, food polyallergies or other indications where an amino acid based diet is recommended.

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Cuties, Creams and Cushing

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Keywords

Cushing's syndrome; infant; topical steroids; creams; iatrogenic

Abstract

Prolonged use of corticosteroids can lead to serious side effects, including Cushing's Syndrome (CS), a disorder caused by abnormally high levels of free plasma glucocorticoids, and hypothalamo-pituitary axis suppression. The cause of CS may be either natural production or external administration of steroids. Iatrogenic CS is most commonly caused by oral or injectable medications and rarely by topical application. The absorption rate is higher with transcutaneous than with topical application. Only few cases of CS after topical application have been reported. We present the case of a 2-month-old girl who developed CS due to prolonged use of topical steroids.

Introduction

Cushing's Syndrome (CS) is a condition associated with excessive cortisol secretion that may result from an ACTH-dependent cause such as ACTH production by a pituitary adenoma or an ACTH-independent cause such as an adrenal adenoma. It can be caused by to the external administration of steroids. The most common cause of CS is the administration of exogenous glucocorticoids, whereas endogenous glucocorticoid excess due to pituitary or adrenal tumors is comparatively infrequent. Patients with CS typically present with a variety of physical symptoms including facial redness and swelling, which can result in a rounded "moon face" appearance, a fatty deposit at the back of the neck called a "buffalo hump," truncal obesity, hirsutism, skin bruises, proximal muscle wasting, hypertension, hypertension, and growth abnormalities (1,2). The diagnosis of exogenous CS is made based on the clinical presentation of specific symptoms and confirmed by measuring basal cortisol levels at 8 AM. There has been a significant increase in incidence of adverse effects associated with the use of topical or systemic steroids. These individuals are often from lower socioeconomic backgrounds, have lower levels of education and awareness, and may have received inadequate or inappropriate information from healthcare providers (2).

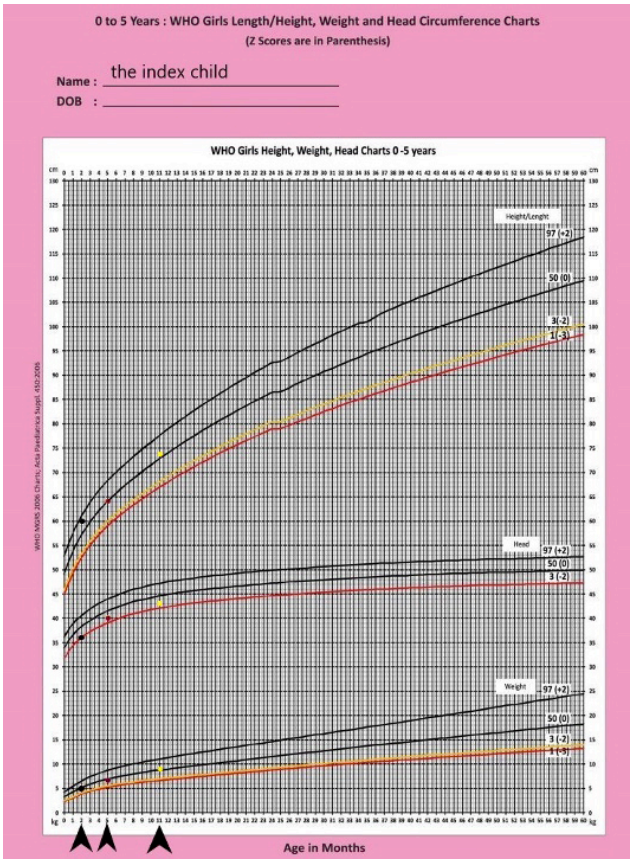
Case report

A 2-month-old baby girl was admitted to the hospital because of excessive growth noticed over the past month. She was born by cesarean section to non-consanguineously married parents and had a birth weight of 2700g. The child had no neonatal admissions and was discharged on the third day of life on exclusive breastfeeding. The baby appeared healthy until 15 days of age when she began to have loose stools for which a local practitioner prescribed antibiotics. Two days after onset, the child developed perianal dermatitis, and a cream containing clotrimazole, beclomethasone, and neomycin was prescribed. As the dermatitis worsened, another topical cream containing clobetasol, neomycin, and clotrimazole was prescribed, and the parents were instructed to discontinue the previous cream. However, they continued to apply both creams inappropriately. Over the next three weeks, the child was observed to gain weight, particularly in the face, with no other associated symptoms. Eventually, the child developed oral lesions, possibly candidiasis, and the parents began using another oral preparation containing triamcinolone for treatment. At admission, child was active and feeding well. She exhibited a characteristic Cushingoid facial appearance, with fat accumulating under the skin of the abdomen, shoulders, genitals, and thighs (as seen in the figure 1a).The child was developmentally appropriate for age. The child's growth parameters were as shown in the figure-2.

The child's blood pressure readings were above the 99th percentile (124/74 mm Hg in the right upper limb, 120/70 mm Hg in the left upper limb, 117/70 mm Hg in the right lower limb, and 118/74 mm Hg in the left lower limb). This hypertension persisted throughout the hospital stay and follow-up visits one week later. Perianal

Figure 1: a: appearance of the child at the time of admission; 1 b appearance at the age of 11

Figure 2: Growth chart



excoriation was noted upon examination, but there were no signs of muscle weakness. Based on the presence of Cushingoid facies and hypertension, Cushing's disease/Cushing's syndrome was considered as a possible diagnosis.

Laboratory evaluation revealed a random blood glucose level of 117 mg/dl (Normal: 70-120 mg/dl); hemoglobin of 11.9 g/dl, white blood cell count 12,350/mm3, platelet count 248,000/mm3, blood urea nitrogen 8 mg/dl, creatinine 0.3 mg/dl; sodium 136 mEq/l, potassium 4.2 mEq/l, chloride 109 mEq/l. Serum cortisol and ACTH levels at 8.00 AM were 0.6 mcg/dl and <5 pg/ml, respectively. Secondary adrenal insufficiency was diagnosed performing a 1mcg ACTH stimulation test and the peak cortisol level was<1mcg/dl. Ultrasonography of whole abdomen showed no demonstrable abnormalities.

Topical and oral corticosteroid were immediately discontinued. Hypertension was controlled with amlodipine (0.1 mg/kg/day). Intravenous hydrocortisone of 50 mg/m^2/day was prescribed for 5 days and tapered to 10 mg/m2/day over a week and discontinued.

During the 3-month follow-up period, the child did not experience any intercurrent illnesses. The child's weight stabilized while her length and head circumference increased appropriately (as shown in figure 2). Morning serum cortisol and ACTH levels returned to normal levels of 13.1 mcg/dl and 56 pg/ml, respectively. The hypertension also subsided and antihypertensive medication was stopped. The features associated with Cushing's syndrome had resolved, and at the age of 11 months, as demonstrated in the figure 1b, all features were within normal ranges.

A descriptive table presents a summary of Iatrogenic Cushing's syndrome caused by topical steroid use in infants below six months of age (2-8). The affected cases were all infants who were suspected to have diaper dermatitis, and the most commonly used steroid was clobetasol. All cases presented with typical symptoms of Cushing's syndrome and had suppressed cortisol and ACTH levels. The median duration of topical steroid application was 2 months, ranging from 1 to 4.5 months. After discontinuation of topical steroid, the median recovery time for the hypothalamic-pituitary-adrenal (HPA) axis was 3 months, ranging from 1 to 12 months. Two infants reported (case 4 and 5) died from severe disseminated Cytomegalovirus (CMV) infection (5,6).

Discussion

Cushing's syndrome (CS) is characterized by excessive cortisol levels resulting from a variety of causes. Under normal conditions, the pituitary gland secretes ACTH, which stimulates the adrenal glands to produce cortisol. However, exogenous administration of corticosteroids can suppress the hypothalamic-pituitary-adrenal

Table 1: Characteristics of children (< 6 months) with exogenous CS from Steroid application

	Age (months)	Age at start of steroid cream (months)	Duration of usage(months)	Steroid used	Cortisol (mcg/dl)	ACTH (pg/ml)	Recovery time (months)	Disease	Reference
1	4.5	2.5	2	Clobetasol	0.5	NA	6	Diaper dermatitis	2
2	4	2	2	0.1% Hydrocortisone butyrate + Clobetasol	1	<5	2	Diaper dermatitis	3
3	3	1.5	1.5	Clobetasol	<1	<5	1	Diaper dermatitis	4
4	3	1	2	Clobetasol	5.2	<5	Death	Diaper dermatitis	5
5	5	1.5	4.5	Clobetasol	<1	6.4	Death	Diaper dermatitis	6
6	4	2.5	1.5	Clobetasol	<1	<5	6	Diaper dermatitis	4
7	2	0.5	1.5	Clobetasol + beclomethasone + oral triamcinolone	<1	<5	3	Diaper dermatitis	Our case
8	3	Birth	2.5	Clobetasol + prednicarbate	<1	<5	12	Diaper dermatitis	7
9	3.5	2.5	1	Clobetasol	<1	<5	2	Diaper dermatitis	7
10	6	3	3	Clobetasol	0.66	7.1	NA	Dry Skin	8

(HPA) axis. While prolonged use of oral or parenteral steroids commonly leads to iatrogenic CS, some cases have reported the development of this condition due to prolonged use of topical steroids. In some instances, severe immunosuppression and fatal secondary infections have occurred in such cases (9).

The infant discussed in this article developed iatrogenic CS due to the excessive and prolonged use of a potent topical steroid i.e., clobetasol propionate, for the treatment of perianal dermatitis. The parents had inadvertently and inappropriately applied high doses of the topical corticosteroid continuously for a period of two months resulting in the absorption of clobetasol through the skin and into the systemic circulation. This resulted in the development of CS.

The child exhibited typical clinical features of Cushing's syndrome, such as moon face and generalized weight gain. Laboratory investigations revealed significant suppression of both cortisol and ACTH levels due to the administration of exogenous steroids. It is noteworthy that the child did not experience life-threatening adrenal insufficiency, which is a known risk associated with the use of various forms of glucocorticoids, including topical creams (10)]. There have been reports of routine doses of corticosteroid creams leading to adrenal insufficiency, with nonspecific symptoms (11). Therefore, it is crucial to maintain a high level of suspicion for iatrogenic causes of adrenal insufficiency and be able to identify such cases. As illustrated in the table, cases have been reported in which iatrogenic Cushing's syndrome developed due to the prolonged use of clobetasol for the management of napkin dermatitis. Nevertheless, our case stands out as it involves a diagnosis of Cushing's syndrome in a very young infant with a significantly elevated blood pressure (>99th centile), accompanied by other typical signs of the condition. Additionally, the infant had extensive perineal dermatitis with inflamed skin, which likely contributed to greater permeation and penetration of the topical medication.

Using a low-potency topical steroid may be sufficient to treat conditions like napkin dermatitis, as opposed to a high-potency steroid such as clobetasol. The use of other screening methods like midnight salivary cortisol may aid in the early detection of potential iatrogenic Cushing's syndrome while using topical steroids. The management of iatrogenic Cushing's syndrome includes discontinuation of the causative medication, close monitoring, administration of physiologic doses of steroids, and gradual tapering them over time (10).

Conclusion

Our case and others published in the literature emphasize the importance of educating patients about proper instructions for the use of topical or oral steroid preparations. High potency steroid applications in infants should be avoided whenever possible, and parents should be strictly instructed to use them only for a short duration. This study was ethically approved by the Institution Review Board.

Acknowledgements

We thank the parents for providing detailed history and permission to use this case for educational purposes.

Conflict of interest

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

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Intra-cardiac thrombi: Behçet's disease?

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Keywords

Behçet's disease; thromboembolic events; heart diseases; anticoagulants; child.

Abstract

We report the case of a 6 years old male child presenting with deep vein thrombosis and intra-cardiac thrombi. Despite anticoagulation treatment, the thrombi progressed leading to cardiovascular failure requiring a surgical approach. The initial clinical presentation, unusual progression and exclusion of differential diagnoses, guided to the suspicion of Behçet's disease. The patient developed new symptoms and responded to anti-inflammatory and immunosuppressive treatments supporting this diagnosis. Behçet's syndrome is a systemic inflammatory disease whose incidence in the paediatric population and aetiology are still unknown. Furthermore there are no evidenced-based treatment guidelines.

Introduction

Behçet's disease (BD) is a chronic autoinflammatory condition. The disease is rare in paediatrics and the incidence is unknown (1). The diagnosis is clinical and no laboratory test can confirm it. The international criteria for BD furnish a clinical score as a guide for diagnosis and classification (2). It can affect different organs, but cardiac presentation is uncommon. Intracardiac thrombus is even more rare (3). We present the case of a child with a catastrophic evolution of deep vein thrombosis and intra-cardiac thrombi formation. Due to progression despite correct anticoagulation treatment, BD was suspected and a treatment with immunosuppressive and anti-inflammatory agents was started.

Clinical case

A 6 year-old previously healthy male child presented with a two-day history of fever and sudden collapse while walking, with complete recovery within one minute. The patient, of Moroccan origin, was born in Europe. In his medical history, the parents reported a severe coronavirus (SARS-CoV-2) related acute respiratory distress syndrome 13 months previously.

The initial physical examination was unremarkable. The patient's vital signs were: oxygen saturation 100% - respiratory rate 41 breaths per minute – arterial blood pressure 100/68 (79) mmHg– heart rate 145 beats per minute – temperature 36.6 °C. Laboratory tests showed moderate inflammation (white blood cells 11010/mm3 [N 7800-13500], C-reactive protein 120 mg/L [N ≤ 5mg/L], erythrocyte sedimentation rate 80 mm/h [N ≤ 20 mm/h]). His electrocardiogram and chest radiograph showed no abnormalities. The patient was admitted for monitoring.

