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

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

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

GSK

Contents

NOUVEAU: PODCAST ACCRÉDITÉ POUR LES MÉDECINS SUR L'ALLERGIE AUX PROTÉINES DE LAIT DE VACHE

Ecoutez le podcast avec le **Dr Kamal EL ABD** (Allergopédiatre, Responsable du secteur d'allergologie pédiatrique au CHC de Liège et secrétaire du BAPALL*) sur la prise en charge de **l'allergie aux protéines de lait de vache** et le **rôle** des **synbiotiques**.

NUTRICIA

*BAPALL: BELGIAN ASSOCIATION OF PEDIATRIC ALLERGISTS (Association belge de pédiatres allergologues). La BAPALL a été créée fin 2023 sous l'égide de la société belge de pédiatrie pour promouvoir l'allergologie pédiatrique en Belgique. Pour plus d'informations: bapall.secretary@gmail.com (en attendant le site internet).

E.R. : Danone Belux sa, Quai des Usines 160, 1000 Bruxelles - 01/2024

Editorial

Spring into action!

Snowdrops and daffodils are already giving way to blossoming trees and birds singing the return of the season of love...spring is back! Spring is a time of renewal, of life waking up, expressing itself, ready to grow, to mature, to shine ...

This cycle of seasons is fundamental to the natural world around us. It is also fundamental to the human species. Since time immemorial, mankind has celebrated through numerous religious festivals, traditions and customs the chance of turning the page, the opportunity to leave behind or forget the hardships and cold of winter and to welcome a new impetus, a new light, a new warmth. In this perpetual movement, we all know, as individuals, how important it is to be able to stop, to pause, simply to look at where we've come from, where we are, and where we're going... where we want to go.

This dynamic is very important in 2024. In many countries around the world, in Europe and particularly in Belgium, we will be called upon to reflect on our plans for society, our models of organization and democracy. We are going to be invited to choose on those who will represent us in defining and deciding the directions of our collective life. In 2024, some 4.1 billion people - half the world's population - will have the opportunity to vote in multiple ballots organized in 68 countries around the globe. This is unprecedented since universal suffrage was instituted in France in 1792! For the first time, this choice will also involve our oldest patients. Young people over the age of 16 will have the right to elect their representatives to the European Parliament. In a continent facing major challenges, it is legitimate to share this responsibility with the adults of tomorrow. It will be essential to inform them, to listen to them and not let them down!

As a scientific society and as a pediatric healthcare community, we have also taken the opportunity to look back and reflect on our past and our future. According to an official announcement *in Paris médical: la semaine du clinician 1923; 48: 160*, the Belgian Society of Paediatrics (BVK/SBP) was founded on Sunday 14th January 1923. The first president was Prof Péchère, rue des Drapiers, Brussels. The annual membership fee was "25 francs". For more than 100 years, the BVK/SBP was managed by many eminent persons with different personalities and has weathered many storms. The BVK/SBP was and still is the only national pediatric scientific society in Belgium. One of its main objectives is to organize, coordinate, support, stimulate scientific and educative activities and initiatives for all Belgian pediatricians and fellows in pediatrics, with the focus on general pediatrics as well as on pediatric subspecialties and in close collaboration with other pediatric-related medical disciplines, nurses, paramedics and all care givers involved in child and adolescent care.

We are very pleased and grateful that 4 distinguished *éminences grises* , who partially shaped the BVK/SBP over the past years, were prepared to share with us their thoughts and reflexions on our Belgian Society of Paediatrics and his activities. In the first issue of the 2024 volume, Prof Willem Proesmans, KULeuven will shed light on one of the flagships of the BVK/SBP: The Belgian Journal of Paediatrics.

A new section is also launched within this current issue. In the last months, the Belgian Academy of Paediatrics (BAOP), in collaboration with other professionals, paediatrics patients and patient representatives, took the initiative to develop a "Care for the Child" -plan. It offers a comprehensive framework to realize the principle of not leaving child behind. The Plan was explained during the 52nd Congress of the Belgian Society of Paediatrics in Antwerp and is available on the website of the BAOP (www.baop.be). We hope that this plan will put our children and patients at the center of our future decision-makers' attention. Through the section "Child Advocacy", the Belgian Journal of Paediatrics is willing to join this initiative and to give children a voice in healthcare. Prof Ann De Guchtenaere, who coordinated the Masterplan development, will introduce the 10 recommendations that were presented on March 14th, 2024.

In addition to these, we are proud to publish several case reports and original studies. The "Made in Belgium" section continues to reflect the quality of the scientific work carried out by Belgian paediatric teams. Levi Hoste from Ghent University summarizes his exploration of the immune horizon through the study of systemic inflammatory diseases in the era of SARS-CoV-2. This PhD was presented on November 16th, 2023. CamTu Nguyen explains her collaborative work between the Free University of Brussels and the City Children's Hospital of Ho Chi Minh City. She studied the burden of Helicobacter pylori infection in children undergoing upper gastrointestinal endoscopy in Vietnam. This thesis was presented in Brussels on November 28th, 2024.

On behalf of the entire editorial board, we wish you a pleasant reading and a rejuvenating spring!

Christophe Chantrain and Marc Raes, editors-in-chief

Uw vragen of commentaar
Vos questions ou commentaires

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The Belgian Society of Paediatrics and its Journals

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Keywords

Belgian Journal of Paediatrics; history.

The Belgian Society of Paediatrics was founded in 1923 supposedly with the title in French only - as was the tradition in Belgium for all kinds of societies those days - namely *Société Belge de Pédiatrie*. Little information is available today on the number of members or the programs of the annual meetings.

After the second world war, in 1946, a journal was created, this time with a Latin title: *Acta Paediatrica Belgica*. This choice possibly made it more comfortable for both Dutch and French speaking Belgian paediatricians to collaborate. Yet, at this time, there were only few medical doctors working as paediatricians and most of them were French speaking working mainly in private practices in Brussels, the capital of the country with French as the increasingly popular language. In contrast, the Society acquired in addition to its original name a bilingual name: *Société Belge de Pédiatrie* (SBP) besides *Belgische Vereniging voor Kindergeneeskunde* (BVK). Both denominations are still in use to this very day.

With increasing numbers of paediatricians, the journal became a bilingual one with French remaining the dominant language for publications and announcements. It is impossible to judge its qualities, impact and popularity by standards of today. There were 4 issues a year and this was still the situation in the late sixties when the Department of Paediatrics at the Leuven University took an important initiative.

Acta Paediatrica incorporated in the European Journal of Pediatrics

After a short but brilliant career in Congo - the former Belgian colony named Zaire by Mobutu some years later - professor Roger Eeckels became head of the Department of Paediatrics at the Leuven University Hospital in 1969 to replace professor Pierre Denys who had died that year. R. Eeckels aimed at a strong collaboration not only among the different Belgian universities in both parts of the country, but also between universities in neighbouring countries especially The Netherlands, Germany and The United Kingdom. Moreover, he judged the *Acta Paediatrica Belgica* out of key with modern times. He was lucky to get acquainted with Jürgen Spranger, *Direktor der Kinderklinik of Mainz*. As the forward-looking editor in chief of the *Zeitschrift für Kinderheilkunde* he decided to transform it into an English journal named *European Journal of Pediatrics* (EJP) which he launched in 1975 with the aim of fulfilling its promising title. To achieve this goal, he laboured for a progressive incorporation of a large number of national journals published in most West European countries, the first such journal included being the Hungarian Pediatric Journal. R. Eeckels was enthused about the idea and the invitation to join this venture. He was, however, not sure whether the Belgian paediatricians would be prepared or eager to deliver papers of high quality for the new journal.

He therefore started a survey among his university colleagues and suggested them to submit, in their language of choice, good quality papers to the *Acta Paediatrica Belgica*. R. Eeckels was a true polyglot, being exceptionally competent in medical Dutch, French and English. He decided not only to translate all new submissions into English but also to write for each one a referee's report with suggestions for improvement in case of adequate potential. Despite some reluctance he succeeded to publish, as the new editor, 4 volumes of the kind starting in 1978.

The time was ripe for the next step. In 1982 *Acta Paediatrica Belgica* was given up and officially incorporated into the EJP. Accordingly, the EJP became the official journal of the Belgian Society of Paediatrics (BVK/SBP). R. Eeckels joined the editorial board as assistant editor.

The birth of the Mini Acta Belgica (1982-1998)

This transition was not immediately supported by all members of the BVK/SBP. To the surprise of many colleagues and friends it turned out to be a perilous undertaking. Even within the Leuven Department of Paediatrics there was some reluctancy. It was felt that many paediatricians were not sufficiently familiar with the English medical terminology to read the journal or to publish their work. There was another problem of financial nature. The BVK/SBP had been supported quite substantially and for ages by the pharmaceutical industry, especially the milk-producing companies in Belgium and surrounding countries. Since J. Spranger decided not to include any publicity in the EJP, the leaders of the BVK/SBP experienced this loss of income as collateral damage.

Professor Lucien Corbeel was an inspired and experienced paediatrician with a double belonging. He combined a parttime supervisorship for infectious diseases at the Leuven University Hospital with a private practice in Vilvoorde, nearby Brussels. Moreover, he had been very active in the BVK/BSP and an efficient mediator for all kinds of Belgian struggles since he had an excellent command of both national languages. Most of all, he personally managed to publish personally quite regularly on topics of general interest in French journals by preference. He found the end of the *Acta Paediatrica Belgica* most regrettable. In spite of his heigh esteem for R. Eeckels he decided to go on with the business as usual for the BVK/SBP by creating on his own initiative what he called "*The Mini Acta*" for which he organized both the scientific and the financial sides of the undertaking as the editor. This was very much appreciated mainly by the pharmaceutical companies as well as by most paediatricians in private practice. The contribution of publicity enabled the editor to deliver the small journal to all Belgian paediatricians for free. Surprisingly, L. Corbeel further contributed on a regular basis to the EJP as a reviewer or a co- author.

Tijdschrift van de Belgische Kinderarts / Journal du Pédiatre Belge

When in 1999 I was elected President of the BVK/SBP I had two projects one for the Society another for its journal. To start with, it was felt that the *Mini Acta* was not only a misnomer but also a mixed blessing for the Society which deserved better given the arrival of many more specialized members of staff in most Belgian universities. In contrast to this, the number of subscriptions to the EJP remained low despite the advantageous fee for members of the BVK/SBP. Thirdly, there was a clear tendency for choosing a French journal as an alternative especially in the ranks of the French-speaking colleagues.

My first proposal to transform the Mini Acta into a bilingual journal with a professional editorial staff was accepted. We gave the journal again a double name: *Tijdschrift van de Belgische Kinderarts / Journal du Pédiatre Belge*. It was rather easy to find motivated collaborators to support L. Corbeel as editor and the first issue of the new volume was published in 1999. The older generation felt this was like a revival of the good old *Acta Paediatrica Belgica*.

My second proposal was to consolidate the combination of membership of the BVK/SBP on the one hand and subscription to the EJP. Springer Verlag made the subscription cheaper and the Society should empower this project among the members. The board agreed as did most influential academic staff members.