The evolution was marked by left leg pain and swelling. Echography confirmed a partial venous thrombus extending from the common femoral vein to the external iliac vein. Basic coagulation tests were normal. Taking into consideration the young age of the patient and the transient loss of consciousness, a chest computed tomography (CT) was performed showing a massive truncal pulmonary embolism. The patient was started on anticoagulant (intravenous heparin infusion) and antibiotic (ceftriaxone) therapy and transferred to the Paediatric Intensive Care Unit.

The evolution was characterized by progression of the thrombus towards the inferior vena cava (IVC), appearance of intra-cardiac thrombus (ICT) (right atrium (RA) and right ventricle (RV)) and clinical deterioration despite adequate anticoagulation (Figure 1A-1B). On day 9 of admission, he developed his first episode of acute cardiovascular failure due to a thrombus in the RV. He underwent a surgical removal

Figure 1A. Transthoracic echocardiogram (TTE) - short axis- showing a thrombus in the common trunk pulmonary artery (blue arrow mark).

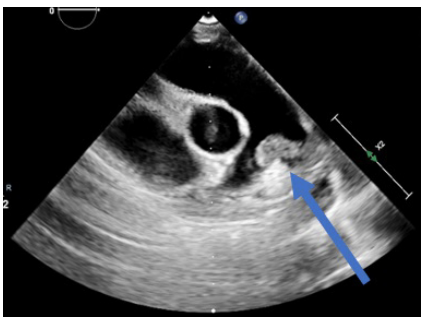


Figure 1B. Transthoracic echocardiogram (TTE) showing the right ventricular (RV) thrombus (blue arrow mark).

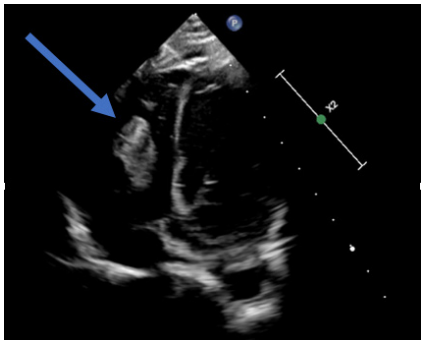


Figure 1C. Computed tomography showing thromboses of the upper vena system.

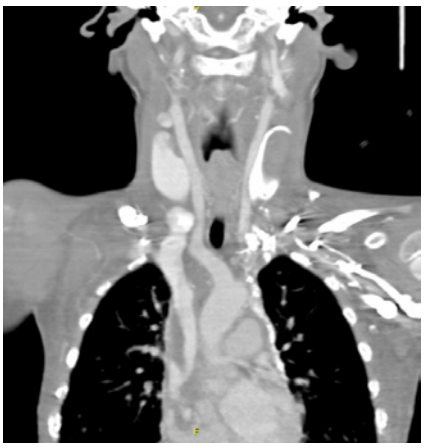
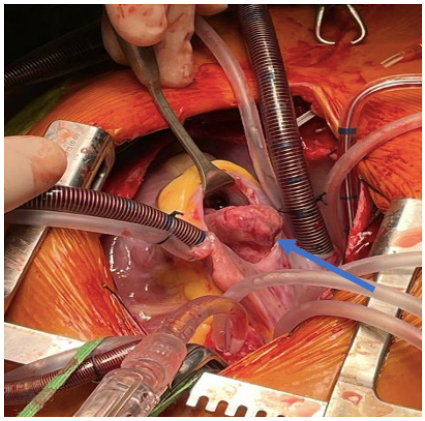


Figure 2. Perioperative aspect of the main pulmonary artery thrombus: irregular, smooth, hard mass adherent to the endothelium (blue arrow mark).



of this right heart thrombus (Figure 2). Two days later, he developed a thrombus in the right atrium with hemodynamic intolerance.

More in-depth assessments were considered and diagnostic tests were performed to confirm or exclude possible disorders that could have caused a similar clinical presentation (Table 1). The hypothesis of a BD associated with ICT and extensive pulmonary embolism was suggested. Other possible pathologies leading to rapid formation of ICT were heparin-induced thrombocytopenia (HIT) or diffuse thrombosis due to SARS-CoV-2 infection. As shown in table 1, the platelet factor 4 (PF4)/ heparin antibodies were negative, thus excluding the diagnosis of HIT. Three polymerase chain reaction (PCR) tests for SARS-Cov-2 were negative during hospitalization.

To support the diagnosis of BD, we screened for HLA-B51 and performed an ophthalmoscopic evaluation and a pathergy test. The three tests were negative not supporting the diagnosis of BD.

Coagulation tests showed that protein S was on the low limit and the patient's mother had a protein S deficiency (Table 1). However, these tests were not conclusive for diagnosis.

The thrombi were rapidly extensive. On day 12 of admission, the patient developed a superior vena cava syndrome. A CT angiogram showed that the thrombus extended from the superior vena cava to the RA. The superior vena cava network was completely thrombosed. On the left side, the thrombus extended to the internal jugular vein, subclavian vein (partial) and brachiocephalic vein (complete). On the right side, the subclavian vein was patent, but the internal jugular vein and the brachiocephalic veins were thrombosed (Figure 1C).

Given the acute severity of the disease, the patient was started on aggressive anti-inflammatory and immunosuppressive therapies. We started with corticosteroids (pulses of methylprednisolone 15mg/kg/day for three days, followed by methylprednisolone 2 mg/kg/day), anti-tumour necrosis factor (TNF)-alpha (5mg/kg, on week 0 – week 1 – week 4) and azathioprine (2mg/kg/day). Almost simultaneously the anticoagulant therapy was switched to antiaggregating therapy. Despite medical treatment the patient's condition was life threatening on three occasions (day 9, 13 and 20) and a multidisciplinary decision was made to proceed three times with surgical thrombectomy under extracorporeal circulation (Figure 2) and IVC ligation.

The clinical evolution was slowly favourable and the inflammatory syndrome decreased. He was finally discharged on day 53, treated with corticosteroids, azathioprine and acenocoumarol, with follow-up

Table 1: Differential diagnosis with pertinent results of findings.

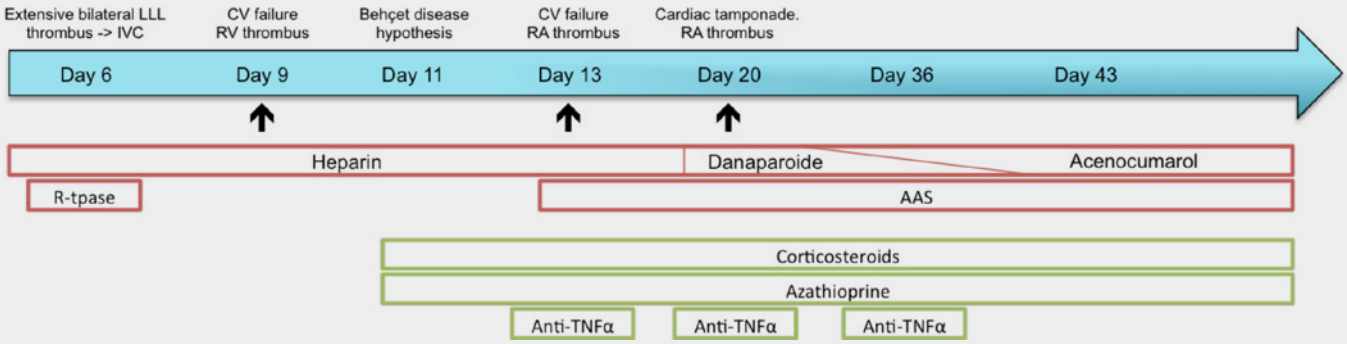
Sars-CoV2 : severe acute respiratory syndrome coronavirus 2 ; PCR: polymerase chain reaction ; PF4/heparin: platelet factor 4/heparin ; HLA B51 : human leukocyte antigen class I, B, 51 ; CT scan : computed tomography scanner ; Whole-body PET CT: whole body positron emission tomography computed tomography.

Causes	Analyses	Results
Coagulation disorder	Patient Mother of the patient	Protein S on lower limit: 65% (68-139%) Protein S deficiency: 45% (60-114%)
Infectious	Inflammatory markers SARS-CoV-2 • PCR tests during hospitalizations • Serology for vaccine induced antibodies	 Negative Positive
Genetic	Prothrombin gene mutation G20210A	No mutation
Iatrogenic	PF4/heparin antibodies	Negative
Systemic	Pathergy test HLA type Ophthalmoscopic evaluation	Negative HLA B51 negative No signs of uveitis
Tumoral	Medullary karyotype Chest CT scan Abdominal echography Whole-body PET CT	Karyotype normal 46,XY No tumour No tumour No tumour

Table 2: Timeline of the evolution of the case depicting the main events, including symptoms and management

LLL: left lower limb; IVC: inferior vena cava; CV failure: cardiovascular failure; RV: right ventricular; RA: right atrial; Anti-TNFα: tumor necrosis factor alpha inhibitors.

The arrows point out the 3 heart surgeries.



by the rheumatology, haematology and cardiology team. At the time of discharge, the diagnosis was uncertain. Our hypothesis was a BD combined with an underlying pro-inflammatory state due to a protein S level on the lower limit.

In July 2022, he had a chest CT which showed no thoracic thrombosis. In September 2022, his mother reported a few mouth ulcers and a penile ulcer, which supports the diagnosis of BD. He continues to be followed closely by a multidisciplinary team.

Discussion

The incidence of Behçet's disease in children is unknown. The average age for the early symptoms in the paediatric population is 8 years old, and the diagnosis is usually made at a later stage (6 years later) (1). This disease affects both genders but severe cases are more common in men than women (1). In a literature review evaluating patients with BD and ICT, Aksu described that there is a male predominance (87%), and thrombi affect mostly the right side of the heart (95%) (3).

The pathology is usually characterized by recurrent aphthous stomatitis, genital ulceration, arthralgia and uveitis (1). It can affect multiple systems and cardiac involvement is very uncommon (1-5%). Pericarditis, myocardial infarction, conduction abnormalities and, very rarely, ICT can be observed. Pulmonary aneurysm and thrombus may also occur (3). In case of vascular complications, venous involvement is more common (nearly 30% of patients) than arterial involvement (5-10% of patients) (1). The prevalence of cardiovascular involvement varies by country. However, ICT is one of the most recognized cardiac presentations in Mediterranean young patients and can precede the diagnosis, as in the present case (3).

The underlying mechanism for thrombosis in this disease remains unclear. One hypothesis is endothelial cell ischaemia and disruption leading to the presence of abundant inflammatory cells and platelet aggregation (4). The thrombi are usually tightly adherent to the vessel wall and have a different consistency from classic thrombi (Figure 2), making the embolization difficult (5,6). They can be confused with embolisms, although in this case the size of the ICT and the rapidity of evolution suggested in situ thrombus formation (6).

Our patient had a delayed diagnosis due to the uncommon initial presentation (thrombosis, ICT) and the lack of more international BD criteria, as described in literature (9,10). Only the development of new symptoms over time (ulcers) and the favourable evolution under anti-inflammatory and immunosuppressive treatment allowed recently to confirm the diagnosis. During his admission, other differential diagnoses were ruled out, mainly heparin-induced thrombocytopenia (HIT). Since the thrombi evolved despite standard therapeutic anticoagulation, heparin was switched to danaparoid and acenocoumarol (Table 2). The PF4/heparin complex turned out to be negative, and HIT was excluded.

High clinical suspicion remains the key for early diagnosis of BD. Once BD is suspected, adopted a multidisciplinary approach should be adopted (Table 2). There are no therapeutic guidelines for BD with cardiac involvement and a combination of anticoagulant, immunosuppressant and corticosteroid is the most accepted treatment. Anti-inflammatory agents act on the presumed inflammatory origin of this vascular complication, leading to a reduction of thrombus size (5, 7). The need for surgery is still discussed (8). In a study published in 2018, The European Alliance of Associations for Rheumatology (EULAR) suggested that the mortality rate is higher in patients undergoing surgery. The reason is that it triggers the vascular pathergy phenomenon that induces thrombosis. Thrombectomy is therefore reserved for life-threatening situations, as in our patient (4,7,8). The efficacy of vena cava ligation or vena cava filter placement in the preventing pulmonary embolism is also controversial (9). It should be considered for patients with a deep vein thrombosis or pulmonary embolism when anticoagulation therapy is not possible or fails (9). Our patient had a significant floating thrombus in the IVC very close to the renal veins and recurrent emboli despite appropriate anticoagulation. A vena cava filter could have compromised renal venous return, so the IVC was ligated without complications (as collaterals had already developed).

Because of the young age of our patient, we could have searched for a Mendelian genetic cause. Since 2016 a new entity of monogenic autoinflammatory diseases has been described. The tumour necrosis factor-α-induced protein 3 (TNFAIP3) gene mutation results in haploinsufficiency of a nuclear factor-κB regulatory protein A20 and patients develop mucosal and cutaneous symptoms resembling Behçet's disease in early childhood (10,11). Other frequent manifestations include recurrent fever and abdominal pain. However, vascular and cardiac symptoms appear to be rare in this entity (10).