In the meantime, a new editorship was created for the EJP: it was a shared job by myself and professor Beat Steinman from the *Kinderspital* in Zürich. This position was a great opportunity for me to make the deal become successful. I also invited two colleagues from two different Belgian universities to join me in the Leuven editorial office. By doing so a substantial effort was made to improve the journal in several ways. Within a short time, more papers were submitted and the number of publications increased accordingly in spite of our policy to be more critical than our predecessors. I introduced several new types of papers in order to attract more authors. Papers entitled **Eponyms** summarized origin and new aspects of well-known syndromes. **What is new?** became the title for invited papers on recent advances in the knowledge of a great variety of disorders. **Short Reports** were meant to replace the too many Case Reports of questionable value. **Clinical Practice** aimed at bringing into the journal the experience of many renown authors from all over the world with according contributions. Finally, a section of papers entitled **Teaching papers** was created with the same intention. Clinical Practice articles were especially popular since they dealt with topics for which very little or no evidence-based material was available

In less than two years the number of pages was doubled. In fact, this was disadvantageous since increasing the number of pages brings about a decrease of the so-called impact factor (IF). When I started in 1999, the impact factor was 0.93 and when I left the editorial board in 2014 it was 1.96. In comparison, the IF of the *Archives of Diseases* in Childhood – just to mention one famous academic journal on General Paediatrics – roughly tripled from 1.7 in 1999 to 5.2 in 2022. In that year, my successor as editor in chief of the EJP, P. Dewinter, obtained IF-score of 3.6 for which he deserves congratulations.

Thanks to L. Corbeel, the new Belgian bilingual Journal was quite successful. Its first volume appeared in 1999. Belgian paediatricians could submit papers in the language of their preference and the journal was free of charge. Yet the younger generation of academic paediatricians felt this was not what they wanted in the light of the "publish or perish" challenge they were facing with. Additional concerns were how to cope with modern technology, the abundance of journals worldwide with easy access and the everlasting linguistic problems typical for the Belgian society. Last but not least, in theory the EJP was still the official organ of the BVK/SBP but in real life there was little flesh on the bone. When L. Corbeel became ill and had to abandon his many tasks, some of his collaborators came up with what they considered a better alternative.

The Belgian Journal of Paediatrics: 2015

Although I was not involved in this process, it looks like there was more enthusiasm than ever among the many institutions involving paediatricians and the care for sick children. Leuven played a key role with doctor Marc Raes who was joined by professor Samy Cadranel staff member at *L'Hôpital Universitaire de l'Enfant* in Brussels and a passionate personality in many of his activities especially within the BVK/SBP. The name chosen for the new Journal was *Belgian Journal of Paediatrics* (BJP) which would become the official journal of the Society. There was an immediate support by the pharmaceutical companies and the publisher of the former format took over. Members of the BVK/BSP have access not only to the new journal but also to a series of journals all around the world. The first edition dates from 2015. There are 4 volumes a year and the publications cover the broad field of Paediatrics. All academic institutions from all parts of the country participate in publishing. It remains however an almost exclusive Belgian journal which is a mixed blessing.

I cannot further comment on the teething troubles of this journal and the obvious progress made. I only want to end this contribution by formulating some general remarks and recommendations although my personal experience is outdated and the recent revolutions, both medical and digital, transcend me.

Reflexions

Can some lessons be taken from the past history of the BVK/SBP and its journals? Generally speaking, if a country has a national Society for Paediatrics, it is natural and desirable to have a journal of its own, the minimal goal being a tool for communication, information and teaching. Such a journal should be linked to membership and the fee for members should include access to the journal. The journal might take advantage from some independency in that the editor is not the president of the Society and the editorial board is constituted of a large group of experts in the field. There is a need for reviewers who provide professional and respectful criticism. They should make the editor's work easier by offering ways to improve the value of the manuscript. Reviewers from abroad are essential. The utmost goal is to provide a journal which is attractive in many ways.

A good example of such a conceptual construction is, I believe, the *Archives of Diseases in Childhood*, the official journal of the *Royal College of Paediatrics*. The question is whether the journal should be an exclusive publication tool for paediatricians working in the country at stake. The problem is to be attracted by potential authors from outside the country. A concern is to find reviewers capable of the work requested.

My experience is limited to the editorial work for the EJP. The major challenges have been to stimulate authors from Belgium and abroad - inviting them did partially resolve the problem, to find motivated and earnest reviewers - and some indeed were brilliant and to offer help for people with a poorly written manuscript carrying an interesting message. To my surprise, many famous authors were poor reviewers and vice versa.

Yet, Belgium is a small and complicated country in every way. There is the language controversy, there are cultural differences between the populations of the north and the south and there is a lot of competition between the many universities. Therefore, general rules are not necessarily applicable when dealing with such an undertaking as establishing a national society and a journal. Therefore, paediatricians should be supportive as well as understanding of those colleagues, courageous enough to put their shoulders under the matter.

The BJP has some imperfections that could be overcome by rather simple technical tools. Each volume is overloaded. The letters are very small and hard to read for older people. The tables as well as the figures are unattractive carrying too much information in a difficult to analyse presentation. A more problematic issue is the length of the manuscripts; in general, they are too long which damages their attractiveness.

My last comment is about the common thread throughout my story on the BVK/SBP and its Journal. The BVK/SBP struggled with title and format of its journal. The choice for the Latin name was, in my view, an ingenious solution for multilingual countries. It is no surprise that the same choice was made for instance in Switzerland (*Helvetica Paediatrica Acta*). Mini-Acta was a rather unfortunate way to cope with the hypothetical fear of losing national identity when progressive academic paediatricians made a praiseworthy attempt to incorporate the Belgian journal into an European project. I am convinced that the BVK/BSP missed an opportunity. When the European project was abandoned, the bilingual name came back together with publications in both Dutch and French. The choice did not satisfy the Belgian academic paediatrician and a logic final (?) choice was made for an English name. The new name implies that the BJP is open to a broader audience than the Belgian paediatrician but I am not sure this is the purpose of the actual editorial board. In my view, it is mainly aiming at stimulating publications by young Belgian paediatricians and this is a respectable target in its own. There is still work to be done and quite some creativity will be needed. I sincerely hope for further progress in spite of the increasing complexity of the medical world and the birth of the unpredictable new player in the field called AI.

The 10 Key Recommendations from the 'Care for the Child' Plan

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Keywords

Child advocacy.

Introduction

Professionals from various child-related sectors support the core principle to *safeguard the children's rights and maximize efforts to ensure children receive opportunities to reach their full potential.*

Recognizing children's complete exclusion from policy-making, the Belgian Academy of Paediatrics (BAOP) -in collaboration with other professionals, paediatric patients and patient representatives- took the initiative to develop this 'Care for the Child'-plan. It offers a comprehensive framework to realize the aforementioned principle, leaving no child behind.

In parallel, and based on the principles of the Plan,10 recommendations for policymakers have been developed and endorsed by a wide range of child health professionals.

Core Principles

All children are entitled to *survival, protection, development and participation*.

The United Nations Convention of the Rights of the Child (UNCRC), ratified by our country will celebrate its 35th birthday in 2024. The UNCRC is comprehensive (one and indivisible) and protects not only the right of children to preventive, promotive and curative health care. It protects the right of every child to grow to his full potential.

Our country is renowned internationally for its robust and high-quality health care system, employing highly trained and specialized health care professionals who deliver state-of-the-art and innovative care; and yet, despite this reputation, our health care system is characterized by fragmentation, a deficiency in integrated coordination, and an emphasis on performance rather than a commitment to quality and outcome-based principles. Consequently, patients in Belgium are at risk to experience unmet needs in health care and health care-related domains of quality of life.

The Plan Care for the Children and Young Persons and the 10 Recommendations are therefore based in every detail on the 'fairness' principle for every child, transcends a disease-oriented approach and is based on two well-known and crucial core principles: Equality and Equity.

The principles of Equality and Equity are pivotal for ensuring quality, sustainable and 'fair' health care, and both principles balance each other. It is this balance that ensures the right health outcomes and a tailored care pathway (1) (Figure 1, Table 1).

Figure 1: Pitfall of discrimination based on for example pathology, age, social situation,…

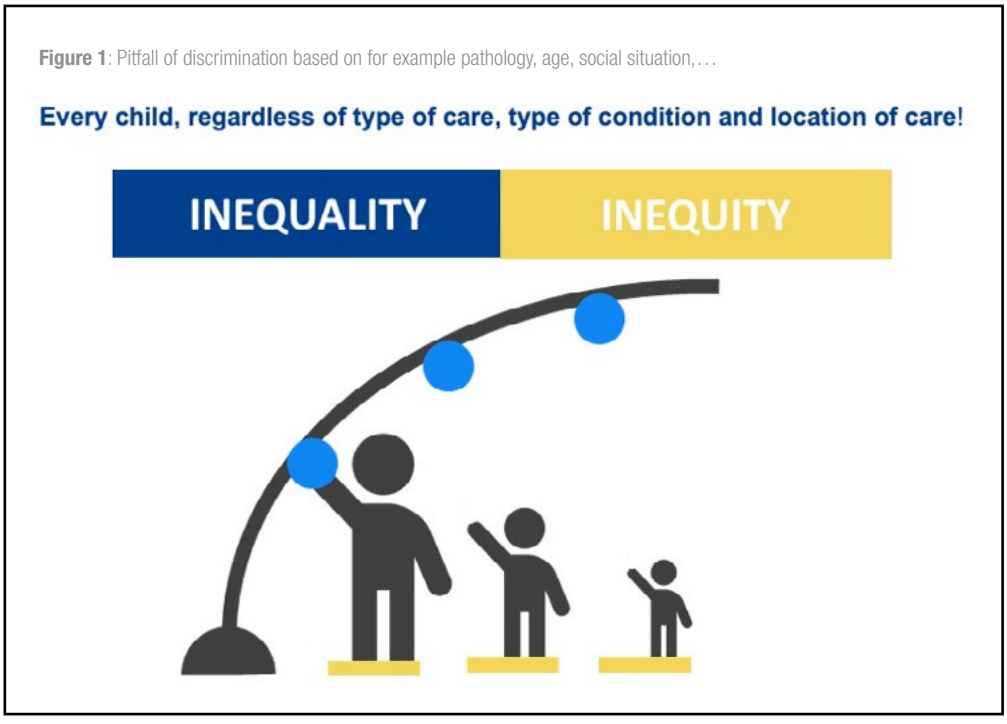

Table 1

EQUALITY	EQUITY
Equality ensures fair and equal-quality, accessible health care for children, regardless of type of illness, type of care, and location of care. Both the UNCRC and the European Association for Children in Hospital (EACH) charter form the core and foundation from which any policy in the care for children initiates and should not deviate. Equality provides a robust structural and equal of quality child health/paediatric care grounded in common core principles.	Equity is about assessing the individual care needs of a child and family, enabling them to achieve the goals of Equality in a way tailored to their unique situation. It emphasizes tailored care with a focus on the unique context of the child. In this sense, Equity represents "context-based practice", serving as a tool for health care professionals to deviate from standards and evidence-based practices. Equity are the specific care paths grafted on the structure and core of Equality.

Figure 2: Equality in de Medical Childcare

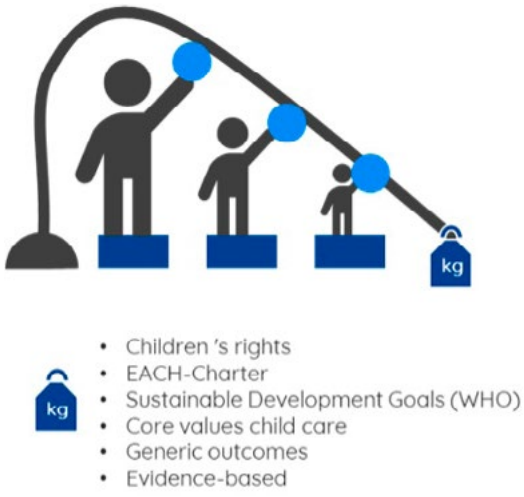

Figure 3: Equity in de Medical Childcare

The 10 Recommendations

1. Base all decisions on children's rights, including within healthcare (EACH charter). Review the Patient Rights Act!
2. Give children, young people, and parents (foster parents, guardians, caregivers, etc.) a structural voice in determining healthcare policies (children's council, etc.).
3. Invest significantly more in all forms of prevention and prioritize prevention on the political agenda.
4. Establish an annual Child Report for Belgium, containing all relevant data on children's health, growth, development and disease (determine this data and all relevant health determinants for children in collaboration with an expert group).
5. Provide short-term incentives for intersectoral collaboration and connection.
6. Ensure a guarantee of quality care for the child through adequate (interprofessional) training on healthy, vulnerable, and sick children, as well as through mandatory child-specific competencies and lifelong learning. Consult children and experts for this. Make these competencies transparent and clearly visible to children, parents and health-care professionals.
7. Acknowledge that (chronically) ill children, children who have a difficult start (such as prematurity) and/or grow up in poverty, are extra vulnerable. Focus on vulnerable children!
8. Value the professionals involved in child healthcare, no longer considering them as an inconvenient appendix to adult care.
9. Establish as soon as possible a structural, Inter-federal expert group and give them a mandate for:
   - Drafting a new care program for paediatrics.
   - Developing a proposal for more preventive and integrated care involving ONE-K&G-Kaleido doctors, CLB and PSE doctors, general practitioners, paediatricians, child- and youth psychiatrists, paediatric nurses, paramedics, etc.
10. Appoint a National Minister for/of the child with coordinating and overarching powers.

Disclaimer

REFERENCE

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Nutrilon PROfutura

Onze meest geavanceerde formule

Ontwikkeld voor de combinatie **met en na borstvoeding**

8 keer minder kans op kolieken[1]
Dankzij onze unieke combinatie van pre-* en postbiotica**

Gemakkelijke gastro-intestinale tolerantie[1-5]

Zachte ontlasting, die lijkt op die van borstgevoede baby's[6-7]
Dankzij β-palmitaat en prebiotica scGOS:lcFOS (9:1)

NUTRICIA

Belangrijk: Borstvoeding is de ideale voeding voor baby's. Informatie uitsluitend bestemd voor het (para)medisch korps. *scGOS/lcFOS (9:1) **Onze postbiotica zijn het resultaat van ons uniek fermentatieproces. Referenties: **1.** Rodriguez-Herrera A, et al. Nutrients, 2019;11(7):1530. **2.** Miles AM & Calder PC. Nutr Res, 2017;44:1–8. **3.** Bronsky J, et al. JPGN, 2019,68:742–60. **4.** Delplanque B, et al. JPGN, 2015;61:8–17. **5.** Kennedy K, et al. Am J Clin Nutr, 1999;70:920–7. **6.** Rodriguez-Herrera A, et al. JPGN. 2016a;62: Abstract G-P-230:422 **7.** Havelicekova Z, et al. Nutrition Journal. 2016;15:28 - V.U.: N.V., Danone Belux – Werkhuizenkaai 160 – 1000 Brussel

Feasibility and safety of early mobilization in critically ill children: A prospective experimental study

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Keywords

Early mobilization ; feasibility ; pediatric intensive care unit ; pediatrics ; critically ill children ; safety.

Abstract

Objectives:

The study aims to evaluate the feasibility and the safety of early mobilization in critically ill children under 2 years old and its impact on comfort scores.

Methods:

Children were recruited in our tertiary care pediatric intensive care unit. One session of upper and lower limb mobilization was performed within 48 hours after admission. The heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressures (SBP and DBP, respectively) and pulse oximetry oxygen saturation (SpO_2) were recorded before (T0) and at the end of the mobilization (T1). Parameters were also noted at 10 min (T2), 30 min (T3) and 1 hour after the end of the mobilization (T4). The EDIN score and the Comfort-B score were used to assess comfort.

Results:

Twenty patients were included and mobilized. HR, SBP and DPB showed no change at the end of the mobilization compared to baseline (138 bpm ± 20 vs 133 bpm ± 15; 101 mmHg ± 18 vs 94 mmHg ± 12; 54 mmHg ± 11 vs 49 mmHg ± 7, respectively). RR and SpO2 did not statistically change during the study. Four sessions of mobilization were interrupted because of discomfort associated with increased EDIN and Comfort-B scores. No technical adverse events were recorded.

Interpretation:

Early mobilization is feasible and safe in most stable critically ill children under 2 years old as long as the height and type of surgery allow for mobilization of the patient. Discomfort was observed in 20% of the children.

Introduction

Children admitted to the pediatric intensive care unit (PICU) can experience cognitive, psychologic, and functional sequelae as a consequence of critical illness. Immobility is associated with complications including muscle weakness, pressure ulcers, and venous thromboembolism that may impact the length of stay in the PICU (1). As a result, there is a great interest in early mobilization. The perceived benefits of early mobilization in critically ill children are a shorter duration of mechanical ventilation, improved wake – sleep rhythm and a shorter length of stay in the PICU (1). Nevertheless, the efficacy of early mobilization in the pediatric population remains unclear due to the low level of evidence (2). Moreover, the feasibility and safety remain poorly described in this population: the main barriers reported were hemodynamic instability, the risk of vascular catheters and endotracheal tubes dislocation, and the sedation level (1,3).

Early mobilization is defined as non-mobility interventions (passive range of motion) to prevent muscle atrophy and maintain range of motion (ROM) and mobility interventions (active ROM, in bed cycling, transfers) to enhance endurance, strength, and balance (3). Early mobilization should be started within 48 hours of PICU admission (4). In a Canadian survey, only 10% of children admitted to the PICUs were mobilized within 48 hours of admission (3). The chest physiotherapy sessions were favored over mobilization (4). Despite different working practices, the physical therapists are infrequently consulted for early mobilization in European PICUs (5). This low frequency of prescription could be explained by the lack of expertise of the medical team to recognize a patient who would require early rehabilitation and the absence of dedicated physiotherapists to the PICU (6). Nevertheless, the numbers of children who received physical therapy increased when a mobilization protocol was implemented in the PICU (7,8).

In addition, the feasibility and safety of early mobilization has been demonstrated in critically ill children older than 3 years (9,10). Younger age has been identified as a barrier to physical rehabilitation, despite reassuring studies on the safety of early mobilization in children younger than 3 years old (4,8,11,12). An inpatient rehabilitation program based on standardized care pathways was shown to be safe for infants (median age: 1.1 years) after extracorporeal ventricular assist device placement (12). Early mobilization after liver transplantation in children (median age: 1.1 years) was also well tolerated (8). No adverse events associated with early mobilization were observed (8,12).

Based on these statements, we hypothesized that an adapted early mobilization program can be performed safely without major changes in parameters. The aim of this study was to evaluate the feasibility and the safety of early mobilization in critically ill children under the age of 2 years by investigating the impact on cardiorespiratory parameters and comfort scores.

Materials and methods

Setting

A prospective experimental study was conducted in the PICU at Cliniques universitaires Saint-Luc from September 2016 to February 2017 following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE statement). The PICU is a polyvalent tertiary unit caring for various pathologies, including pediatric cardiac surgery and liver transplantation. This study was performed in line with the principles of the Declaration of Helsinki. The protocol study was approved by our institutional research ethics board (2016/11JUI/316). The clinical trial was recorded in the National Library of Medicine registry (NCT02958124).

Written informed consent was obtained from parents or legal guardians for all patients included in the study.

Participants

All children younger than 2 years of age admitted for 24 to 48 hours in our PICU were eligible for inclusion. Children with cardiorespiratory instability were excluded. Cardiorespiratory stability was defined as no sweating, no signs of respiratory distress (nasal flaring, increased work of breathing, paradoxical breathing, stridor, grunting), adequate oxygenation [pulse oximetry within the target values of the child, oxygen index (OI) ≤ 20 (OI is a marker of the severity of hypoxic respiratory failure, combining FiO_2, PaO_2 and mean airway pressure (MAP): $OI = FiO_2 \times MAP \times PaO_2\text{-}1$. The higher the value, the more severe the oxygenation disorder), Positive End Expiratory Pressure (PEEP) between 4 and 8 cmH2O], inspiratory pressure ≤ 30 cmH_2O, adequate respiration (respiratory rate or RR twice maximum the target values), adequate heart rate (HR) and systolic arterial blood pressure (increased by maximum of 20% compared to basal state), arterial or venous pH ≥ 7.25, no inotrope/vasoactive drugs (except for dobutamine ≤ 5 µg/kg/min or milrinone ≤ 0.8 µg/kg/min, corresponding to a low severity of hemodynamic impairment allowing safe mobilization), lactic acid ≤ 2.5 mmol/L. The cardiorespiratory parameters were collected 30 min before the start of the mobilization session.

Children receiving high frequency oscillatory ventilation or extracorporeal membrane oxygenation or with delayed chest or abdomen closure were also excluded.

Protocol study

Monitoring data and scores were documented at the first mobilization session between 24 and 48 hours after admission. Only one mobilization session per patient was included in the study; further sessions were not recorded. Passive mobilization of the upper and lower limbs was performed by the same trained physiotherapist. Shoulder circumductions, elbow flexions and extensions, wrist and fingers flexions and extensions, pelvis movements, triple bilateral flexions (like pedaling) and feet flexions and extensions were performed bilaterally. All these movements were performed in all patients and each movement was repeated for 10 times. The range of motion was maximal. Mobilization was carried out 30 min after morning care. During one hour after the session, no procedure or manipulation was carried out to ensure the validity of measurements. Each child received continuous or discontinuous enteral feeding. At the time of the study, there were no institutional guidelines for early mobilization.

Use of sedative and analgesic medications were based on local protocols according to international recommendations. The specific choice of drug and its administration interval depended on the personal evaluation of the physician in charge of the child, with the help of the bedside nurses and comfort scales. Continuous or discontinuous sedation or analgesia are administered to ensure safety and to control discomfort while keeping children awake. In case of minor agitation or crying during the session, some non-pharmacological facilitators such as pacifier, glucose, cuddly toys, music or massage were used to comfort the child. No additional sedation was given during the mobilization.

The mobilization was interrupted in case of important agitation, defined by reaching the discomfort threshold (Echelle Douleur Inconfort Nouveau-né (EDIN) and Comfort-Behavior (Comfort-B) scales) accompanied by one of the following criteria: increased work of breathing (nasal flaring, paradoxical breathing, stridor, grunting), increase in HR > 20% compared to basal state, increase in systolic or diastolic blood pressure (SBP or DBP) > 20% compared to basal state, occurrence of hypotension, increase in RR > 2 times the normal values, decrease in oxygen saturation (SpO_2) of > 4% below the target values of the child for > 60 sec, or accidental catheter removal (arterial, central venous, peripheral or urinary catheter).

Outcome measures

The primary outcome was the feasibility and safety of early mobilization in children aged 0 - 2 years old admitted in the PICU. The feasibility was defined as the ability to perform one full mobilization session of all upper and lower limbs through their full range of motion in critically ill children. The safety was assessed by the stability defined by change of respiratory and hemodynamic parameters. All the variables (HR, RR, SBP, DBP and SpO_2) were measured using a bedside monitor (Philips, Amsterdam, the Netherlands). These parameters were recorded continuously and noted before (T0), at the end (T1), 10 min (T2), 30 min (T3) and 1 hour after the mobilization (T4) (Figure 1). Adverse events such as endotracheal tube removal or catheter loss (arterial, central venous, peripheral or urinary catheter) were also recorded.

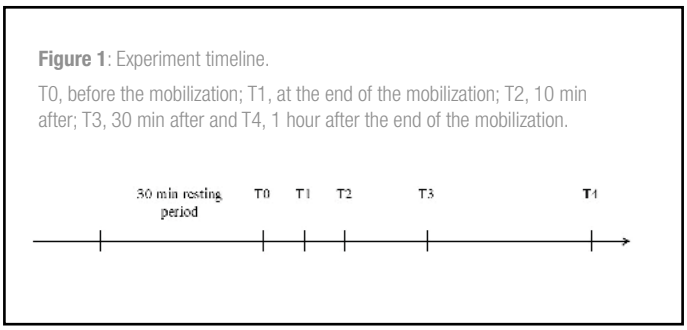


Figure 1: Experiment timeline.