Conclusions

In this report, we present a case of deep vein thrombosis and intracardiac thrombosis in the right heart ventricle, revealing Behçet's disease. This is an uncommon initial presentation of a rare disease in children. Only a high index of clinical suspicion and the exclusion of other potential causes allows a prompt diagnosis and optimal treatment. There are no therapeutic guidelines and several treatments have been used with varying outcomes. The patient was successfully

treated with anticoagulants, immunosuppressants, anti-inflammatory drugs and surgery. Surgical treatment should be reserved for life-threatening complications of Behçet's disease.

Conflict of interest

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

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Contre-indications • Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP. • Patients porteurs d'un cathéter veineux central, patients dans un état critique ou immunodéficients en raison du risque de fongémie (voir rubrique 4.4. du RCP). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745. Effets indésirables Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. Affections vasculaires Très rare : choc anaphylactique. Affections respiratoires, thoraciques et médiastinales Très rare : dyspnée. Affections gastro-intestinales. Très rares : constipation, épigastralgies, météorisme abdominal (épigastralgies et météorisme abdominal ont été observés lors d'études cliniques). Affections de la peau et du tissu sous-cutané. Très rares : prurit, exanthème, Œdème de Quincke. Troubles généraux et anomalies au site d'administration. Très rares : soif. 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Extrapyramidal symptoms as a side effect of Risperidone Use in children, a case-series

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Keywords

Atypical antipsychotic drugs; risperidone; extrapyramidal symptoms.

Abstract

Atypical antipsychotics are increasingly prescribed to treat behavioural problems in children, including in children with autism. Although exhibiting fewer side effects than typical antipsychotics, paediatricians should remain aware of side effects such as extrapyramidal symptoms. These can be very severe and even irreversible if not timely detected. Therefore continued vigilance and monitoring of side effects remains extremely important.

Introduction

Risperidone, an atypical antipsychotic drug, is increasingly prescribed in children for various indications (1, 2). The European Medicines Agency approved risperidone for treatment of aggression in children with conduct disorder aged 5 years or older and aggressive behaviour in adolescents with mental retardation for a short treatment period up to six weeks (3). Even though adverse effects in atypical antipsychotics are claimed to be low, a higher rate is observed in children than in adults, including extrapyramidal symptoms such as dystonia, akathisia and parkinsonism (2, 4). In Belgium, over the past fifteen years, prescriptions for antipsychotics in minors have increased by 75.5% (5). In 2014, the prevalence of antipsychotic use in children reached 0.6% (5). With this article, we present two cases of children treated with risperidone who experienced severe side effects requiring hospitalisation. We want to raise awareness among paediatricians and emphasise that children treated with atypical antipsychotics are still at risk of these potential serious side effects.

Case

The first patient is a 14-year-old girl known with GLUT-1 (glucose transporter type 1) deficiency and juvenile absence epilepsy; she was diagnosed with autism spectrum disorder at the age of 10 years. Since the age of ten, she has been taking risperidone for psychotic symptoms and at the moment of presentation she was taking 1 mg in the morning and 1.5 mg in the evening (=0.05 mg/kg/d). Other medications included lamotrigine 100 mg twice a day. She consulted because of an already longstanding torticollis causing increasing discomfort and pain. She was diagnosed with dystonia as a side effect of risperidone which was treated with biperiden (0.1 mg/kg/dose) intravenously. Immediate beneficial effect was seen but repeated administration was required. Biperiden was continued as maintenance therapy while risperidone was slowly tapered to stop. There was a favourable evolution over time with decrease in dystonia.

The second patient is a 16-year-old boy who consulted because of neurological deterioration with complaints of torticollis, a resting tremor, bradykinesia, and rigidity. His past medical history included a diagnosis of autism spectrum disorder, and he was also followed up with a paediatric rheumatologist in the context of suspected juvenile idiopathic arthritis (JIA) and associated guttate psoriasis. He was treated with methotrexate 20 mg, omeprazole 40 mg, vitamin D supplements, folic acid 1 mg daily, prednisolone 5 mg daily and topical calcipotriol/betamethasone and ketoconazole. For several years he has been treated with risperidone 0.8 mg in the morning and 0.9 mg in the evening for treatment of psychotic symptoms (=0.02 mg/kg/day).

Despite treatment for JIA, a painful torticollis remained present as well as regression in motor functioning that could not be explained by arthritis. Clinically, in addition to torticollis, there was also pronounced rigidity, bradykinesia, and a tremor. Biochemically, no inflammation was present. Additional imaging of the cervical spine showed no inflammatory abnormalities. To rule out an underlying neuroinflammatory disorder, central imaging was performed as well as additional blood sampling and lumbar puncture. In this patient, we noted two presentations of possible side effects of antipsychotics: dystonia and parkinsonism. Risperidone was slowly tapered to stop. At the outpatient clinic, we observed significant improvement in symptoms towards normalisation.

Discussion

First-generation antipsychotics (FGA) exert their therapeutic effect mainly through dopamine D2-receptor blockade (6). Despite beneficial effects on aggressive behaviour and psychotic symptoms, the side effects associated with the use of FGA also result from dopamine receptor blockade (6-8). These primarily include extrapyramidal symptoms and are one of the main reasons for the development of second-generation antipsychotics (SGA) (2). SGA have a broader mechanism of action and block numerous other receptors in addition to dopamine receptors, including cholinergic, noradrenergic, and histaminergic receptors (2, 6). Risperidone acts as a strong potent 5-hydroxytryptamine (5-HT) antagonist and to a lesser extent also as a dopamine D2-receptor antagonist (7). In addition to antiserotonergic and antidopaminergic activity, it also binds alpha-1-adrenergic, alpha-2 adrenergic and histamine-H1 receptors (7). Unfortunately, side effects such as extrapyramidal symptoms also result from D2-receptor blockade (7). Since atypical antipsychotics also antagonise dopamine receptors to a lesser extent, the use of atypical antipsychotics may also be associated with extrapyramidal symptoms (2, 7).

Extrapyramidal symptoms can be divided into four categories: (acute) dystonia, akathisia and parkinsonism and tardive dyskinesia (9). Acute dystonia generally occurs in the early phase after initiation of an antipsychotic drug or when the dose is increased and is defined by an abnormal contraction of muscles of the head, eyes, neck, limbs and trunk that persists for a prolonged period of time (9, 10). These spasms can give rise to torticollis and oculogyric crises, for example, and can be severely painful (10). In children treated with atypical antipsychotics, acute dystonia is seen in 2.2% (11). Akathisia is characterised by restlessness (9, 10). This includes constant movements, not being able to sit still, pacing and many other and generally occur in the early phase, several weeks after starting therapy (9, 10). Side effects such as resting tremor, bradykinesia and rigidity can occur with the use of atypical antipsychotics, which is referred to as medication-induced parkinsonism (9, 10). Onset of these side effects tends to occur early after initiation of the antipsychotic drug (9, 10). Unlike acute dystonia, akathisia and parkinsonism, tardive dyskinesia comprises a group of side effects that occur in a later phase of treatment, sometimes only after months to years of therapy (9, 10). Movements of the face, tongue, jaw, and extremities are most common, and these are involuntary and choreatic (9, 10). A systematic review reports a low one-year incidence rate of tardive dyskinesia for children treated with risperidone of 0.3% (12). Considering tardive dyskinesia has a tendency to present after several months, it is possible that these data are an underestimate due to the short duration of various studies (12).

Discontinuing the causative antipsychotic is the most critical step in treatment (8, 9). If this is not feasible, an attempt should be made to move to the lowest therapeutic dosage and if possible switch to an alternative therapy (8). Extrapyramidal symptoms are generally reversible on cessation of the causative neuroleptic drug although tardive dyskinesia may be persistent and irreversible even after cessation of the eliciting drug (8). Regarding pharmacological treatment of extrapyramidal symptoms induced by antipsychotics, limited data can be found on treatment in children (9). For acute dystonia, diphenhydramine or an anticholinergic (biperiden) may be considered and intravenous administration of benzodiazepines can be used in severe cases (9). Evidence and recommendations for treatment are primarily obtained from studies with adults implying generalisation to paediatric population remains difficult (9).

Therapeutic drug monitoring might be of interest for monitoring serum concentrations in children treated with risperidone, especially given side effects are linked with serum concentrations (13, 14). A recent prospective study shows that higher levels of active moiety, the sum of risperidone concentration and its active metabolite, 9-hydroxyrisperidone, are associated with weight gain, which in turn is related to long-term metabolic and cardiovascular risks (13). Higher serum levels in children are also associated with sedation, and higher prolactin levels (2, 13). In adults, there is a well-established correlation between higher serum concentrations and extrapyramidal symptoms (14). A therapeutic range of 20-60 µg/L for the treatment of schizophrenia is suggested in adults (13, 14). Physicians prescribing risperidone to children should be aware that pharmacokinetics and pharmacodynamics in children differ from those of adults, which reflect variations in side-effect profiles (2, 13). Children are more susceptible to weight gain and sedation than adults and paediatricians and general practitioners are probably most aware of these side effects (2, 13). While in adults, neuromotor symptoms are well-recognised side effects (2). With this article, we want to emphasise that children are also susceptible to extrapyramidal symptoms. Lastly, risperidone is primarily metabolised by CYP2D6 thereby caution is required when using comedication which include CYP2D6 inhibitors (14). In general, determining serum concentrations is rarely used in practice and more controlled specific studies are needed to determine a therapeutic range of risperidone for different indications in children.

Conclusion

Neuroleptic drugs are increasingly used in children and adolescents with behavioural disorders and are associated with serious acute and long-term adverse effects. Children are more sensitive to side effects in comparison to adults due to differences in pharmacokinetic and pharmacodynamic characteristics. In addition, it is best to aim for the lowest possible therapeutic dose. Close monitoring of side effects and, if they occur, adjustment of therapy with tapering to stop or switching to an alternative drug is crucial.

Acknowledgements

Informed consent was obtained from both patients.

Conflicts of interest

The authors have no conflict of interest to declare.

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*L'allaitement déclenche chez la mère un stimulus de soif qui provoque une augmentation de **12 à 16%** de la prise quotidienne de liquide. Les mamans allaitantes doivent donc augmenter leurs apports hydriques. Par ailleurs, le lait maternel étant composé à 85% d'eau, le type d'eau choisi par la maman va avoir un impact direct sur la qualité de l'hydratation du bébé. Par ailleurs, le rein du nourrisson continue sa maturation jusqu'à l'âge de 2 ans. Dès lors, durant cette période, tout excès d'apport (sels minéraux, nitrate, sodium...) doit être évité. Le choix de l'eau est donc crucial.*

QUELLE EAU RECOMMANDER DURANT L'ALLAITEMENT ?

Sachant qu'une mère allaitante doit boire chaque jour entre 2 litres et 2,5 litres d'eau, il lui est recommandé de choisir une eau répondant à des critères stricts par exemple la Spa® Reine. En effet, cette eau, captée dans une zone protégée des Fagnes, est naturelle et pure. En outre, sa composition est faible en minéraux (38 mg de résidu sec par litre); elle contient peu de nitrates (1,5 mg par litre) et peu de sodium (3 mg par litre). Autant d'éléments qui permettent à Spa® Reine de bénéficier de l'allégation de santé : « convient pour la préparation des aliments des nourrissons».

PRÉVENIR LA DÉSHYDRATATION DE LA MAMAN ALLAITANTE

***54%** des mamans allaitantes n'atteindraient pas les apports hydriques quotidiens recommandés.(1) D'où la nécessité de bien les informer et de procéder, si besoin, à des mesures. Une option est l'emploi de l'échelle colorimétrique des urines. L'objectif est de déterminer la quantité des apports hydriques en fonction de la couleur des urines et éventuellement, d'augmenter ces apports. Le contrôle peut être effectué par la maman, à domicile. Les résultats sont probants : **83%** des femmes ayant reçu une échelle colorimétrique des urines s'en sont servi pour savoir si leur consommation d'eau était suffisante.(2)*

***(1)** Bardosono et al. Pregnant & Breastfeeding Women: Drinking for two? Ann Nutr Metab 2017; 70 suppl 1) : 13-7. **(2)** Rigaud M et al Assessing a tool for self-monitoring hydratation using urine color in pregnant and breastfeeding women: a cross-sectionnal, online survey. Ann Nutr Metab 2017; 70 (suppl 1) : 23-9.*

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Facial swelling caused by pneumoparotid: a case report and literature review

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Keywords

Pneumoparotitis, pneumoparotid, pneumoparotis, facial swelling, self-inflicted injury.

Abstract

Facial swelling in children is a common symptom in paediatric patients. Despite its frequent occurrence, searching for the right diagnosis can often be a challenge for the clinician. With this case report and review of the literature we intend to highlight a very specific cause of facial swelling: pneumoparotid. Pneumoparotid is described as the presence of air within the parotid system and can be complicated with subcutaneous emphysema and pneumomediastinum. We aim to make clinicians familiar with this syndrome, so they can recognize it in future patients and take the proper steps to diagnose and treat the patient.