T0, before the mobilization; T1, at the end of the mobilization; T2, 10 min after; T3, 30 min after and T4, 1 hour after the end of the mobilization.

The secondary outcome was to evaluate the impact of early mobilization on comfort assessed by the EDIN score for extubated children and the Comfort-B score for intubated children. The EDIN score is a score used to quantify the pain and discomfort in preterm and neonatal children (13). Nevertheless, this scale was chosen because it was already used in daily standard care to assess the comfort of children up to 9 months in our PICU. Five criteria (face, body, sleep, relational and reassurance necessity) are rated from 0 to 3 points. The higher the score, the worse the comfort: a cutoff score above 5 suggests discomfort. The Comfort-B score was developed and validated to measure pain and discomfort in mechanically ventilated children from birth to adolescence in PICU (14). When using the Comfort-B score, no other pain or sedation scale is necessary. We used the new version of Comfort-B score, without the physiological items: the arterial blood pressure and HR are difficult to assess. Each item (alertness, calmness or agitation, respiratory response, movements, muscle tone and facial tension) is rated from 1 to 5. The total score is calculated by adding up all individual scores: a score below 10 indicates excessive sedation, between 11 to 17 is the child comfortable, from 17 to 22 (potentially painful or discomfort) and a score > 23 indicates a clearly uncomfortable, painful child. We defined our discomfort threshold as a score greater than 5 on the EDIN score and above 17 on the Comfort-B score (13-14). Comfort assessments were performed before (T0) and at the end of the mobilization (T1), and 10 min after the session (T2).

During the mobilization, four patterns of behaviors were also recorded (calm, grimace, crying and agitation).

Statistical methods

The sample size was estimated on HR variation. Preliminary data from 10 subjects were used. Considering a standard deviation (SD) value of 14 bpm, adopting a significance level of .05, a power of 80%, the sample size was estimated to be 19 participants. This change of 14 bpm is also described as a reference from a pediatric study (15). Statistical analyses were performed using SPSS Statistics 25.0 (IBM Company, Armonk, New York, USA). The analysis of all outcomes followed the intention-to-treat principle. All values were expressed as mean ± standard deviation,

when data were normally distributed, otherwise by median, minimum and maximum values. Parametric and nonparametric analyses were used in accordance with the results of the Kolmogorov-Smirnov test. Repeated measures analysis of variance were used to evaluate the effect of mobilization on hemodynamic and respiratory parameters (within factors: time). Mauchly's sphericity was verified. Friedman test was used in the absence of the distribution normality. This nonparametric test was also used to measure the comfort of the child. All these statistical tests used a significance level of 5%.

Wilcoxon rank-sum tests were applied for post hoc comparisons using the Bonferroni correction, comparing each time point to another to find the significant change. Significance level was therefore set at $p < .01$.

Results

A total of 135 infants were eligible for inclusion. Ninety-three patients were excluded, of whom 72 due to cardiorespiratory instability, 18 due to absence of parental consent and 3 due to delayed chest or abdomen closure. Forty-two children were recruited. Among them, 14 children discontinued the study for inapplicable protocol due to their height: their height did not allow triple bilateral flexion of the lower limbs (pedaling). Eight post-surgical patients had contraindications to the mobilization because the surgical site involved the spine or the esophagus (esophageal anastomosis). A total of 20 infants were included (Figure 2). The baseline characteristics of the patients are described in Table 1.

Primary outcomes

Feasibility and safety

Twenty patients were included and mobilized: 15 spontaneously breathing without respiratory support and 5 invasively mechanically ventilated children. Sixteen sessions were completed and 4 sessions (3 cardiac patients and 1 patient with head trauma) were discontinued because of important agitation.

Table 2 shows physiologic and safety outcomes. The HR varied during the study period ($p = .03$) and changed significantly between T1 and T3 ($p < .01$). The SBP and DBP were also influenced by mobilization during the study period ($p = .02$ and $p = .04$, respectively). The SBP significantly decreased between T1 and T3 and, T1 and T4 ($p = .009$ and $p = .005$, respectively). The DBP also significantly decreased between T1 and T2 ($p = .006$). HR, SBP and DBP showed no change at T1 compared to baseline. RR and SpO_2 did not statistically change during the study.

Four mobilization periods were early discontinued because of a 20% increase in HR (n=2), a 20% increase in SBP and DBP (n=3) or a 4% decrease in SpO_2 (n=3). All the parameters returned to baseline 10 minutes after early discontinuation.

Table 1: Clinical characteristics of the patients at baseline.

Variables	Total (n = 20)
Age (days)	162 [1; 434]
Weight (kg)	6 [3; 10]
Female gender	12 (60)
Reasons for admission	
Congenital heart disease	14 (70)
Neurologic disease	3 (15)
Lung disease	2 (10)
Digestive disease	1 (5)
Ventilation	
Spontaneous breathing without NIV	15 (75)
Invasive ventilation	5 (25)

NIV, non-invasive ventilation.

Values are expressed as median with min-max values in square brackets, or numbers with percentage in round brackets.

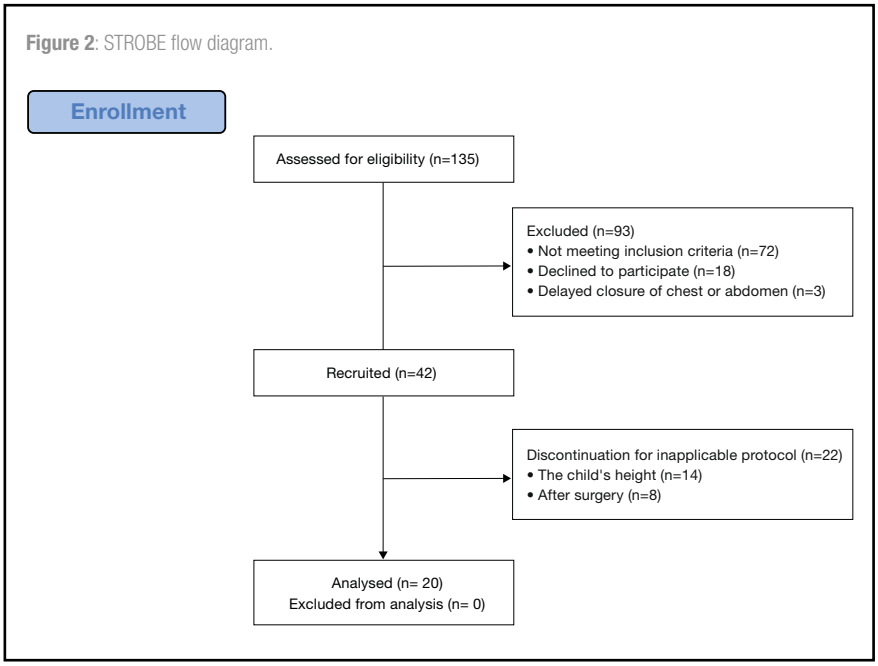
No adverse events were observed.

Secondary outcomes

EDIN scores changed over time ($p = .02$). EDIN scores showed no significant difference between T0 and T1. However, EDIN scores changed significantly between T1 and T2 ($p < .01$). Before mobilization, all the 15 spontaneously breathing patients were non-painful with EDIN scores ranging from 0 to 5. After mobilization, 3 of these 15 children had a score above 5. Mobilization was discontinued in 2 of them due to an increase in EDIN score from 2 to 7 and from 5 to 14. In the 5 ventilated patients, mobilization was discontinued in 2 patients due to an increase in Comfort-B score from 8 to 22 and from 10 to 19 (Figure 3).

Four types of reactions were noticed during the mobilization session: calm (n=8), agitation (n=6), tears (n=4) and grimaces (n=2). Half of the children needed facilitators such as glucose, cuddly toys or massage to calm down.

Figure 2: STROBE flow diagram.



Discussion

The aim of this study was to examine the feasibility and safety of early mobilization for children from 0 to 2 years in the PICU. Practical recommendations for early mobilization in critically ill children are lacking (4,16).

The feasibility and safety of early mobilization were evaluated in 20 children aged 1 day to 14 months admitted to the PICU. HR, SBP and DBP showed no change at the end of the mobilization (T1) when compared to baseline. RR and SpO_2 did not change significantly during the study period. In some children some parameters changed after the mobilization session without clinical importance. No technical adverse events were recorded. Our results are similar to other pediatric studies. Choong et al. showed no difference in cardio-respiratory and hemodynamic parameters after

Table 2: Change in parameters at different times.

	T0	T1	T2	T3	T4	p-value
HR (bpm)	133 ± 15	138 ± 20	129 ± 15	128 ± 14	131 ± 14	.03 [a,*]
RR (cycles/min)	31 ± 13	33 ± 12	32 ± 12	30 ± 10	32 ± 13	.64 [a]
SBP (mmHg)	94 ± 12	101 ± 18	96 ± 14	93 ± 13	93 ± 13	.02 [a,*]
DBP (mmHg)	49 ± 7.0	54 ± 11	49 ± 8.0	48 ± 8.0	49 ± 7.0	.04 [a,*]
SpO_2 (%)	99 [87; 100]	98 [81; 100]	98 [88; 100]	99 [89; 100]	98 [89; 100]	.44 [b]
EDIN scale (point)	2 [0.0; 5.0]	2 [0.0; 14.0]	2 [0.0; 6.0]			.02 [b,*]

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, peripheral oxygen saturation.

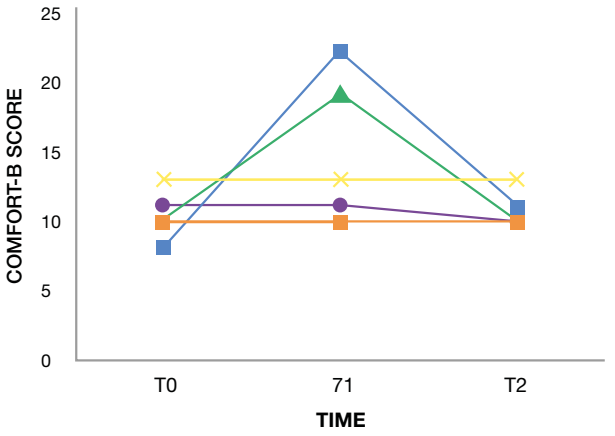
T0, before the mobilization; T1, at the end of the mobilization; T2, 10 min after; T3, 30 min after and T4, 1 hour after the end of the mobilization.

Values expressed as mean ± *SD* or median with min–max values in square brackets.

[a] *p*-value (Within Subjects – Factor = Time); [b] *p*-value (Friedman test); * $p < .05$.

Figure 3: Evolution of Comfort-B scores.

T0, before the mobilization; T1, at the end of the mobilization, T2, 10 min after the end of the mobilization.



passive mobilization with a cyclo-ergometer or active mobilization with a video-game in children aged 3 to 17 years (17). Abdulsatar et al. also reported feasibility of a 25 minutes Wii™ session for 8 children aged 3 to 18 years without changes in HR, RR, blood pressure and SpO_2, compared baseline (18). Additionally, these studies, like ours, showed no accidental tube displacements or extubations.

Sessions were feasible in 16 cases (80%) and discontinued in 4 cases (20%). All the children were calm and stable before treatment but they wiggled and turned during the mobilization.

Discomfort in these children was shown by changes in EDIN and Comfort-B scores, as well as hemodynamic and respiratory parameters. They all calmed down without need for sedative drug administration. Few studies focus on discomfort expressed by agitation as an adverse event (19). In the pediatric population, study data suggest that rates of potential safety events range from 1% to 6% (5,11,19). The European PARK-PICU study reported 6% potential adverse events: the most frequently reported events were a decrease in SpO_2, a change in HR and blood pressure (5). Adverse events are also described in critically ill adults. Schweickert et al. encountered one severe adverse event in 498 mobilization sessions in ventilated patients (desaturation less than 80%) (20). Hickmann et al. reported that adverse events, such as hypotension, hypertension and tachycardia, occurred in 10 activities (0.8% of total sessions) (21). The incidence of early mobilization adverse events in critically ill adults ranges from 1% to 6% including parameters changes, tube removals, skin injuries and falls (22–25).

We used facilitators such as a pacifier, glucose, cuddly toys, music or massage to relax the child during the mobilization. These facilitators can be considered as bias for evaluation of the child's behavior in the face of early mobilization. However, our nursing staff regularly uses these non-pharmacological techniques during treatments to avoid increasing sedation and analgesics. We therefore considered this technique to be common during the physiotherapy session with infants.

Several limitations to our study should be noted. First, our cohort was small due to strict inclusion criteria and surgical contraindications, the main limiting factor regarding external validity. Second, we did not include sedative and analgesic drug doses which could have had an impact on our results. Nevertheless, our unit has a strong culture of optimizing analgesia and minimizing sedation while maintaining infant safety and comfort. In addition, the comfort scales do not allow good discrimination of agitation and pain. Finally, our study did not assess the benefits of early mobilization. Muscle strength in young children is difficult to evaluate in clinical settings due to lack of non-invasive and reliable assessment tools. Peripheral muscle ultrasound could be a promising tool for bedside muscle assessment in children, as demonstrated in adults (26–29).

Conclusion

Early mobilization is feasible and safe in most stable critically ill children under 2 years old as long as the height and type of surgery allow for mobilization of the patient. Discomfort expressed by agitation is described as an adverse event. Future large-scale studies are still needed to assess the effect of early mobilization in children under 2 years old.

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Conflict of interest

GR has received research support from the Institut de Recherche Expérimentale et Clinique (Université catholique de Louvain, Brussels, Belgium).

Ethical considerations

This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was granted by the regional Ethic Committee in Cliniques universitaires Saint-Luc and Université catholique de Louvain in Brussels (2016/11JUI/316).

Written informed consent was obtained from parents or legal guardians for all patients included in the study.

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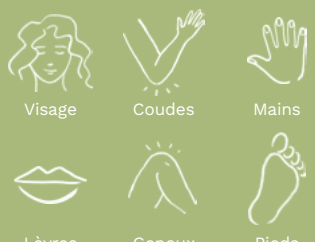

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Success rate of primary percutaneous balloon angioplasty in children with Pulmonary Stenosis and Noonan syndrome

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Keywords

Noonan syndrome ; supravalvular pulmonary stenosis ; balloon valvuloplasty.

Abstract

Background: Noonan syndrome (NS) is associated with different types of congenital heart defects (CHD), the most common of which is supravalvular pulmonary stenosis ((SV)PS). Possible treatment options are percutaneous balloon pulmonary valvuloplasty (BVP) or surgical intervention. The anatomical location of the PS may help predict BVP failure. We aimed to identify factors predicting treatment outcome and reintervention rate of BVP in these patients.

Methods: Medical records of children with a diagnosis of NS and in follow-up at Antwerp- and Ghent University Hospitals from 2000 to 2022 were retrospectively reviewed.

Results: Thirty-two children were identified with a SVPS, either isolated or in combination with other CHD. Sixty-nine percent of the children with PS had SVPS. Isolated SVPS was identified as a risk factor for intervention.

Surgical or percutaneous intervention was necessary in 17/32 patients with PS (53%). All but 2 children with pulmonary valve stenosis had SVPS. Fifteen (13 with SVPS) underwent percutaneous balloon dilatation, of which 10 (67%) needed a second intervention, but all of them ultimately needed surgical repair due to persistent stenosis. The global success rate of percutaneous intervention in children with Noonan and SVPS was (31,1%).

Conclusion: SVPS is a frequently encountered CHD in children with NS. The prevalence of SVPS was similar for all NS associated genes. Isolated SVPS is a risk factor for intervention. The success rate of BVP in patients with NS and SVPS is low. BVP might still be useful in selected cases.

Introduction

Noonan syndrome (NS) is a genetically heterogeneous condition with a high prevalence of heart disease (70-90%) (1). A genetic mutation of the RAS-MAPK signalling pathway can be identified in 75% *(PTPN11, SOS1, KRAS, NRAS, RAF1, RIT1, BRAF, SHOC2 or CBL)* of cases (2). The predominant cardiac lesion is pulmonary stenosis (PS), affecting 50% of patients with NS (3,4). Approximately half of these patients will require treatment (5). First-line treatment of PS consists of a percutaneous balloon valvuloplasty (BVP) (6). This treatment is highly successful in non-syndromic patients with PS, with a re-intervention rate of 5-10% (7). However, the results in syndromic patients (e.g. NS) are suboptimal with a high re-intervention rate (60-65%), and the need for surgery after (repeated) BVP is significant (5,8). The reason why BVP fails to alleviate the stenosis is still not clear. One possible explanation is the associated dysplastic morphology of the pulmonary valve leaflets as the root cause of a suboptimal response (9). Other authors describe the presence of a supravalvular pulmonary stenosis (SVPS) as a predictor of BVP failure (10). Other possible contributing factors that have been studied (age, weight, pre-BVP haemodynamic parameters (e.g. pulmonary valve (PV) pressure gradient), associated cardiac defects) were proven not to be significant predictors of treatment success (5,6). Genotype-phenotypes studies showed higher prevalence of PS and a more severe stenosis in carriers of a pathogenic variant in *PTPN11* compared to other genes (11). Due to the high prevalence of severe PS requiring intervention and the high rate of re-intervention after BVP, identification of risk factors for treatment and re-intervention is warranted. A change in approach to the treatment of PS in NS might be necessary considering that a primary surgical intervention could avoid the need for multiple procedures.

The aims of our study were to examine factors predicting the need for a primary intervention for PS in patients with NS, to evaluate the success rate of BVP as first-line treatment in these patients and to identify possible predictors for re-intervention (treatment failure).

Methods

A retrospective medical record review was performed on all clinically diagnosed NS patients at Antwerp and Ghent University Hospitals between January 2000 and December 2022. Only patients with a PS were included in this study. Patients with a concomitant genetic diagnosis in addition to NS or with an age of more than 18 years of age at the time of diagnosis were excluded from the study.

The subtype of PS was defined according the anatomical location as described by echocardiography and/or catheterisation. Identification of an SVPS by echocardiogram was based on the interpretation of the anatomic location by the operator during catheterisation. PS subtype was determined by the anatomical narrowing of the pulmonary valve as seen during the performance of the angiogram. When a PS was classified differently by angiogram than echocardiogram, the result of the angiogram was deemed superior and therefore decisive as echocardiogram is known to have a significantly lower diagnostic yield (10).

All relevant demographic characteristics such as associated pathogenic gene variant, PV pressure gradient, PS and subtype, other congenital heart

Table 1: Comparison of patients who underwent an intervention for PS with patients who did not.

	Total cohort	Intervention	No Intervention	p-value
Total number of patients	32 (100%)	17 (53%)	15 (47%)	
Sex	19 female (59%)	9 female (53%)	10 female (67%)	0,491
Age	2,0 months [1,0 – 6,0]	2,0 months [1 – 4,5]	3,0 months [1 – 27]	0,100
Weight	4,1 kg [4,1 – 6,2]	4,9 kg [4,1 – 6,2]	4,9 kg [3,7 – 10,4]	0,807
Associated gene				0,051
PTPN11	17 (53%)	10 (59%)	7 (47%)	
SOS1	6 (19%)	1 (6%)	5 (33%)	
RIT1	4 (13%)	4 (23%)	0 (0%)	
RAF1	1 (3%)	0 (0%)	1 (7%)	
BRAF	1 (3%)	1 (6%)	0 (0%)	
Unknown	3 (9%)	1 (6%)	2 (13%)	
Subtype PS				**0,005**
VPS	10	2 (11,5%)	8 (53%)	
SVPS	9	4 (23,5%)	5 (33%)	
Combined VPS and SVPS	13	11 (65%)	2 (14%)	
PV pressure gradient	40,0 mmHg [25,0 – 70,0]	70,0 mmHg [45,0 – 75,0]	25,0 mmHg [18,0 – 39,0]	**< 0,001**

Abbreviations: VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis ; PS = Pulmonary Stenosis.

malformations, type of intervention (BVP or surgery) and complications were reviewed. Intervention decision was based on thegradation of PS after multidisciplinary meetings with (interventional) pediatric cardiologists and pediatric cardiac surgeons. Patients were treated whose peak systolic gradient across the pulmonic valve was 60mmHg or greater. Treatment success was defined as not requiring further interventions during the study period.

Statistical analysis was performed using 'IBM SPSS Statistics 26'. All included continuous parameters were assessed for a normal distribution through the use of a Shapiro-Wilk test. None of the included parameters were normally distributed. Continuous data are expressed as median [interquartile range]. Intergroup comparisons were analysed by the Mann-Whitney U-test, Fisher's exact test or Kruskal-Wallis test as appropriate. A p-value of $< 0,05$ was considered as statistically significant.

The study was approved by the medical ethical committee of both the Antwerp- and Ghent University Hospital (EC2022/0141).

Results

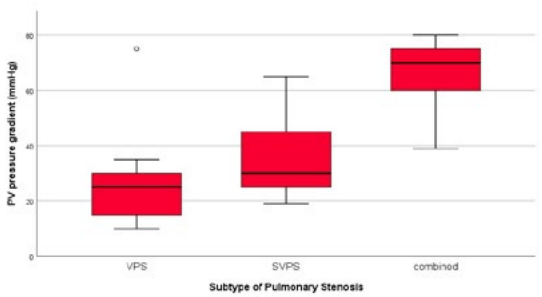
We identified 32 patients with NS that met the inclusion criteria. The median age at diagnosis was 2 months. Of these patients 59% were female. A comparison of patients who underwent an intervention and those who did not is shown in table 1. There were no differences in demographics between the two groups. There were significantly more patients with a combined valvular pulmonary stenosis (VPS) and SVPS who underwent a BVP.

Seventeen patients (53%) had a pathogenic variant in the *PTPN11* gene. Six patients (19%) had a pathogenic SOS1 variant. Four patients (13%) had a pathogenic *RIT1* variant. There was one patient with a pathogenic RAF1 variant and one patient with a pathogenic *BRAF* variant. The other patients did not have a known associated genetic cause. There was no significant difference in the distribution of associated pathogenic gene variants between the two groups.

A total of 22/32 (69%) had an SVPS (either alone or combined with a VPS). The other ten children had an isolated VPS. No subvalvular PS was found in our cohort. A comparison between the three groups is shown in table 2. There were no demographic differences.

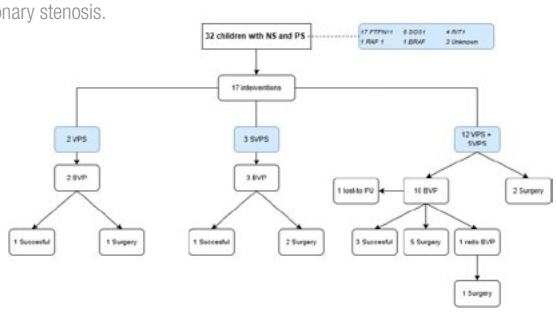
When comparing the existence of isolated VPS with isolated SVPS or a combination of both, there is a significant difference in the PV pressure gradient ($P<0,001$). The PV pressure gradient is highest when a combination of VPS and SVPS is present (figure 1). When comparing the three groups separately, a significantly higher PV pressure gradient

Figure 1: Comparison of the PV pressure gradient by subtype of PS.