Introduction

Facial swelling in children is a common symptom in paediatrics, and often a reason for parents to visit the emergency department. When a child presents with facial swelling, many physicians will quickly rule out an allergic reaction. Physicians will also take acute swelling caused by inflammation into consideration. History, clinical examination, medical imaging and the biochemical work-up will help the clinician differentiate between different causes of inflammation, such as lymphadenopathy, sinusitis, odontogenic infections and orbital / pre-septal cellulitis. It is also important to rule out renal causes of oedema. When these frequent aetiologies have been ruled out a broader differential diagnosis is needed (1). Knowledge of the facial anatomy, the different aetiologies and their clinical presentation is essential to differentiate between the several possible causes of facial swelling. The different causes of facial swelling can be divided into several groups. Firstly, there are possible allergic causes of acute facial swelling caused by food allergies, contact allergies or hereditary angio-oedema. Second there is acute facial swelling with infection or inflammation, caused by underlying lymphadenitis (viral or bacterial causes), sinusitis, odontogenic infections or orbital/pre-septal cellulitis. Thirdly, there is facial swelling in combination with generalised oedema caused by underlying renal or cardiac pathology. Fourth, there is the possibility of vascular malformations such as lymphangiomas and haemangiomas. If the swelling is not caused by any of the above, a clinician will consider tumoral lesions such as rhabdomyosarcoma, Langerhans cell histiocytosis, Ewing sarcoma, osteosarcoma and neuroblastoma.

Another important cause of facial swelling is pathology of the parotid gland. The parotid gland in itself can be the cause of unilateral or bilateral facial swelling. When one looks at parotid pathology in particular, the differential diagnosis of parotid swelling is very broad. These include infections, neoplasms, auto-immune pathology, iatrogenic causes and parotid duct pathology. With this case report and review of the literature we aim to highlight another very specific cause of parotid pathology: pneumoparotid.

Case report

A twelve year old boy presented to the emergency department with an acute exacerbation of facial pain and swelling. Initial swelling of the face started three days ago. There were no other significant elements in the patient's history, in particular no fever, no itch and no previous trauma. There were no respiratory or gastro-intestinal complaints. Diuresis was normal. He was fully vaccinated. One week prior to this presentation, he had already been admitted to the hospital for intravenous analgesia and antibiotics for a suspected bilateral parotitis following parotid duct infiltration.

Clinical examination revealed swelling of the face and neck and bilateral swelling of the eyelids. The overlying skin was intact and no lymphadenopathy was palpable. The patient did not have a rash or urticaria. Cardiorespiratory assessment was normal. There was no oedema of the extremities. Upon presentation, he was hemodynamically stable with no fever and no signs of anaphylaxis.

The initial differential diagnosis consisted of an allergic reaction with angio-oedema, generalised oedema caused by a nephrotic syndrome or cardiac pathology, parotid pathology and an EBV infection.

Laboratory examination showed a leucocyte count of 17.56x10E9/L (ref range 4.50 – 13.00x10E9/l), neutrophil count 13.7x10E9/L (ref range 1.8 – 8.0x10E9/L), CRP 0.8 mg/L (ref range < 5.0 mg/l) and amylase 120 U/L (ref range 28 – 100 U/L). Urinalysis excluded a renal cause of the symptoms in the absence of proteinuria. The patient was admitted to the ward with a working diagnosis of recurrent parotitis and was treated with intravenous fluids, antibiotics and corticosteroids.

During his hospital stay, a more detailed study of his medical record revealed that he had been hospitalised nine times in different hospitals in the past year. He presented each time with bilateral swelling of the parotid glands and once with diffuse facial oedema. Each time he was treated with corticosteroids, antibiotics or analgesics. The working diagnosis at that point was a recurrent parotitis of childhood. Because of the extremely recurrent nature of the disease in this case, two-monthly infiltrations with corticosteroids in the parotid duct were performed, but this was insufficient to stop the episodes.

There were some elements in this case that challenged this working diagnosis. Firstly, this boy presented with a painful swelling of the face with bilateral oedema of the eyelids, a presentation that is not typical for a recurrent parotitis of childhood. Secondly, he did not respond well to the therapy that had been initiated. We therefore decided to consider a wider differential diagnosis of bilateral parotid swelling (see table 1) (2, 3).

Recurrent infections are not a likely diagnosis in our case as his white cell counts and acute phase reactants were within normal limits. Auto-immune pathology was excluded by consultation with the paediatric rheumatologist and biochemical testing. No ductal lithiasis or other types of obstruction were observed on the sialogram. We could exclude malignancies with radiological examinations. An iatrogenic cause was unlikely as he had not undergone any recent procedures. The only remaining diagnosis was pneumoparotid. A clinical re-evaluation revealed trismus, crepitus and pain on palpation of the swelling. A head CT showed discrete bilateral pneumoparotid and extensive subcutaneous emphysema in the head-neck area, extending into the parapharyngeal space, but also subcutaneously into the upper mediastinal space. The diagnosis of a pneumoparotid with subcutaneous emphysema and pneumomediastinum was made. When re-examining his past investigations we came upon one CT report from the previous year which already mentioned the term 'pneumoparotid', but apparently this diagnosis was not pursued. His other past investigations (sialography, two MRI's and ultrasounds) were all negative.

Extensive questioning could not reveal the underlying cause, but the recent loss of his father in combination with the loss of school days prompted us to consider an underlying psychological problem. Review of the literature showed that self-induced pneumoparotid has been described in adolescents with psychosocial issues. Extensive questioning could not reveal the mechanism of how the self-induction came about, but self-induced pneumoparotid can be subconscious. The boy was referred to a psychologist for further evaluation. Six months after the diagnosis, he still had symptoms twice a month. He was scheduled for an observation during a one week hospitalisation, followed by possible botox injections or ductal clipping to stop the flow of air through the duct. Unfortunately, the patient was lost to follow-up. Re-evaluation of his medical record revealed that he did not present to the emergency room with pneumoparotid again.

Literature search

We performed a systematic search of the literature for paediatric case

Table 1: Differential diagnosis of facial swelling and parotid pathology.

Facial swelling	Parotid pathology
Allergies - Food allergies - Contact allergies - Hereditary angio-oedema	**Neoplasms** - Malignant - Benign
Inflammatory / infectious causes - Lymphadenitis (viral (EBV), bacterial) - Sinusitis - Odontogenic infections - Orbital / pre-septal cellulitis	**Infections** - Bacterial sialadenitis - Viral (HIV, mumps) - Tuberculosis
Generalised oedema - Cardiac pathology - Nephrotic syndrome	**Auto-immune pathology** - Recurrent parotitis of childhood - Sjögren disease - Granulomatous disease
Vascular malformations - Haemangioma - Lymphangioma	**Iatrogenic** - Anaesthesia mumps - Iodide mumps - Radioactive iodine sialadenitis
Tumours - Rhabdomyosarcoma - Langerhans cell histiocytosis - Ewing sarcoma - Osteosarcoma - Neuroblastoma	**Parotid duct pathology** - Sialolithiasis - Strictures - Pneumoparotid
Parotid pathology (cf. next column)	

Differential diagnosis of facial swelling and parotid pathology

Figure 1: Literature search and selected paediatric case reports.

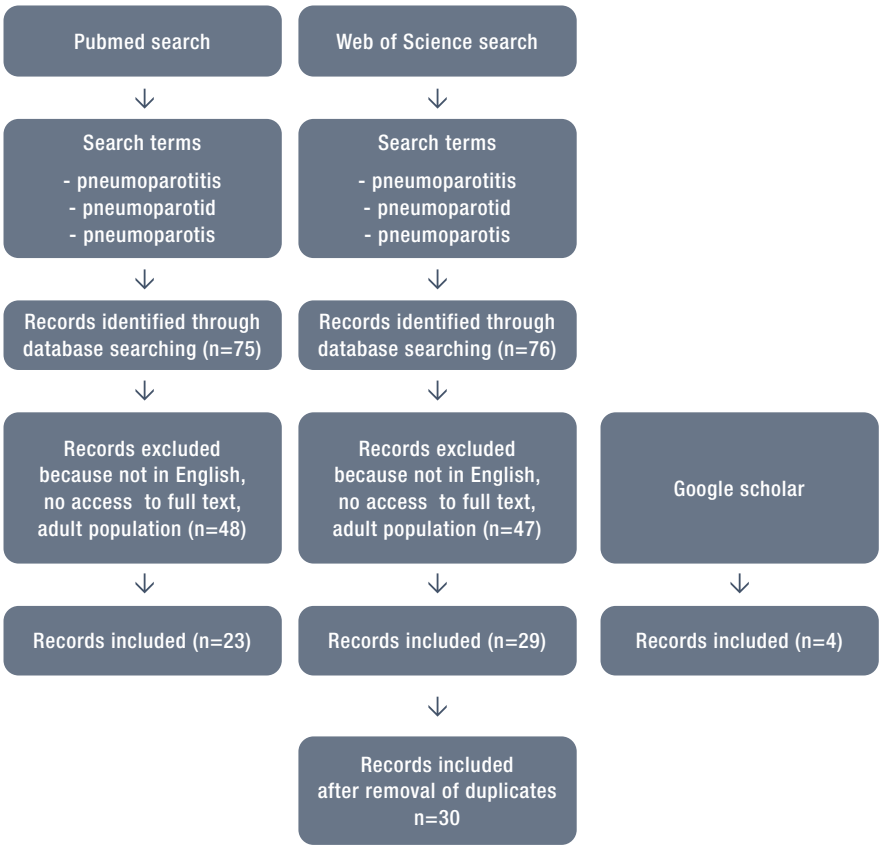
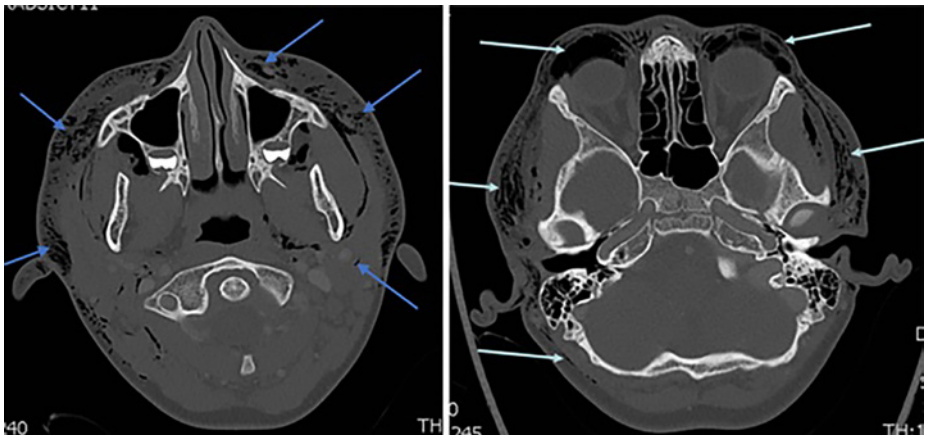


Table 2: Summary of the relevant clinical findings from the paediatric case reports.

Author	Date	Gender	Age	Complaints	Uni-bilateral	Recurrent	Investigations	Therapy	Cause
Ros et.al. (13)	1996	Boy	3 yrs	Pain, swelling	Unilateral	No	//	//	Blowing up balloons
Mutaf et.al.(14)	2006	Boy	3 yrs	Pain, swelling, redness	Unilateral	No	Blood test	NSAID	Anesthesia
Bowden et.al. (15)	2015	Boy	4 yrs	Pain, swelling, crepitus	Unilateral	No	X-ray, head CT	Reassurance	Blowing up balloons
Martin-Granizo et.al.(16)	1999	Girl	5 yrs	//	Uni- and bilateral	Yes	Blood test, X-ray, ultrasound, head CT	Antibiotics, hydration, warm compresses	//
Moschetta et.al. (8)	2021	Boy	5 yrs	Swelling, crepitus	Unilateral	No	Blood test, head CT	Antibiotics, anti-allergic therapy	Dental procedure
David et.al (17)	1988	Girl	6,5 yrs	Pain, swelling, warmth, redness	Unilateral	No	X-ray, MRI, head CT, cultures	Antibiotics, cannulating Stenson duct, positive reinforcement	Blowing the cheeks
Kyung et. al.(18)	2010	Girl	7 yrs	Pain, swelling	Bilateral	Yes	X-ray, head CT	Analgesia, antibiotics, stop trigger	Wind instrument player
McCormick et.al (10)	2012	Boy	7 yrs	Pain, swelling	Bilateral	Yes	Head CT	Antibiotics, NSAID, warm compresses, sialogogues	//
Martin-Granizo et.al. (16)	1999	Girl	8 yrs	Pain, swelling, crepitus	Unilateral	Yes	Sialography, head CT	//	//
Goguen et.al.(6)	1995	Girl	9 yrs	Pain, swelling, crepitus	Bilateral	Yes	Sialography, head CT	Antibiotics, massage, superficial parotidectomy	Valsalva manoeuvre
Gray et.al. (19)	2020	Girl	9 yrs	Swelling	Unilateral	No	Fine needle aspiration, head CT	//	Blowing the cheeks
Goguen et.al. (6)	1995	Boy	9 yrs	Swelling	Unilateral	Yes	Blood test, head CT	Antibiotics	Blowing against palm of hand
Krief et.al.(20)	1992	Boy	10 yrs	Pain, swelling, redness, crepitus	Bilateral		Blood test, fine needle aspiration, head CT, sialography	Antibiotics	Blowing the cheeks
Golz et. al.(21)	1999	Boy	10 yrs	Pain, swelling	Bilateral	Yes	Blood test, head CT	Psychological counseling	Blowing the cheeks
Luaces et. al.(22)	2006	Boy	11 yrs	Pain, swelling	Bilateral	Yes	X-ray, head CT	Antibiotics	Blowing the cheeks
Balasubramanian et.al. (7)	2007	Boy	11 yrs	Swelling, crepitus	Bilateral	Yes	Blood test, sialography, biopsy, head CT	Antibiotics	Valsalva manoeuvre
Lee et.al.(23)	2017	Boy	11 yrs	Pain, swelling, crepitus	Bilateral	No	Blood test, X-ray, ultrasound, nasolaryngoscopy, head CT	Antibiotics, analgesia, oxygen	
Markowitz-Spence et al. (24)	1987	Girl	12 yrs	Swelling	Bilateral	Yes	Blood test, sialography, head CT	Antibiotics, psychological evaluation	Valsalva manoeuvre
Grainger et al.(25)	2005	Girl	12 yrs	Pain, swelling	Bilateral	Yes	Sialography, head CT	Analgesia, antibiotics	Cold weather
Nassimbeni et al.(26)	1995	Boy	12 yrs	Swelling, crepitus	Bilateral	Yes	Blood test, sialography, head CT	Psychiatrist, psychologist	Wind instrument player, blowing the cheeks
Prabhu et al.(27)	2008	Boy	12 yrs		Bilateral	Yes	Head CT	Antibiotics	//
Ambrosino et. al. (11)	2019	Boy	12 yrs	Pain, swelling	Bilateral	Yes	Blood test, head CT, lip biopsy, sialendoscopy	Antibiotics, steroids, analgesia, massage	//
Raczkowkska-Labuda et.al. (28)	2019	Boy	12 yrs	Pain, swelling	Unilateral	Yes	Blood test, ultrasound, head CT, sialography	Antibiotics, intraductal dexamethasone	Blowing the cheeks
Aljeaid et.al.(29)	2020	Boy	12 yrs	Swelling	Unilateral	Yes	Blood test, head CT	Counseling	Blowing up balloons
Goguen et.al.(6)	1995	Boy	13 yrs	Swelling	Bilateral	Yes	Sialography, X-ray	Antibiotics, steroids, psychiatric counseling	Blowing the cheeks
Han et.al.(30)	2004	Boy	13 yrs	Swelling, crepitus	Uni- and bilateral	Yes	Sialography, head CT	Antibiotics, steroids, superficial parotidectomy, parotid duct ligation	//
Lagunas et.al.(9)	2017	Boy	13 yrs	Swelling	Bilateral	Yes	Head CT	Antibiotics, NSAID	Blowing the cheeks
Barros et.al. (31)	2022	Boy	13 yrs	Pain, swelling, crepitus	Bilateral	No	Blood test, ultrasound, head CT, X-ray	Antibiotics	Blowing up balloons
Sittel et.al.(32)	1999	Girl	14 yrs	Swelling	Bilateral	Yes	MRI	Antibiotics	Blowing the cheeks
Ferlito et.al.(33)	1992	Boy	14 yrs	Pain, swelling	Bilateral	Yes	Blood test, ultrasound, sialography, X-ray, fine needle aspiration	Antibiotics, NSAID, corticosteroids	Blowing the cheeks
Al Ohali et.al.(12)	2020	Boy	14 yrs	Swelling, crepitus	Unilateral		Head CT	Counseling	Blowing the cheeks
Birzgalis et.al.(34)	1993	Boy	16 yrs	Pain, swelling, crepitus	Unilateral	Yes	Blood test, head CT, fine needle aspiration	Antibiotics, parotidectomy	Valsalva manoeuvre
Alnaes et.al. (35)	2017	Girl	//	Pain, swelling, redness	Unilateral	Yes	Blood test, ultrasound, head CT, fine needle aspiration	Antibiotics	Blowing on a paper trumpet / sucking water bottles

reports of pneumoparotid. PubMed and Web of Science were searched on 09/12/2022 using the search terms 'pneumoparotid', 'pneumoparotitis' and 'pneumoparotis'. We retrieved all case reports in English, with full access texts and summarized the clinical findings in detail. We excluded 95 manuscripts based on age of the patients, language or full text access. After removal of duplicates, we reviewed 30 manuscripts from 1987 until present. Four case reports were selected after a search on Google Scholar (figure1). An overview of the relevant clinical findings from the paediatric case reports is shown in table 2.

Figure 2: Head CT. Arrows = air.



Discussion and comparison with the international literature

Definition

Pneumoparotid, first described in 1865 by Hyrtl, is defined as 'the presence of air within the parotid system' (gland and Stenson duct) (4, 5). The earliest reports from pneumoparotid cases date from 1915 and involved soldiers from the French Foreign Legion in North Africa, who blowed into a bottle to mimic mumps and as such avoid duty (2, 6). Pneumoparotid with associated infection is described as pneumoparotitis, and is a common complication (2, 4).

Mechanism

There are natural protective mechanisms that prevent air insufflation, but because of a supra-normal or sudden increase of intraoral pressure or defects in the preventive mechanisms of reflux, a retrograde insufflation of air through the Stenson duct can cause pneumoparotid (2, 5, 7, 8). Hypotonia of the buccinator muscle, hypertrophy of the masseter muscle and obstruction of the Stenson's duct by mucus are all risk factors (2, 4).

Cases of self-induced pneumoparotid are described in the literature (9).

Pneumoparotid is often misdiagnosed as parotitis, because of the presence of oedema and local pain in the parotid gland (4).

In a few cases there is a presence of air in the parapharyngeal and retropharyngeal space, an uncommon complication. This happens when glandular acini break down because of high intra-oral pressure. This causes an air leak to the surrounding cervicofacial subcutaneous tissues and facilitates communication with the para- and retropharyngeal space. In these cases it is possible that the air extends to the mediastinum and causes a pneumothorax or a pneumomediastinum (2, 9).

Patient population

One can divide the patient population into four subgroups: occupational cases (wind instrumentalists, glass blowers, underwater divers), iatrogenic cases (anaesthesia, dental procedures, CPAP, spirometry), cases associated with inhalation (nitrous oxide, deodorants) and self-induced cases (Valsalva manoeuvres, aggressive nose blowing, chewing gum, chronic cough suppression) (2, 4, 6, 9). In our case we strongly suspect self-induced pneumoparotid, an entity that has been described in adolescents with psychosocial issues. It can be a subconscious or a deliberate attempt to gain secondary benefits (6). In the literature, cases of adolescents who have conflicts with parents, problems with adolescent adjustment, nervous tics, abnormal behaviour or previous psychiatric treatment are reported (7). Self-induced pneumoparotid has been associated with secondary benefits, such as school absenteeism, which should alert clinicians to look for a psychological cause (7, 9, 10).

Physical examination

Pneumoparotid is a rare condition and many patients with this symptom are misdiagnosed and therefore wrongly treated as a 'bilateral parotitis' or a 'recurrent parotitis of childhood'. These patients present with uni- or bilateral swelling at the site of the parotid gland (11). Some authors describe it as a painful swelling, others describe a pain-free swelling (9, 11). Sometimes there is erythema or subfebrillity and sometimes there is crepitus over the parotid area. In some patients air bubbles exude from the Stenson's duct during massage or palpation of the parotid gland (4, 6, 9, 10, 12). Pneumoparotid can predispose to sialectasis, bacterial parotitis, subcutaneous emphysema, pneumomediastinum and pneumothorax (4, 7).

Diagnosis

The gold standard for diagnosis is computed tomography (Fig 2.). The CT scan usually shows air in the parotid system and by extension air in the surrounding tissues, ductal dilation is also a common finding (2). Ultrasound is performed in many cases and is a useful tool to differentiate superficial swelling in the head-neck area. It shows multiple hyperechoic areas, corresponding to air in the glandular parenchyma (2). A sialography shows absence of stones in the parotid duct and can sometimes show a dilated Stenson duct or air within the ductal system (6, 9). Laboratory examination shows no evidence of systemic pathology. A slight elevation in the white blood cell count is possible, as well as an elevation in the amylase level. A biopsy of the gland is not necessary, but can show acute and chronic inflammatory changes in the parotid gland.

Treatment

The enlargement and swelling of the parotid resolves spontaneously over the course of a few days (2). In the literature there are suggestions to give prophylactic antibiotics to prevent pneumoparotitis, because of the increased risk of retrograde introduction of oral microbes in the gland (4). Other suggestions are the use of anti-inflammatory drugs, massaging the parotid, hydration, application of heat or sialagogues (2, 9, 10).

When one encounters a case of self-induced pneumoparotid it is important to educate the patient. Sometimes it is necessary to refer the patient for psychotherapy (2).

The last option for severe recurrent pneumoparotid is surgical treatment. Suggested treatment options are transposition of Stenson's duct to the tonsillar fossa, ligation of the Stenson's duct or superficial parotidectomy. Surgical treatment should only be considered in recurrent cases and when the quality of life is significantly impacted. (2, 9, 10).

Conclusion

Pneumoparotid is a phenomenon where there is air in the Stenson's duct and throughout the gland. In some cases there is subcutaneous emphysema and pneumomediastinum because of breakdown of the acini in the gland and presence of air in the parapharyngeal and retropharyngeal space. The most frequent cause in adults and children is self-induced pneumoparotid, most often because of frequently blowing up the cheeks. The gold standard for diagnosis is a cranial CT. There is no consensus in the literature regarding treatment. Numerous treatment options, such as antibiotics, corticosteroids, are already explored because of a delay in diagnosis. Self-induced pneumoparotid is best managed with psychological counselling to stop the behaviour. Sometimes the condition is complicated with an infection on the gland, namely pneumoparotitis. In that case, therapy with antibiotics is warranted. When there is a high recurrence rate, surgical treatment is an option.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest with regards to the acquisition and reporting of the data of the study presented in this manuscript, all procedure were in line with the editorial policy of the Belgian Journal of Paediatrics.

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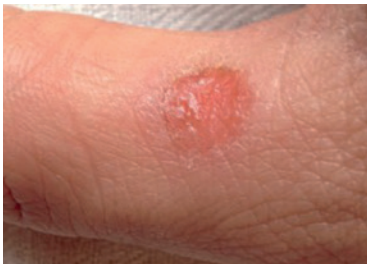

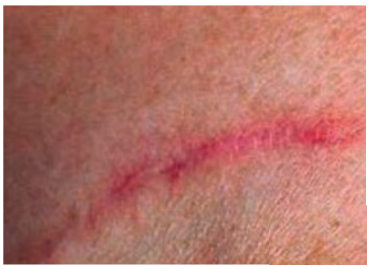

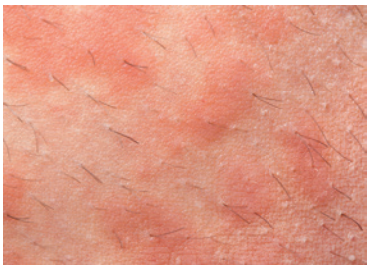

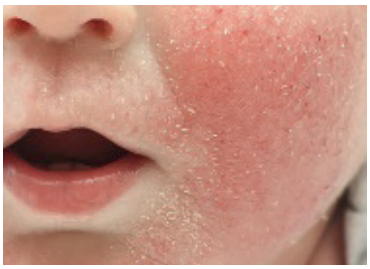

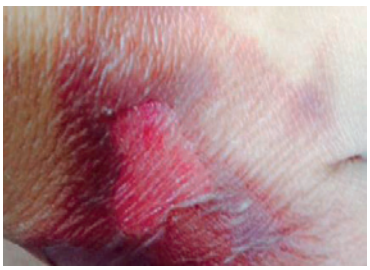

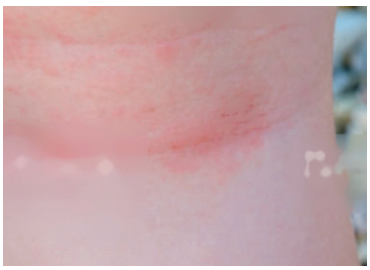

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Early recognition and access to terminal complement blockers in patients with atypical HUS significantly improves their outcome: a case report

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Keywords

Thrombotic microangiopathy, atypical haemolytic uremic syndrome, eculizumab, anti-factor H antibodies, case report.

Abstract

A 7-year-old boy presented with fever, pruritus and petechiae. Laboratory analysis revealed haemolytic anaemia with presence of schistocytes, thrombocytopenia and acute kidney injury, diagnostic for a thrombotic microangiopathy (TMA). Given the severe clinical presentation, the lack of evidence for verotoxin positive TMA and a normal ADAMTS13, treatment with eculizumab was started. This resulted in a complete resolution of the TMA course with recovery of the kidney injury. Workup revealed high titre of anti-factor H antibodies, diagnostic for an atypical haemolytic uremic syndrome (aHUS). This case demonstrates that early recognition and treatment of TMA is essential to optimize the outcome of these patients.

Background

Thrombotic microangiopathies (TMA) are a group of rare disorders characterized by microangiopathic haemolytic anaemia, non-immune thrombocytopenia, and organ dysfunction (1-4). Early diagnosis and treatment of TMA to prevent end organ damage has a high impact on the outcome and prognosis of these patients (3). This is especially true for the subgroup of children with atypical haemolytic uremic syndrome (aHUS), where dysregulation of the alternative complement pathway is involved (5-7). Early access to the terminal complement inhibitor eculizumab has drastically improved the prognosis of these vulnerable patients (1, 7). This case report describes a patient with aHUS who received successful treatment with eculizumab early in the course of the disease.

Case description

A previously healthy 7-year-old boy consulted the general paediatrician with fever, pruritus and cough. Physical examination revealed normal cardiocirculatory parameters and normal neurological status. Skin inspection during clinical examination revealed multiple petechiae on the upper body, together with some scratches. High normal blood pressure was noted with systolic values ranging between the 90th and 95th percentile. Other vital signs were unremarkable and there was no history of oliguria or anuria. Laboratory analysis revealed thrombocytopenia of 68 000/µL (reference range, 205 000 – 450 000/µL), haemoglobin of 11,5 g/dL (reference range, 11,3 – 14,2 g/dL) and an elevated lactate dehydrogenase (LDH) titre of 822 U/L (reference range, 120 – 300 U/L). Since several family members had an upper respiratory tract infection in the week prior to the patients' symptom onset, a working diagnosis of post-viral thrombocytopenia was presumed. The patient was subsequently sent home from the outpatient clinic.