Abbreviations: PA = Pulmonary Artery ; VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis.

Figure 2: Flowchart of treatment outcome of children with Noonan and (supra)valvular pulmonary stenosis.



Abbreviations: PS = Pulmonary Stenosis ; NS = Noonan Syndrome ; BVP = Balloon Valvuloplasty; SVPS: Supravalvular pulmonary stenosis ; VPS = Valvular Pulmonary Stenosis ; FU = Follow-up.

Table 2: Comparison between groups according to the anatomical location of the PS.

	Total cohort	VPS	Isolated SVPS	Combined	p-value
Number of patients	32 (100%)	10 (31%)	9 (28%)	13 (41%)	
Sex	19 female (59%)	5 female (50%)	6 female (67%)	8 female (61%)	0,815
Age	2,0 months [1,0 – 6,0]	4,5 [0,8 – 88,8]	1,0 months [1,0 – 2,0]	4,0 months [2,0 – 4,5]	0,051
Weight	4,1 kg [4,1 – 6,2]	5,1 kg [3,1 – 11,4]	4,8 kg [4,3 – 5,2]	5,0 kg [4,1 – 6,7]	0,726
Associated gene					0,876
PTPN11	17 (53%)	5 (50%)	5 (56%)	7 (54%)	
SOS1	6 (19%)	2 (20%)	1 (9%)	3 (23%)	
RIT1	4 (13%)	1 (10%)	1 (9%)	2 (15%)	
RAF1	1 (3%)	0 (0%)	1 (9%)	0 (0%)	
BRAF	1 (3%)	0 (0%)	1 (9%)	0 (0%)	
Unknown	3 (9%)	2 (20%)	0 (0%)	1 (8%)	
PV annulus	7,0 mm [7,0 – 8,5] (n=20)	7,5 mm [5,5 – 9,5] (n=4)	7,0 mm [6,5 – 8,5] (n=7)	8,0 mm [7,0 – 8,8] (n=9)	0,709
PV pressure gradient	40,0 mmHg [25,0 – 70,0]	25 mmHg [12,5 – 32,5]	30,0 mmHg [22,5 – 46,0]	70,0 mmHg [55,0 – 75,0]	**<0,001**
Intervention performed	17 (53%)	2 (20%)	4 (44%)	11 (85%)	**0,005**

Abbreviations: VPS = Valvular Pulmonary Stenosis ; SVPS = Supravalvular Pulmonary Stenosis ; PV = Pulmonary Valve.

is found in a combined PS in comparison to an isolated VPS (respectively 70,0 mmHg [55,0 – 75,0] vs. 25,0 mmHg [12,5 – 32,5] ; p = 0,001) and in comparison to an isolated SVPS (respectively 70,0 mmHg [55,0 – 75,0] vs. 30,0 mmHg [22,5 – 46,0] ; p = 0,001). No statistical difference was found between an isolated VPS and isolated SVPS (respectively 25,0 mmHg [12,5 – 32,5 vs. 30,0 mmHg [22,5 – 46,0] ; p = 0,286).

The need for intervention is significantly higher in the combined group (11/13 (85%)) compared to isolated SVPS (4/9 (56%)) or VPS (2/10 (20%)) (p = 0,005).

Seventeen patients (53%) needed treatment for PS. In five (33%) patients PS subtype was classified differently due to the results of the angiogram. A flowchart of the treatment outcome can be found in figure 2.

Fifteen patients (2 VPS and 13 SVPS) underwent BVP as first-line treatment. Of these patients, ten (67%) required re-intervention due to treatment failure. The success group was compared with the re-intervention group in table 3. There were no differences in demographics. Carrying a pathogenic variant in the *PTPN11* gene was significantly associated with a successful treatment (p = 0,010). Of the patients who needed a second intervention, one underwent a repeat BVP. All other patients underwent a surgical correction (commissurotomy (with shaving) and autologous patching of the main pulmonary artery) either as a second or third re-intervention. All BVP's were done with a Tyshak II balloon. Median time to re-intervention was 1 month [1 – 3,5]. Eight (89%) re-interventions were performed within three months. One re-intervention was performed after approximately 3 years. One patient requiring a re-intervention was transferred to another centre. One patient died after surgical intervention due to cardiac failure. Median time to follow-up in the success group was 134 months [67 – 144]. Two patients had primary surgical treatment to correct multiple cardiac defects during one intervention.

Within the subgroup of patients with SVPS fifteen patients (4 with isolated SVPS) underwent treatment of which 2 surgical treatment and 13 BVP. Six patients (4 in the BVP group) were successfully treated and did not need a re-intervention. Nine were unsuccessful (of which one lost to follow-up). There was no statistical difference between the two groups (p = 1,0). Due to the low number of patients it was not possible to perform a survival analysis.

Discussion

The main goals of this study are to identify factors predicting treatment for PS in children with NS, to evaluate the success-rate of BVP as first-line treatment and to identify factors predicting treatment failure with BVP.

The main results are listed below. These results will be discussed one by one.

1. In children with NS and PS there is a high prevalence of SVPS.
2. SVPS is associated with a significantly higher PV gradient in comparison to other subtypes of PS, leading to more interventions.
3. Children carrying a pathogenic variant in *PTPN11* were less likely to need a re-intervention.
4. The re-intervention rate after failed BVP for PS in patients with NS is high.
5. Higher immediate drop in PV gradient after BVP was associated with treatment success.
6. SVPS is associated with high re-intervention rates but could still benefit from BVP.

Our study showed that 70% of patients with NS and PS actually had SVPS (either isolated or in combination with VPS). It has been widely described that the most common congenital heart defect in children with NS is a PS. The prevalence of SVPS as a subtype of PS however has not been clearly stated in other cohorts (3,7). Only two studies treated SVPS as a separate entity and reported a prevalence of 35-50% (5,10), which is markedly lower than in our study. However, both studies excluded patients with a mild stenosis (defined as a PV pressure gradient < 40mmHg) which could explain the differences between their findings and ours.

Valve dysplasia has been regularly discussed as a possible reason for treatment failure. Patients with NS are recognised to have dysplastic pulmonary valve leaflets that may inherently be more refractive to relief of obstruction by BVP resulted in a high re-intervention rate after BVP (7).This was in agreement with McCrindle et al. who described that the associated dysplastic morphology of the pulmonary valve leaflets in NS patients was thought to be the root cause of a suboptimal response (9). In our cohort the main reason of re-intervention or intervention failure seems to be the existence of an SVPS.

Table 3: Comparison between success group and re-intervention group after BVP.

	Total cohort	Success group	Re-intervention group	p-value
Total number of patients	15 (100%)	5 (33%)	10 (67%)	
Sex	8 female (53%)	1 female (20%)	7 female (70%)	0,119
Age	4,0 months [2,0 – 7,0]	6,0 months [3,0 – 41,5]	3,0 months [2 – 6,3]	0,201
Weight	6,3kg [4,7 – 6,5]	6,0 kg [5,6-15,0]	5,0 kg [4,1 – 6,4]	0,061
Associated gene				0,093
PTPN11	8 (53%)	5 (100%)	3 (30%)	
SOS1	1 (7%)	0 (0%)	1 (10%)	
RIT1	4 (27)	0 (0%)	4 (40%)	
BRAF	1 (7%)	0 (0%)	1 (10%)	
Unknown	1 (7%)	0 (0%)	1 (10%)	
Type of PS				0,660
SVPS	3 (20%)	1 (20%)	2 (20%)	
SVPS + VPS	10 (67%)	3 (60%)	7 (70%)	
VPS	2 (13%)	1 (20%)	1 (10%)	
PV annulus	7,0 mm [6,25 – 8,75] (n=13)	7,5 mm [6,25 – 9,5] (n=4)	7,0 mm [5,0 – 9,0] (n=7)	0,600
PV pressure gradient pre-intervention	74,0 mmHg [62,5 – 75,0]	67,5 mmHg [60,0 – 75,0]	75,0 mmHg [70,0 – 80,0]	0,232
PV pressure gradient post-intervention	55,0 [36,0 – 69,0]	40,0 mmHg [28,0 – 42,0]	66,5 mmHg [58,8 – 72,5]	**0,006**
BVP balloon dm to PS annulus ratio	1,29 [1,17 – 1,40]	1,2 [1,18 – 1,43] (n = 3)	1,33 [1,14 – 1,4] (n = 7)	0,967

Abbreviations: PS = pulmonary stenosis; SVPS = supravalvular pulmonary stenosis; VPS = valvular pulmonary stenosis; PV = pulmonary valve; PA = Pulmonary Artery; BVP = balloon valvuloplasty; dm = diameter.

Among all NS patients screened, pathogenic variants in the *PTPN11* gene were most frequently reported (56%). This is similar to previous literature reports (11). Although carrying a *PTPN11* gene variant has been associated with more severe PS, needing treatment in approximately 50% of cases, we were unable to confirm this association (11). We found that there was a significantly higher proportion of patients carrying a variant in the *PTPN11* gene that had a successful treatment in comparison to patients carrying a variant in a different involved gene or to patients in whom the molecular cause was not found. It was not possible to evaluate other genes as a separate group due to the low number of patients. RAF1 for example is known to be associated with the risk of a more severe PS (12). However in our study only one patient had a RAF1 mutation and did not require any treatment.

The re-intervention rate of BVP after primary treatment was 67%. Of the nine patients needing a re-intervention and in whom follow-up data was available, only one underwent a second BVP. This treatment was unsuccessful. The other nine patients underwent a successful surgical repair. Although in non-syndromic patients re-intervention rates were reported to be as low as 15% (8), the re-intervention rate in NS has been shown to be much higher, ranging from 41% to 65% (5,7,12). These results are similar to those found in our study.

In our study there is a significantly lower post-procedural PV pressure gradient in the success group. This is consistent with McCrindle et al. who found that a higher post-BVP residual gradient is associated with a suboptimal outcome in non-syndromic patients (9). Holzmann et al. however found no difference in the residual gradient in patients with NS. Notably, the results in the study of Holzmann et al. showed a lower PV pressure gradient in the success group, although it did not reach statistical significance (5).

In our study, there was no significant difference in the need for re-intervention in patients with VPS versus patients with an SVPS. This result is consistent with the work by Holzmann et al. who reported similar results (5). However, a recent study by Abumehdi et al. reported that SVPS is significantly associated with the need for a re-intervention after BVP (12). A major difference is that our cohort size is smaller than the cohort size of Abumehdi et al. (n = 15 vs. n = 52), which is the largest reported series of performed BVP's in children with NS until present. In our study there were only 2/15 (13%) patients with a VPS that needed treatment in comparison to 22/54 (41%) in the study by Abumehdi et al. It is possible that a larger cohort could lead to a different result. In these studies, there are no children reported with an isolated SVPS. It would be beneficial in future studies to include this as a separate entity.

None of the patients in the success group needed a second intervention. However, follow-up is short so far. It should be noted that the time to re-intervention was around 1-3 months. The success group has a median follow-up of 134 months, making the need for re-intervention unlikely.

Limitations

This study is performed retrospectively over more than 20 years. Therefore the information gathered from older patients is subjected to unavailability and therefore leads to missing data.

Secondly, the small number of patients in this cohort means results should be interpreted with caution. For example, the genotype-phenotype correlation between carriers of pathogenic variants in *PTPN11* and success rate could be a random finding due to the low number of included patients.

The decision to perform a re-intervention was done in a multidisciplinary setting with cardiologist and cardiac surgeons. However, in about 20 years the treating clinicians have changed. It can't be excluded that this has resulted in a different threshold to perform a(n) (re)intervention.

The definition of supravalvular stenosis is not clearly defined in the literature which could lead to interpretation bias. It would be relevant for future studies to address the lack of definition to reduce heterogeneity and facilitate comparisons.

Conclusion

SVPS is a frequent manifestation of PS in patients with NS and leads to a more severe PS when combined with a VPS, frequently mandating early treatment. Isolated SVPS was found in approximately 1/3 of all pulmonary stenoses and seems to be less severe. No other factors could be found predicting treatment necessity.

The re-intervention rate after BVP of a PS in children with NS is higher than in non-syndromic patients. SVPS may be a risk factor predicting failure, though could not be withheld in this study. Next to that, the underlying pathogenesis of an isolated SVPS is most likely different from that of combined VPS and SVPS. One of the problems identified in this study is that the echo prediction of SPVS is unreliable as catheterization laboratory findings frequently differed (33%). Therefore, BVP might still be useful as the intervention is significantly less invasive compared to surgery and has a success rate of 31,1%. These findings need to be discussed with the parents in order to make a joint decision on the best primary treatment option on an individual basis. A greater post-procedural drop in PV pressure gradient seems to be predictive of successful treatment, also in children with NS but obviously this is known only after having performed the procedure. A pathogenic *PTPN11* gene variant in association with NS with PS might be associated with a higher success rate of BVP. Larger studies are needed to hopefully identify which patients will benefit most from primary BPS and in whom it should not even be attempted.

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Conflicts of interest

The authors declare that they have no conflicts of interest to report regarding the present study.

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SPA® Reine

Natuurlijk zuiver, van de bron tot de fles.

“ EEN STRIKT GECONTROLEERD WATER. ”

Interview met Arnaud Collignon, Water Ressources Manager bij SPA®, die uitleg geeft over de beschermingsmaatregelen in de stroomgebieden in de Venen en over de uitgevoerde controles om zuiver, zwak gemineraliseerd water met een constante samenstelling te garanderen.

“ CRITERIA VOOR HET LABEL “ GESCHIKT VOOR DE BEREIDING VAN BABYVOEDING. ”

AC: Om het label “ geschikt voor de bereiding van voeding voor zuigelingen ” te verkrijgen, moet water aan verschillende criteria voldoen: een zeer hoge zuiverheidsgraad, constant in de tijd en een lage minerale samenstelling, wat het geval is voor SPA® Reine omdat het laag gemineraliseerd is met een zeer laag gehalte aan calcium, fluoride, chloride en natrium, maar ook aan nitraten en nitrieten. SPA® Reine beantwoordt perfect aan al deze criteria. Daarom is het water van SPA® Reine de eerste keuze voor baby’s en voor moeders die borstvoeding geven. SPA®

Uiterst mineraalarm
SPA® Reine is uiterst mineraalarm: het heeft een droogrest van slechts 38 mg per liter. Dit is de hoeveelheid mineralen die overblijft na verdamping van het water. Mineraalarm water belast je lichaam niet onnodig.

Zeer laag natriumgehalte (zout)
SPA® Reine bevat slechts 3 mg natrium per liter, waardoor het geschikt is voor zoutarme diëten.

Uiterst zuiver
Dankzij de pure, ongerepte natuur, de uitzonderlijke bescherming sinds meer dan 125 jaar en de lange ondergrondse reis is SPA® Reine een van de zuiverste waters van Europa.

“ DAGELIJKSE ANALYSES, UITGEVOERD DOOR EEN ERKEND LABORATORIUM. ”

AC: Het Spa-water voldoet aan alle vereisten van de Europese regelgeving op dit gebied. Zo wordt het water dagelijks geanalyseerd om zijn microbiologische kwaliteit en chemische samenstelling te evalueren. Het wordt gecontroleerd bij de bron, en voor en na het bottelen. Om uitmuntendheid te garanderen, gaat de controle van het water zelfs verder dan de regelgeving met regelmatige controles op een brede waaier aan microbiologische, fysisch-chemische en organische parameters door het Spadel Laboratorium (gecertificeerd volgens ISO 17025). Bovendien controleren onafhankelijke laboratoria het water regelmatig op de afwezigheid van opkomende verontreinigende stoffen (bestrijdingsmiddelen en hun metabolieten, residuen van geneesmiddelen, hormoonverstoorders, virussen...). Naast de wekelijkse microbiologische controles analyseerde Spadel in 2020 zo’n 53.204 parameters van het Spa-water.

“ EEN STROOMGEBIED VRIJ VAN MENSELIJKE ACTIVITEIT. ”

AC: Het beschermingsgebied van het mineraalwater van Spa is meer dan 13.000 hectare groot Binnen deze perimeter is er geen enkele industriële activiteit, geen landbouw en geen pesticiden, om de zeer hoge zuiverheid van het water te garanderen. Van de bron tot de fles blijft het water in een gesloten circuit en ziet het geen daglicht. Alle materialen die met het water in contact komen, of het nu gaat om leidingen of verpakkingen, worden regelmatig getest en geanalyseerd om te garanderen dat zij inert en niet-verontreinigend zijn. Ook de verpakking garandeert de kwaliteit en de zuiverheid van het water. De productielijnen worden continu gecontroleerd. Al deze procedures en controles, van de bron tot de fles, maken het mogelijk om een water van hoge kwaliteit en met een onberispelijke zuiverheid aan te bieden en te garanderen.

Beter drinken. Beter leven.

In vitro measurement of the deposition of budesonide, ipratropium bromide and salbutamol, administered by jet nebulizing into a neonatal high flow nasal cannula system

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Keywords

Aerosols ; cannula, high flow neonatal ; drugs, in vitro deposition ; infant, newborn ; nebulizers.

Abstract

Objective: to determine what proportion of nebulized drugs is deposited through the prongs of a neonatal high flow nasal cannula circuit. Methods: Total cannula output, aerosol deposition in the tubes of the oxygen nasal cannula and the amount of compounds residue in the sidestream disposable were determined by two different and independent *in vitro* experiments performed in triplicate. Quantification of the compounds was performed using high-pressure liquid chromatography with high resolution mass spectrometric detection. Setting: nebulization of budesonide, ipratropium bromide and salbutamol with a jet nebulizer into a humidified and heated (37˚C) Optiflow™ nasal cannula system for 20 minutes at a flow of 6 L/min. Main outcome measures: Percentage of compounds in cannula output. Results: For all compounds, both *in vitro* experiments resulted in a total cannula output of less than 1%. A small amount of the compounds (i.e., 0.27 to 3.62 % of the nominal dose) could be measured in the rinsing water of the nasal cannula tubes and the highest amount (i.e., 28.43 to 53.63%) remained in the sidestream disposable nebulizer chamber. Conclusion: Routine use of nebulization in neonatal high flow nasal cannula circuits is not recommended. Further research is needed to determine if optimizing nebulizing conditions can result in a therapeutic amount of drugs delivered through an Optiflow™ nasal cannula system in order to simultaneously deliver oxygen and medication without patient manipulation.

Introduction

Nebulization of corticosteroids (e.g., budesonide), anticholinergics (e.g., ipratropium bromide) and beta-agonists (e.g., salbutamol) has been widely accepted in the treatment of neonatal respiratory illnesses, yet its efficiency remains matter of debate (1). Generally, a face mask connected to a jet nebulizer is used for the delivery of pulmonary aerosol medication. However, in neonatal units, newborns frequently receive high flow nasal cannula (HFNC) oxygen therapy for respiratory support. If these patients additionally require aerosolized drugs, the connection of a jet nebulizer to the HFNC circuit may be considered as a simple solution to deliver medication without the interruption or modification of the concomitant oxygen therapy, thereby improving the efficiency and tolerance of the overall procedure (2-5). However, clinical studies on the delivery of drugs via HFNC observed controversial efficacy, questioning the in vitro delivery adequacy of the system (6-8). In vitro studies exhibit controversial results as well. In some studies significant amounts of aerosolized drugs have been measured at the cannula outlet and other studies reported insufficient cannula outlet due to several barriers, like aerosol deposition, impeding efficient nebulization through HFNC circuits (9-11). Several settings like type nebulizer system, nebulizing time, flow rate, temperature, the starting volume, position of the nebulizer, size of nasal cannula and type of humidification system were found to influence aerosol efficiency through an HFNC system (10-13). Nevertheless, an optimized aerosol drug delivery system through an HFNC circuit for infants still does not exist. Consequently, for every specific setup, an in vitro study on the cannula outlet is recommended. According to Rubin and Fink an effective nebulizer should deliver at least 50 % of the total dose as respirable aerosol (14).

The objective of this study is to measure what proportion of frequently used nebulized drugs in neonates (i.e., budesonide, ipratropium bromide and salbutamol) is delivered from the nasal cannula after nebulizing them with a jet nebulizer through a humidified and heated (37˚C) Optiflow™ nasal cannula system for 20 minutes at a flow of 6 L/min, and what proportion remains in the tubing and chamber.

Materials and methods

1. Materials

The setup for this experiment was the same as we use in clinical practice in the neonatal intensive care unit and consisted of an Optiflow™ tubing kit, the Optiflow™ nasal cannula, a heating element (Fisher & Paykel Healthcare, Auckland, New Zealand) and a Sidestream Disposable Nebulizer Chamber (Philips Respironics, Chichester, UK). Commercially available budesonide (0.25 mg/mL), ipratropium bromide (0.25 mg/2mL) and salbutamol (0.5 mg/mL) were used for both the experimental design and as reference standards for the mass spectrometric analysis of budesonide, ipratropium and salbutamol respectively. NaCl 0.9% solution was obtained from Braun (Meisungen, Germany), the internal standard salbutamol-D3 from the National Measurement Institute (North Ryde, Australia) and triamcinolone acetonide-D6 from Clearsynth (Mumbai, India). The collection device for drug detection, ExaBreath®, was placed at our disposal by SensABues (Stockholm, Sweden). Acetonitrile and methanol were purchased from Biosolve (Valkenswaard, The Netherlands). For all experiments, ultrapure water produced by a Milli-Q® Reference A plus system from Merck KGaA (Darmstadt, Germany) was used.

2. In vitro Optiflow™ system setup

The position of the nebulizer is close to the nasal prongs, downstream of the humidifier (Fig. 1). To the sidestream disposable nebuliser chamber, 0.250 mL of commercially available budesonide, ipratropium bromide and salbutamol were added and diluted with 1.250 mL of NaCl 0.9% solution. This 2 mL suspension was nebulized using a jet nebulizer through a humidified and heated (37˚C) OptiflowTM nasal cannula system for 20 min at a flow rate of 6 L/min and FiO2 = 21%.

Total cannula output was determined by collecting the nebulized aerosol on the basis of two different and independent in vitro experiments performed in threefold. In the first experiment the nasal prongs of the oxygen nasal cannula were directly plugged into the ExaBreath®. The ExaBreath® was tightly sealed with Parafilm. This device contains an electrostatic based filter which is used to capture and retain the aerosol particles originating from the nebulizer. The mouthpiece and control bag from the ExaBreath® were not used. After completion of the nebulization experiment, compounds were extracted from the filter of the ExaBreath® by removing the filter from the device, spiking it with 50 µL internal standard solution (50 mg/L salbutamol-D3 and triamcinolone acetonide-D6 in methanol) and placing it in a 10 mL test tube containing a 1 mL sterile pipet tip (Fig. 2). The sterile pipet is used as a tool to hold the filter at the top of the tube so that after centrifugation the centrifuged solution can be separated from the filter. The pipet is sterile to minimize any contamination or effect of the tip on the analysis. The inner part of the ExaBreath® was rinsed with 2 mL of methanol to collect the aerosol drops that stayed behind on the inner surface of the device. The 2 mL rinsing solution was then added to the filter. The test tubes were vortexed (10 seconds), placed on a roller mixer (5 min) and centrifuged (10 min, 3200 rpm). The filter and pipet tip were removed from the test tube and 100 µL of the centrifuged solution was transferred to an autosampler vial containing 900 µL of ultrapure Milli-Q water. Vials were manually vortexed for 15 seconds and budesonide, ipratropium and salbutamol were quantified (see below). To determine the percentage of the compounds that reached the ExaBreath® after nebulizing, the ExaBreath® filter was, in a separate experiment also performed in threefold, spiked with the same total amount of compound that was added to the sidestream disposable (i.e., 0.250 mL of the respective solutions) and with the same amount of internal standards. These filters were not subjected to any nebulization and subsequently extracted with the same extraction protocol. The mean instrumental response obtained from these experiments was regarded as a 100% recovery and compared with the mean response from the in vitro experiments.