However, the following day the patient returned to the clinic with worsening pruritus and petechiae, and new-onset vomiting. Laboratory analysis revealed haemolytic anaemia: haemoglobin 10,3 g/dL, LDH 1288 U/L and haptoglobin < 0,1 g/L (reference range, 0,3 – 2,0 g/L) with the presence of schistocytes. He also had thrombocytopenia (33 000/µL) and acute kidney injury with creatinine value of 1,28 mg/dL (reference range, 0,29 – 0,47 mg/dL), diagnostic for TMA. The boy was admitted to the paediatric intensive care unit for monitoring and initiation of treatment.

Timeline and interventions

Given the absence of an episode of bloody diarrhoea preceding this acute episode of TMA, as would be suspected in typical haemolytic uremic syndrome (HUS), an aetiological workup for atypical HUS was initiated. ADAMTS13 (also known as von Willebrand factor-cleaving protease) level was normal (0,79 IU/mL with reference range of 0,4 – 1,3 IU/mL), the Coombs test was negative and no Shiga toxin could be detected in serum and repeated stool samples (by culture and PCR). Complement levels were low to normal: complement component 3 (C3) was 0,729 g/L (reference range, 0,680 – 1,270 g/L) and C4 was 0,17 g/L (reference range, 0,230 – 0,470 g/L). Additional tests revealed low alternative pathway 50 (AP50) levels of 21% (reference range, 30-113%) but normal total haemolytic complement (90% with reference range between 69 and 129%). At the time of diagnosis, the boy's blood pressure was 114/83 mmHg (between 95th and 99th percentile). This remained fairly stable during admission, although the patient's renal function deteriorated (peak creatinine level of 8,32 mg/dL) and he subsequently developed signs of uremic encephalopathy. As initial investigations were negative for Shiga toxin-associated *Escherichia coli* haemolytic uremic syndrome (STEC-HUS) and TTP (thrombotic

thrombocytopenic purpura), he received a first dose of eculizumab after vaccination against *Neisseria meningitidis* serogroups A, B, C, W and Y (with *Menveo*® and *Bexsero*®) and initiation of antibiotic prophylaxis. Initially third generation cephalosporins were given intravenously, but after 4 days the patient was switched to oral amoxicillin. Eculizumab was administered 10 days after the boy's initial presentation. The patient was on supportive care only until the first dose of eculizumab. Two days after eculizumab administration, the patient was started on peritoneal dialysis.

Following his first eculizumab infusion a marked clinical and biochemical improvement was observed. Figure 1 clearly shows that thrombocytopenia and haemolysis parameters recovered within 30 days. Due to a significant improvement in renal function, peritoneal dialysis could be discontinued seven days after treatment initiation (figure 1). On day 23 of hospitalisation, the patient was discharged while maintained on eculizumab.

Subsequent results showed high levels of anti-complement factor H (CFH) antibodies (titre: 19 584 arbitrary units (u Arb), normally < 150 u Arb) with only 27% of factor H activity (reference range, 78-108%), confirming the diagnosis of aHUS. In addition, genetic analysis detected a homozygous deletion of CFHR1 and CFHR3.

One month after the first infusion of eculizumab, corticosteroids and mycophenolate mofetil were added to treat the autoimmune basis of the disease, resulting in a decrease in anti-CFH antibody titre (< 200 UAb) two months later.

12 months after initial presentation, the patient has an excellent renal outcome with a normal glomerular filtration rate (GFR), no proteinuria and normal blood pressure while on a low dose of angiotensin-converting enzyme (ACE) inhibitors.

Discussion

TMA consists of a triad of microangiopathic haemolysis, thrombocytopenia and evidence of endothelial cell damage leading to a life-threatening systemic disease characterized by acute kidney injury, neurological or gastrointestinal complications with high morbidity and mortality (figure 2) (2, 3, 5). Shiga toxin-associated haemolytic uremic syndrome (STEC-HUS), thrombotic thrombocytopenic purpura (TTP) and atypical HUS (aHUS) are the most important disorders within the TMA group (5). Differentiation between these three disorders must be made, which can be done with verotoxin screening (culture or PCR) to exclude STEC-HUS and ADAMTS13 diagnostics for TTP. The distinction between these diseases is important because of the need for different therapeutic approaches: i.e. supportive therapy for STEC-HUS versus plasmapheresis for TTP (2, 5, 6). In children, aHUS must always be considered in previously healthy patients with HUS who have no evidence of STEC-HUS and a normal ADAMTS13 activity (2, 8). In addition to STEC, other infectious causes such as *Streptococcus pneumoniae* or viral agents (e.g. HIV, influenza, hepatitis B or C, etc.) can cause TMA and always have to be considered. In patients with comorbidities, TMA can be associated with the co-morbid condition itself, for example in patients with malignancies or those who have undergone haematopoietic stem cell transplantation. Autoimmune diseases, malignant hypertension, pregnancy, cobalamin C deficiency and some drugs (e.g. cocaine) are also known to trigger TMA (3, 9).

In the paediatric population, STEC-HUS (also previously called "typical HUS") is the most prevalent underlying cause of TMA. Hallmark in the pathophysiology of STEC-HUS is the production of verotoxin by an infectious pathogen (most commonly *Escherichia coli*) in the gut. After absorption of verotoxin from the gut into the circulation, verotoxin is translocated to the microvascular endothelial cells making it responsible for renal and colonic endothelial cell injury. This stimulates the generation of thrombin and the deposition of fibrin in the microvasculature. The concentration of PAI-1 (Plasminogen Activator Inhibitor 1) rises, which blocks fibrinolysis, exacerbating the thrombotic injury (10). Typically, patients with STEC-HUS present with fever and bloody diarrhoea. In the majority of patients these symptoms occur in the early phase, with a typical complaint free interval before the TMA, but are not required for diagnosis. Additionally, the central

Figure 1: Evolution of laboratory findings, illustrating creatinine, haemoglobin, LDH and thrombocyte values according to treatment.
RPC: red packed cell transfusion; PD: peritoneal dialysis; MMF + P: mycophenolate. mofetil + prednisolone.

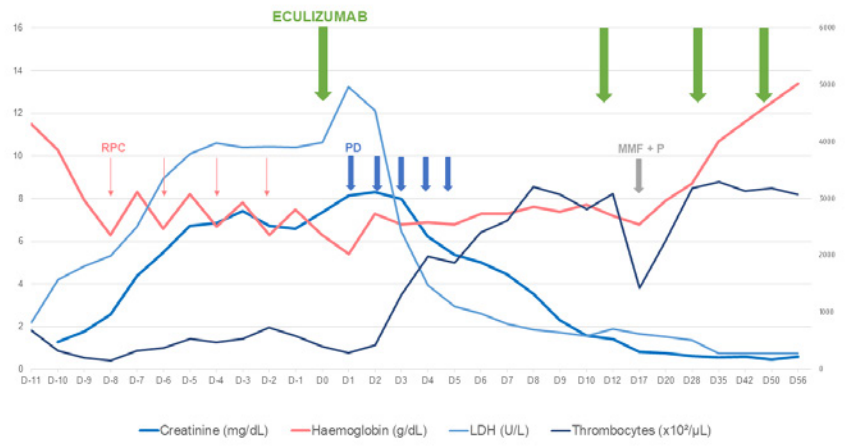
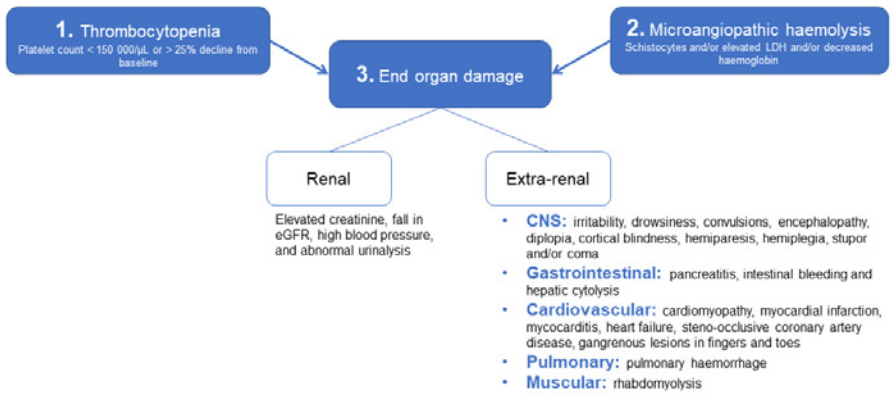


Figure 2: Visualisation of the triad of TMA with clinical and biochemical manifestations (3,5).
CNS: central nervous system.



nervous system, pancreas and other organs can be affected by the Shiga toxin, which explains the clinical variability of STEC-HUS (3).

In contrast, atypical HUS (aHUS) is a rare cause of TMA, characterized by a loss of control of especially the alternative pathway of the complement, which will also result in the classical triad of TMA (1, 3). The most important regulators of the alternative complement pathway are complement factor B (CFB), factor H (CFH), factor I (CFI), membrane cofactor protein (MCP) and thrombomodulin (3, 5, 8). About 65% of patients with aHUS carry mutations in complement genes that result in the loss of protection from formation of the membrane attack complex and eventually in TMA lesions (4). Production of anti-CFH antibodies as presented in this case, also causes an overactivation of the alternative complement pathway, leading to the pathogenesis of aHUS (1, 5). The presence of anti-CFH antibodies is strongly associated with a genomic homozygous deletion of *CFHR1* and *CFHR3*, which was also the case in our patient (1, 2, 6, 9). Kavanagh et al. suggest that a deficiency of CFHR1 is a predisposing factor in the development of autoantibodies (1). Although not all patients with *CFHR1* deletion will display anti-CFH antibodies. According to Raina et al., nearly 10% of the patients with anti-CFH antibodies do not show a deletion in *CFHR1* (11). Studies show that between 21% and 25% of patients presenting with aHUS have CFHR deletions (1, 5). The incidence of these CFHR deletions varies regionally, for example in a South-Korean study 29% of children with aHUS had a homozygous deletion in the *CFHR1* gene and 73% of patients with anti-CFH antibodies had this deletion (2). The homozygous deletion of *CFHR1-R3* is a polymorphism carried by 2-9% of Europeans, 16% of Africans and less than 2% of Chinese people (6).

Eculizumab is a humanized monoclonal IgG antibody that inhibits C5 cleavage and thus the generation of the pro-inflammatory molecule C5a and the formation of the cell membrane attack complex preventing downstream effects of overactivation of the alternative complement pathway efficiently (5, 6, 12). Most recent studies show a complete TMA response in 50-85% of the patients with aHUS (5). Before the availability of eculizumab, prognosis of aHUS was poor, with 30-50% of children developing renal failure stage 5, high relapse after transplantation and a total mortality rate of 8-25% (7, 12). Two decades ago, the gold standard for management of aHUS was plasma exchange, aiming to replace the non-functioning complement proteins and remove the CFH autoantibodies out of the circulation. Unfortunately, in children, the complication rate of plasma exchange is high. Liver transplantation was also considered in the past, especially in patients with CFH mutations, although studies showed limited success with a lot of perioperative morbidities. Donor shortage also makes this a less favourable option. Given the high cost of eculizumab, plasma exchange is still the only available option in low-income countries (1, 2).

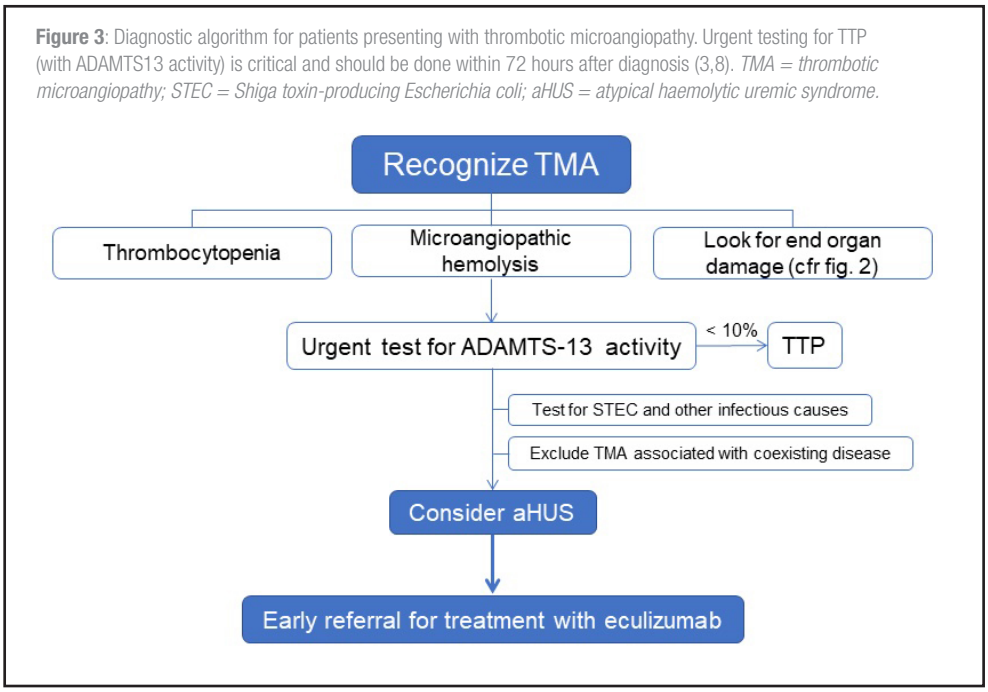
The introduction of eculizumab has significantly improved the outcome of patients with complement mediated aHUS. In the 2016 international consensus approach it is suggested to use eculizumab as first-line treatment in children with a suspicion of aHUS (6). The existence of a window-of-opportunity has also been demonstrated, with earlier treatment initiation leading to a better renal outcome (1, 6, 8). Patients receiving eculizumab should be immunised against meningococcal and pneumococcal infections, as the use of eculizumab implies a hampered immune response to encapsulated bacteria (4, 7, 12).

Initially, life-long treatment with eculizumab was claimed, but there is increasing evidence that there might be several subtypes where discontinuation of therapy after six months is defendable. The highest relapse rates after interruption of therapy are in patients with factor H mutations (1, 6, 9). After the initial treatment with eculizumab in patients with an autoimmune form of aHUS, long-term immunosuppressive treatment should be initiated to maintain a reduced level of anti-CFH antibodies and to prevent relapses, allowing to stop eculizumab (8). In our case the association of corticosteroids and mycophenolate mofetil led to a favourable decline in the anti-CFH antibody titre. With the observed immediate and persistent recovery from dialysis, our case confirms that eculizumab is efficient in patients with aHUS with severe renal involvement.

Nevertheless, eculizumab is widely accepted as a highly effective therapy for children with aHUS. The downside of this therapy is the need for intravenous administration every two weeks often over a long period of time, which has a major impact on the child's quality of life: frequent veinpunctures and hospital visits, frequent absences from school, etc. New complement inhibitors with longer treatment intervals and/or subcutaneous administration (i.e. ravalizumab and crovalimab), allowing administration at home are on their way to tackle the burden of the current therapy (13, 14). In addition to the psychosocial impact of treatment with eculizumab, this therapy remains a very expensive drug that imposes a high financial burden on society. To date, the drug is not available in all countries and initiatives are needed to both improve equitable access of this therapy worldwide and to guarantee that is it used in the correct indications (15).

Although aHUS is a rare disorder in the paediatric population, every paediatrician should be aware of the disease when a patient presents with TMA, especially if a non-STEC-HUS is likely. Early recognition and screening for this condition is essential to maximise the outcome of these children, especially in the current era of life-changing biologic treatments such as eculizumab. With this case report, we would like to highlight the importance of an early referral of the patient to a specialised centre in parallel with an early initiation of TMA diagnostic work-up (figure 3). Early referral and diagnosis will promote early

Figure 3: Diagnostic algorithm for patients presenting with thrombotic microangiopathy. Urgent testing for TTP (with ADAMTS13 activity) is critical and should be done within 72 hours after diagnosis (3,8). *TMA = thrombotic microangiopathy; STEC = Shiga toxin-producing Escherichia coli; aHUS = atypical haemolytic uremic syndrome.*



access of those patients with non-STEC-HUS to specialised treatment such as plasmapheresis and eculizumab and to expertise in metabolic diseases and others. Therefore, we recommend prompt contact with TMA reference centres upon diagnosis of TMA and urgent diagnostic screening within 72 hours of diagnosis of TMA for STEC-HUS and other types of post-infectious TMA, TTP and secondary forms of TMA (2, 5, 6).

Conclusion

Early recognition of thrombotic microangiopathy and referral to reference centres is essential to optimise the outcome of patients with TMA. Every patient with TMA should receive an urgent and comprehensive work-up with Shiga toxin screening, ADAMTS13 diagnostics and exclusion of secondary forms of TMA. In this way, patients with a negative initial work-up may qualify for first-line treatment with eculizumab early in the course of the disease, which may subsequently improve the prognosis of these children.

Conflicts of interest

The authors did not receive support from any organization for the submitted work.

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Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden: fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745. Frequentie niet bekend: sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden: anafylactische shock Bloedvataandoeningen Zeer zelden: anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden: dyspneu Maagdarmstelselaandoeningen Zeer zelden: verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden: jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden: dorst Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijk bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem (Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg.be). HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Marie Curiesquare 20 - 1070 Brussel - België Tel: 0032(0)23704790. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026. Enterol 250 mg harde capsules in glazen flesje: BE 269035. Enterol 250 mg harde capsules in blisterverpakking: BE 397896. AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 01/2023. Goedkeuring: 03/2023.

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Infant feeding practices and probiotics effects on nutritional recovery and morbidity of severely malnourished infants in Democratic Republic of Congo

PhD thesis defended on June 15th, 2023 at UCLouvain, Brussels, Belgium

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Keywords

Infant feeding practices; malnutrition; diarrhea; nutritional recovery; probiotics.

Abstract

Severe Acute Malnutrition (SAM) is a major public health concern. Recent evidence has shown that dysbiosis leads to malnutrition and recurrent infections. Several interventions targeting the gut microbiota, including probiotics, have emerged as promising treatment. We assessed infant and young child feeding (IYCF) practices, infectious diseases experienced by children with SAM, and the effect of probiotics on the pneumonia, diarrhea, and nutritional recovery in children with SAM in Democratic Republic of Congo. IYCF practices were suboptimal; the main infectious diseases of children with SAM were pneumonia, diarrhea, bacteremia and malaria; probiotics reduced the number of days with diarrhea, if any, and the risk of diarrhea in children aged 16 months and older; a higher proportion of children receiving probiotics reached nutritional recovery after 6 weeks, but at 12 weeks, no effect was found. Optimization of mother-child nutrition, microbiological surveillance of children with SAM, and implementation of local probiotic-based foods may improve the survival of children with SAM.

Background

Malnutrition is a major public health concern, affecting around 45 million children worldwide. Malnutrition increases incidence, severity and case fatality of common infections, and underlying 35% of all child deaths globally. Recent evidence has shown that malnutrition is not due to food insecurity alone, but reflects a combination of factors, including an important role of the gut microbiota, which fails to develop properly during the first two years of life in malnourished children. Dietary interventions alone are insufficient to comprehensively reduce the burden of child malnutrition and fail to address the persistent infectious burden of the disease. With the advancement in knowledge of the key role of gut microbiota disruption in childhood malnutrition, several interventions targeting the gut microbiota have emerged as promising treatment modalities.

This thesis aimed to (i) assess infants' feeding practices in a general population sample from South Kivu; (ii) identify the main infectious diseases experienced by children with severe acute malnutrition (SAM) and, (iii) assess the effect of probiotics on the main childhood killer infectious diseases (pneumonia and diarrhea), and on nutritional recovery in children with SAM

Methods

The thesis reports the results of four studies: two cross-sectional studies, one systematic review with meta-analysis, and one randomized controlled trial (RCT) (1, 2, 3, 4). Except for the systematic review, all studies were conducted in South Kivu province, (eastern Democratic Republic of Congo (DRC)), in 3 Health Zones: Ibanda (urban area) and Kabare (rural area) Health Zones for the first cross-sectional study; and Kadutu Health Zone (urban area) for the second cross-sectional study and the RCT. Selection of these Health Zones was based on demographic, epidemiological, accessibility, and logistical criteria.

In the first cross-sectional study assessing infants' feeding practices in urban and rural areas of South Kivu, the sample size was 750 mother-infant's pairs (375 in each area). The second study assessed the main infectious diseases experienced by children with SAM. An exhaustive sampling was used. The systematic review included 15 RCTs. Finally, in the 4th study assessing the effect of probiotics on diarrhea, pneumonia and nutritional recovery, the sample was 400 infants (200 in probiotics group and 200 in placebo one). The study was performed in accordance with the principles in the Declaration of Helsinki of 1975 as revised in 1983. Children were enrolled after verbal and written consent had been provided by their caregivers. Caregivers were made aware of their right to withdraw from the study at any time. Ethical approval was granted by the Université catholique de Bukavu Ethics Committee (Bukavu/DRC, UCB-CIES 01-05/2020) and the Comité d'Ethique hospitalo-Universitaire of the Université catholique de Louvain and Cliniques Universitaires Saint-Luc (Brussels/Belgium, 04-01-2021).

Findings

Main findings are summarized as follows:

- Less than 30% of infants consumed flesh foods, dairy products, eggs, fruits and vegetables, predominantly in rural areas.
- The rate of minimum acceptable diet was 33%.

- Mothers living in urban area [Adjusted Odds Ratio (AOR) 2.39; 95% CI 1.43, 3.85], those who had postnatal care visits (AOR 1.68; 95% CI 1.12, 2.97), those with secondary or post-secondary education level (AOR 1.83; 95% CI 1.20, 2.77), and those with good household socioeconomic level (AOR 1.72; 95% CI 1.14, 2.59) were more likely to give recommended minimum acceptable diet compared to their counterparts.
- Pneumonia (16%), bacteremia (6%), gastroenteritis (5%) and malaria (5%) accounted for 32% of confirmed diagnosis in children suffering from SAM.
- For children suffering from diarrhea, the number of days of disease was lower in probiotics [4.11 (95%CI: 3.37, 4.51)] compared with placebo group [6.68 (95%CI: 6.26, 7.13)] ($p<0.001$).
- For children aged 16 months or older, the risk of diarrhea was lower in probiotics [75.6% (95%CI: 66.2, 82.9)] compared with placebo group [95.0% (95%CI: 88.2, 97.9)] ($p<0.001$), but no significant difference of the risk for the youngest.
- In probiotics group, nutritional recovery happened earlier: At the 6th week, 40.6% of the infants were waiting for nutritional recovery, contrasting with 68.7% of infants in placebo group; but the nutritional recovery rate at the 12th week was similar between groups.
- Probiotics had no effect on pneumonia incidence.

Conclusions

Our thesis research has shown that the minimum acceptable diet rate remained low among infants, especially among mothers with low school attendance and those non-attending prenatal care. As part of nutrition optimization among those at risk, the nonadherence to minimum acceptable diet should urgently be addressed through appropriate and widespread counseling.

This thesis further demonstrates an increased incidence of pneumonia, gastroenteritis, bacteremia and malaria among children with SAM. Since data are lacking on pathogens and their antimicrobial susceptibility in children with SAM in DRC, future research should fill this gap to distinguish children with SAM who require antimicrobial therapy and the type of antimicrobial that is appropriate.

Finally, this PhD research has shown that probiotics significantly reduced the number of days of diarrhea, the risk of diarrhea in older infants (>16 months), and the time to reach nutritional recovery. Future research is needed for economic analysis of scaling up probiotic's use nationally and internationally, and exploration of local microbiota-directed complementary foods.

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Erratum

ERRATUM

In the publication of the article 'Familial chronic metallic mercury intoxication due to a broken sphygmomanometer, a case report, by Louise Callewaert et al' (Belg J Paediatr 2023;25,1:45-48), a paragraph was printed incorrectly due to a publishing problem. We apologise for this. The correct version of the article can be found below.

The Editorial Team

Familial chronic metallic mercury intoxication due to a broken sphygmomanometer, a case report

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Keywords

Chronic mercury intoxication; metallic mercury; acrodynia; DMPS; case report.

Abstract

Background. Chronic intoxication with metallic mercury is rare in children in industrialised countries and is usually accidental.

Case. We report the case of a 10-year-old boy who presented with thigh pain, maculopapular rash, acral skin desquamation and hypertension (acrodynia) and neuropsychiatric symptoms such as insomnia and behavioural changes (erethism mercurialis). In addition, four other family members showed similar symptoms. A broken mercury sphygmomanometer was found in their house. Urinalysis revealed elevated mercury levels. They were treated with chelation therapy using DMPS.

Conclusion. Knowledge of the disease is crucial for diagnosis. Prompt therapy start is necessary to avoid residual neurological damage.

Introduction

Mercury intoxication is a rare phenomenon that can occur acutely or chronically. Mercury exists in different chemical forms: elemental or metallic (Hg^0), mercurous (Hg_2^{2+}) and mercuric (Hg^{2+}). The mercuric state is found in different inorganic and organic compounds (1). Elemental mercury, also called metallic mercury or quicksilver, is found e.g. in medical measuring instruments (thermometers) and dental amalgam. Inorganic mercury is used as a preservative in vaccines (ethylmercury, thimerosal) and organic mercury is found in seafood (methylmercury) (2).

In industrialised countries, the cause of metallic mercury intoxication in children is usually accidental (2). When a source of liquid mercury breaks, toxic vapours (Hg^0) are released. These are absorbed mainly by inhalation into the lungs (80%) and thus into the bloodstream. Also, there is a minimal absorption of metallic mercury via the gastrointestinal system (10%) and the skin (1%). In pregnant women, mercury also passes transplacentally to the foetus. Hg^0 preferentially passes through the blood-brain barrier into the central nervous system. In the bloodstream, Hg^0 is oxidised to the more toxic Hg^{2+} state. From there, it spreads to several organs and leads to organ dysfunction. Consequently, organs such as adrenal glands, kidneys, liver, muscles, skin and peripheral nervous system are damaged (1).

'Acrodynia', also called 'Pink's disease', is considered a hypersensitivity reaction to mercury in young children. It involves a maculopapular skin rash with swelling and subsequent acral desquamation. There is itching, tingling and burning pain in the extremities. There are also headache, fever, anorexia, diaphoresis, hair loss and gingivitis with hypersalivation. Hypertension and tachycardia are also observed. Chronic intoxication with mercury vapours mainly results in neuropsychiatric symptoms, called 'erethism mercurialis'. Features include insomnia and asthenia, behavioural changes with irritability, memory impairment, personality changes and tremor or ataxic gait. Prenatal intoxication causes delayed foetal development resulting in neurocognitive and motor deficits (2,3).

Case presentation

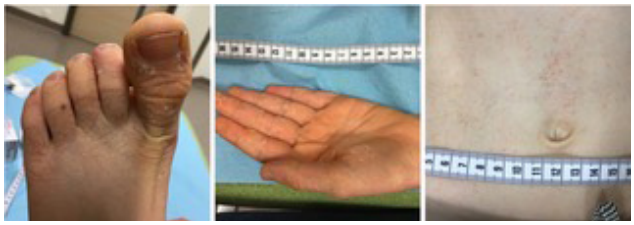
Patient information

A 10-year-old boy presented to the emergency department with thigh pain, a maculopapular rash on the trunk and acral skin desquamation as chief complaints. Figure 1 shows the course of complaints over time. The complaints arose after a paucisymptomatic covid infection three months before and evolved progressively. The thigh pain was bilateral, described as pressing, and continuously bothersome. Simultaneously, a truncal maculopapular rash developed as well as swelling of the fingers and toes with subsequent skin desquamation. He further complained of hypoesthesia of the extremities and tremor of the hands. Also, there was fatigue and anorexia with weight loss. He experienced occasional frontal headaches. He had attacks of diaphoresis and generalised pruritus and, recently, hypersalivation. Psychologically, the school noted attention and concentration disorders. He had not attended school for one month because of these problems. This was also noted at home with concomitant agitation as behavioural changes and insomnia for three months.

Four other family members showed similar symptoms. The 3-year-old brother had insomnia and deteriorating behavioural changes since

Figure 1: Timeline: the course of complaints over time until presentation at the emergency department.

Figure 2: Pictures of acrodynia: swelling, erythema and desquamation of the acra and truncal rash.



three months. He also presented with a rash with acral desquamation, tingling legs, pruritus, anorexia with weight loss and hair loss. The 8-year-old sister presented with anorexia, extremity pain, behavioural changes and nightmares. The 42-year-old father had complained of difficulty concentrating, irritability, insomnia and fatigue for five months. The 39-year-old mother had similar complaints as the father to a lesser extent. No visible peculiarities were found in the 8-month-old daughter.

Clinical findings

On clinical examination, the boy looked uncomfortable and dystrophic. As shown in Figure 2, a papular rash with excoriations was visible on the trunk and the skin on the hands and feet showed swelling, erythema and desquamation. Detailed general clinical examination was reassuring. A blood pressure of 140/94 mmHg and a heart rate of 150 bpm were noted. The boy was hospitalised for further investigations.

Diagnostic assessment

An infectious or toxicological cause was considered most likely as other family members displayed similar symptoms.

Except for mild leucocytosis, blood analysis was not abnormal. Inflammatory-immunological parameters (such as CRP, ESR, ferritin, immunoglobulins and complement factor) and rheumatological markers (such as RF, CCP, ANA, ANCA, ENA, CK and aldolase) were negative. Transaminases and complete blood count with differential were normal. Evaluation for infectious pathogens on urine sample, nasal swab, throat culture, serology and stool sample was negative. Blood pressure monitoring and ECG confirmed arterial hypertension and sinus tachycardia. Blood analysis for renal function, thyroid tests, aldosterone, renin and electrolytes were within normal values. Urinalysis showed elevated catecholamines, mild haematuria and no proteinuria. Abdominal ultrasound and doppler revealed neither masses nor vascular abnormalities. Toxicology screening for common heavy metals (Cu, Zn, Pb, Se, As, Tl) was negative. Furthermore, in the context of headache and behavioural problems, EEG and brain

Table 1: Mercury levels in urine and blood pre- and post-chelation therapy.

family members		10-year-old boy	8-year-old sister	3-year-old brother	8-months-old sister	39-year-old mother	42-year-old father
urine (µg/g creatinine)	pre-therapy (normal value <3 µg/g creatinine)	33.0	22.4	69.6	66.3	21.0	13.8
	post-therapy day 0 day 1 day 3 day 12	 2727.1 301.7 43.7 29.7	 2397.6 143.0 42.2 23.9	 1676.6 125.6 41.3	 1035.0 437.4 73.9	 57.2 48.2	 34.0 34.9
blood (µg/L)	pre-therapy (normal value <10 µg/L)	4.8	2.4	5.7	5.8	3.9	2.5
	post-therapy day 2 day 10	 2.3 2.0	 2.5 1.1	 4.7 2.8	 5.2 2.3	 1.7	 1.2

MRI were performed that were normal. To investigate the pain in the thighs, an EMG and MRI of the upper legs were done. Microscopic examination and culture of the skin showed no abnormalities.

Finally, a broken mercury sphygmomanometer was found in the garage. Mercury was then determined in a 24-hour urine collection with a positive result of 33.0 µg/g creatinine. After the diagnosis, the whole family was tested. The other children and parents also showed excessive mercury levels in the urine, see Table 1. In the blood, the mercury levels were within normal values.

Therapeutic intervention

Because of the suspicion of mercury intoxication, the family moved house to end the exposure. Mercury chelation was started with DMPS (2,3 dimercapto-1-propanesulphonic acid) intravenously 5mg/kg according to this schedule: day 1 6x/24h, day 2 4x/24h and day 3 3x/24h. From day 4 1x/24h taken orally until the urinary mercury levels normalise. As seen in Table 1, a significant increase in urinary mercury levels was observed in the children after starting chelation therapy. Levels also increased in the parents. Amlodipine at 0.67mg/kg/day provided good control of hypertension. For neuropathic pain, gabapentin at 40mg/kg/day offered relief. For the itching, desloratadine and topical corticoid cream were given.

Follow up and outcomes

The complaints decreased with treatment. Urinary mercury levels were also on a downward trend, see Table 1. The family was closely monitored and their symptoms fully disappeared.

Discussion

Children are vulnerable

The urinary mercury levels were higher in the children than the parents and the children had more symptoms than the parents. Children typically have higher body concentrations at similar exposures than adults. Their vulnerability lies, on the one hand, in increased exposure to mercury vapours. Being heavier than air, they sink to the ground, hence closer to the smaller child. Children also inhale more vapours due to their higher respiratory rate. Also, they come into contact with the peculiar substance more because of their curiosity. On the other hand, children are more susceptible to intoxications due to their still developing nervous system. Consequently, persistent neurological damage is more common in children (2,4). Note that the detection of neuropsychiatric changes in a baby can be more challenging.

Neither children nor adults should have any mercury in their bodies because it provides no physiological benefit. Prenatal and postnatal mercury exposures occur frequently in many different ways. Paediatricians, nurses, and other health care providers should understand the scope of mercury exposures and health problems among children and be prepared to handle mercury exposures in medical practice. Prevention is the key to reducing mercury poisoning.

Diagnosis

Chronic mercury intoxication is diagnosed based on environmental history, clinical presentation and response to chelation therapy (2). Normally, the urinary mercury determination is done on a 24-hour collection but for the two youngest children, a single sample was used because of practical considerations. Urine and blood mercury levels only reflect recent exposure. Therefore, they do not correlate well with disease severity. Urine mercury levels after provocation with a chelator correlate better with total body burden in the organs (1,5). For non-professional exposure, urinary values are normally <3 µg/g creatinine or <10 µg/L. For professional exposure, they increase to <30 µg/g creatinine. Values >10-20 µg/L are indicative of overexposure. All family members had elevated pre-therapy urinary mercury levels consistent with overexposure. After provocation with DMPS, there was a significant increase in urinary mercury levels in the children, implying a large body burden. See Table 1. All blood levels were within normal ranges (<10 µg/L). One explanation may be that the blood samples were taken days after the mercury exposure ended (2,6).

Chelation therapy and response

Chelation therapy aims to bind the accumulated mercury in the organs for faster renal clearance. DMPS was chosen because of its high affinity for metallic mercury, its safety and its frequent use in Europe compared to DMSA (dimercaptosuccinic acid) (1,5). The dosing schedule of UMC Utrecht antivenom centre was used (7). Therapy response was evaluated by symptom reduction and urinary mercury levels. The levels usually show an increase at therapy initiation due to release of mercury from the kidneys followed by a gradual decrease (5). Additionally, a decrease in urinary catecholamines can be expected as mercury no longer inhibits their catabolism (8).

Conclusion

Chronic mercury intoxication is rare in industrialised countries and therefore little known. Greater awareness is crucial for diagnosis, saving resources, appropriate therapy and avoiding complications. In children presenting with neuropathic pain, skin rash with desquamation, insomnia, behavioural changes and hypertension, one should always consider mercury intoxication. Once the diagnosis is considered based on clinical presentation, it is easily made by urine mercury levels before and after provocation with chelation therapy. Prompt therapy start with DMPS reduces the risk of permanent neurological damage.

Informed consent

The family provided verbal informed consent for publication.

Acknowledgments

The authors gratefully acknowledge the contribution of the doctors and staff working on this case at the Paediatrics Department of the Brussels University Hospital. Also, they would like to thank the professionals contacted for toxicology advice and English translation.

Competing interests

The authors state no conflict of interests.

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Late onset neonatal Candida albicans osteomyelitis and arthritis: a case report and literature review

To the Editor

Dear Editor,

Reading the article "Late onset neonatal Candida albicans osteomyelitis and arthritis" in the March 2023 issue of the Belgian Journal of Paediatrics, I was surprised that immunologic screening and/or the possibility of an immune deficiency was not discussed in more detail (1).

Severe / recurrent fungal infections are, in my limited immunologic knowledge, an immune deficiency until proven otherwise. IgG, IgA, IgM and C3/C4 were determined, but I don't think these are the most logical tests for this infection. For example, neutrophil dysfunction or T cell problems would be better to check.

It might be interesting to discuss this with an immunologist. I think making doctors more aware of immune deficiencies would be very helpful.

Yours sincerely,

Susanne van Steijn

Koningin Paola Kinderziekenhuis, Department of Pediatrics and Pediatric Pulmonology, Antwerp, Belgium

1. Kirat N, Van Mechelen K, De Beaumont J, Driessche KV, Fabry K, De Smet E, et al. Late onset neonatal Candida albicans osteomyelitis and arthritis: a case report and literature review. Belgian Journal of Paediatrics. 2023;25(1):11-7.

Author's reply

Dear Editor,

We thank Dr. Suzanne van Steijn for her comment on our manuscript entitled "Late onset neonatal Candida albicans osteomyelitis and arthritis" published in BPJ 2023;25(1).

We acknowledge that cellular immunodeficiency is a significant risk factor for invasive Candida infection, as shown in the table of potential risk factors for Candida infection in our manuscript. Undoubtedly, extreme prematurity in neonates weighing less than 1000 grams as an underlying immunodeficiency is a well-recognized risk factor, along with other additional factors in our patient's case, such as prolonged exposure to intravenous lipids, broad-spectrum antibiotics, and prolonged use of central lines.

However, we did not exclude the possibility of a primary cellular immunodeficiency in this child, as suggested by Dr. van Steijn, for several reasons. First, the risk factors mentioned above. Second, the blood volume required to perform neutrophil function tests and flow cytometry for T-cell and B-cell quantification was not available. Third, the favorable clinical response to antifungal treatment. Finally, the patient was lost to follow-up after clinical improvement and relocation outside Belgium.

Furthermore, to the best of our knowledge, there are no reported cases of invasive Candida infection as the initial manifestation of primary immunodeficiency in neonates.

Yours sincerely,

Nesrine Kirat, Karen Van Mechelen, Joelle De Beaumont, Koen Vanden Driessche, Kristof Fabry, Eline De Smet, Ludo Mahieu

University of Antwerp, Antwerp University Hospital, Department of Neonatology, Edegem, Belgium

Prix public **€ 86,52**

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

qui le fera ?

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

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

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

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT : Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT :** Bexsero suspension injectable en seringue préremplie. Vaccin méningococcique groupe B (ADNr, composant, adsorbé) ; EU/1/12/812/001,EU/1/12/812/002. EU/1/12/812/003, EU/1/12/812/004. Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09. **COMPOSITION QUALITATIVE ET QUANTITATIVE :** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de *Neisseria meningitidis* groupe B[1,2,3] : 50 microgrammes • Protéine recombinante NadA de *Neisseria meningitidis* groupe B[1,2,3] : 50 microgrammes • Protéine de fusion recombinante fHbp de *Neisseria meningitidis* groupe B[1,2,3] : 50 microgrammes • Vésicules de membrane externe (OMV) de *Neisseria meningitidis* groupe B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4[2] : 25 microgrammes • [1] produite dans des cellules d'*E. coli* par la technique de l'ADN recombinant - [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) - [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H). Pour la liste complète des excipients, voir rubrique 6.1 du RCP complet. **Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a] : **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b,c]. - **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b,c]. • **Age lors de la première dose :** Nourrissons de 6 à 11 mois : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 12 à 23 mois : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 2 à 10 ans : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose :** Adolescents (à partir de 11 ans) et adultes* : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 *mois*. [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **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 entraîner 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. **4.8 Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000) - Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée - Peu fréquent : convulsions (y compris convulsions fébriles). - Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). - Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). - Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). - Peu fréquent : eczéma. - Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. - Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. - Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet : **www.notifieruneffetindesirable.be** - e-mail : **adr@afmps.be**. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé - Site internet : **www.guichet.lu/pharmacovigilance**. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 09/2022 (v14). **MODE DE DELIVRANCE :** Sur prescription médicale.

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