A second independent in vitro setup to determine total cannula output was additionally performed. In that experiment, the nasal prongs of the oxygen nasal cannula were directly submerged into a test tube containing 1 mL ultrapure water, that was tightly sealed with Parafilm. After completion of the nebulization, the solution was directly analyzed as described below. The mean instrumental response from these experiments (n=3) was compared with the mean response obtained from dissolving the total amount of compound that was added to the sidestream disposable into 1 mL ultrapure water (same volume as in the test tube of the experiment).

Besides determining the total cannula output, in all experiments, the substantial deposition (droplets that remained in the tubes of the oxygen nasal cannula) and amount of compound that remained in the sidestream disposable were also determined by rinsing both devices with 1 mL ultrapure water after completion of the nebulizing experiment. Compounds in this rinsing solutions were quantified as described below.

3. Quantification of the compounds

For every experiment, 1 µL of extract, solution or rinsing water was injected into an Ultimate 3000 ultra-high pressure chromatographic system (Thermo Fisher Scientific Waltham, MA, USA) consisting of an Accucore phenylhexyl-column (2.6 µm, 100 mm x 2.1 mm, Thermo Fisher Scientific). The column and autosampler temperature were set at 40°C and 4°C respectively. The mobile phase consisted of a mixture of A (2 mM ammonium formate, 0.1% formic acid in ultrapure water) and B (2 mM ammonium formate, 0.1% formic acid, 1% water in 50/50 (v/v) methanol/acetonitrile). A linear gradient with the following proportions of solvent B was applied: 0.0 – 2.0 min at 2%, 2.0 – 5.0 min from 2% to 80%, 5.0 – 6.0 min at 80%, 6.0 – 6.5 min from 80% to 90%, 6.5 – 7.0 min at 90%, 7.0 – 7.5 min from 90% to 95%. The flow rate was 0.4 mL/min. After separation, the compounds were detected using a Q-Exactive Hybrid Quadrupole orbitrap mass spectrometer (Thermo Fisher Scientific) equipped with a heated electrospray ionization source, operating in positive ionization mode. The following ionization source parameters were used: sheath, auxiliary and sweep gas flow rate at 45, 15, and 0 arbitrary units (au), respectively; heater and capillary temperature at 350 and 300 °C respectively, spray voltage at 350 kV and S-lens RF level at 70.0. A full scan mode was used, scanning from 150 to 500 mass to charge ratio (m/z) with a resolution of 70000. The automatic gain control target was set at balanced (1 × 1e6 ions) with a maximum injection time of 200 ms. Diisooctyl phthalate (391.28429 m/z) was used as lock mass. The data were processed using Tracefinder 3.3 (Thermo Fisher Scientific). Detection of each compound was based on their retention time and exact mass to charge ratio (Table 1). Analysis of components was performed by ultra-high-performance

Figure 1: Experimental setup for the collection of nebulized aerosol by the ExaBreath®. A: Sidestream disposable nebuliser chamber with aerosol solution, B: ExaBreath® with electrostatic based filter, C: Tube connected to compressed air, D: Optiflow™ tubing kit, E: Optiflow™ nasal cannula.

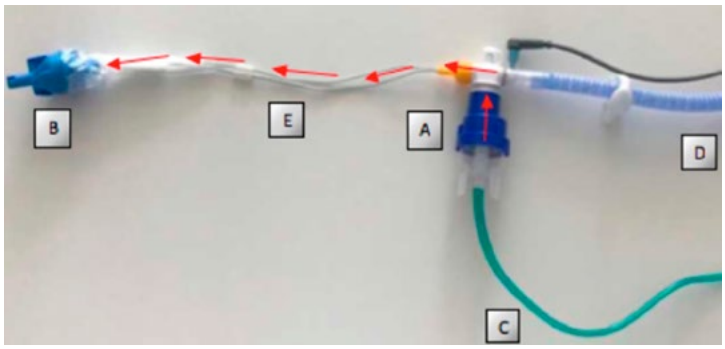

Figure 2: Extraction of budesonide, ipratropium and salbutamol from the filter.

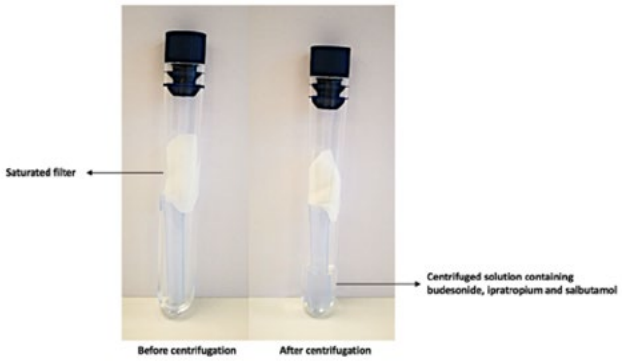

Table 1: Ions used for quantification, exact masses and retention times of the compounds. m/z = mass to charge ratio; (M+H)+ = protonated parent ion; (M)+ = parent ion.

Compound	Ion used for quantification	*m/z*	Retention time (min)
Budesonide	$(M+H)^+$	431.24282	5.48
Ipratropium	$(M)^+$	332.22202	4.04
Salbutamol	$(M+H)^+$	240.15942	3.26
Salbutamol-D3	$(M+H)^+$	243.17825	3.25
Triamcinolone acetonide-D6	$(M+H)^+$	441.25540	5.15

Table 2: Mean percentage (± standard deviation) of budesonide, ipratropium and salbutamol initially added to the sidestream disposable measured in the ExaBreath®, the sidestream disposable nebulizer chamber and the rinsing water of the nasal cannula tubes after completion of the experiment (n=3).

	ExaBreath® (%)	Residue in sidestream disposable (%)	Nasal cannula tubes (%)
Budesonide	0.22 ± 0.10	33.15 ± 3.91	0.45 ± 0.22
Ipratropium	0.35 ± 0.20	48.89 ± 3.86	2.07 ± 1.10
Salbutamol	0.42 ± 0.21	44.99 ± 4.71	1.93 ± 1.34

liquid chromatography-high resolution mass spectrometry, resulting in a chromatogram for each component and for an internal standard. Quantification of the compounds was performed by calculating the corresponding responses (ratio of area of the compound and area of the corresponding internal standard). For budesonide, the deuterated internal standard triamcinolone-acetonide-D6 was used. For salbutamol and ipratropium, salbutamol-D3 was chosen as internal standard.

As no human or animal subjects were involved, ethical committee approval was not obtained for this study.

Results

Based on the mean instrumental response obtained from the spiked ExaBreath® filter experiment without nebulizing (100% recovery) and the mean instrumental response obtained from the in vitro experiment, the amount of budesonide, ipratropium and salbutamol that reached the ExaBreath® after nebulizing was found to be only 0.22 ± 0.10 %, 0.35 ± 0.20 % and 0.42 ± 0.21 % respectively of the initial amount of compound added to the sidestream disposable nebulizer chamber (Table 2). In a second experiment where nasal prongs of the oxygen nasal cannula were directly submerged into a test tube containing 1mL ultrapure water, no budesonide and salbutamol could be detected and the total cannula output from ipratropium was less than 1%. The solution that remained in the sidestream disposable nebulizer chamber and in the tubes of the oxygen nasal cannula after the experiment were also collected and analyzed. The collected data showed that 33.15 ± 3.91 %, 48.89 ± 3.86 % and 44.99 ± 4.71 % of the initial amount of budesonide, ipratropium and salbutamol, remained in the sidestream disposable nebulizer chamber after completion of the experiment. For all the compounds, only a small fraction could be detected in the nasal cannula tube (Table 2).

Discussion

When budesonide, ipratropium bromide and salbutamol were nebulized using a jet nebulizer through a humidified and heated (37˚C) Optiflow™ nasal cannula system for 20 minutes at a flow of 6 L/min, for all compounds, less than 1% actually leaves the nasal prongs of the oxygen nasal cannula. A small amount of the compounds could be measured in the rinsing water of the nasal cannula tubes and the highest amount remained in the sidestream disposable nebulizer chamber. These results are in line with Dugernier et al. who found that pulmonary drug delivery of diethylenetriaminepentaacetic acid using a jet nebulizer through the HFNC was between 0.7 and 2.0 % of the nominal dose and substantial deposition was observed in the single limb circuit, the humidification chamber and the nasal cannula (13). Zhou et al found that 65 to 67% of solution left behind after nebulization with the SideStream, irrespective of relative humidity conditions (15). O'Callaghan and Barry found that more than 90 percent of the primary droplets become trapped on internal structures or remained in the sidestream disposable nebulizing chamber when using jet nebulizers (16).

The nebulizer performance is much less for budesonide than for salbutamol. Budesonide is a suspension medicine, with a particle size distribution peak during nebulization that is larger than the one of a solution medicine, such as salbutamol (15). That is one of the reasons why the output of a suspension is less than that of an aqueous solution when nebulization is used (17).

As nebulizing budesonide, ipratropium and salbutamol using a jet nebulizer through a humidified and heated (37˚C) Optiflow™ nasal cannula system for 20 minutes at a flow of 6 L/min resulted in a delivery percentage far less than 50%, routine use of this specific set-up is not recommended. Numerous in vitro studies reported a range of factors strongly affecting delivery efficacy (i.e., nebulizer system, delivery gas type, nebulizing time, flow rate, temperature, droplet size, the starting volume, positioning of the nebulizer, size of nasal cannula), of which the administered gas flow rate is believed to play a critical role (8,9,11-14,18,19). Both Perry in 2013, and Daily in 2017 demonstrated that increasing gas flow rates significantly decreases the inspired dose of aerosol (11,12). High flow gas rates might induce particle impaction in the HFNC circuit. In our set-up, we suspect that temperature played an important role in the low delivery efficacy. The concentration of budesonide, ipratropium and salbutamol in the sidestream disposable was higher after the experiment than before the experiment, indicating that water had evaporated. A likely cause is the use of heated air (37˚C), necessary for the HFNC. The conventional procedure for nebulizing compounds involves the formation of an aerosol, without the use of heated air. In a conventional setup, the concentration of the compounds in the liquid droplets will be equal to the concentration of the compounds in the sidestream disposable nebulizer chamber. However, when the nebulizer is coupled to an Optiflow™ nasal cannula system for the administration of oxygen, heated air is required. Furthermore, budesonide, ipratropium and salbutamol are known to be thermolabile compounds (20-22). This explains the low efficiency when using heated air during nebulizing and why the combined amount of compound measured in the ExaBreath®, nasal cannula tubes and the sidestream disposable after nebulizing does not add up to 100%. On the other hand, it might be that not the full amount of component in the tubes was collected after rinsing.

In our neonatal unit we used to position the nebulizer downstream of the humidifier. In adult intensive care units the nebulizer is mainly placed at the inlet of the humidifier (23). Réminiac demonstrated that, in adult HFNC circuits, placing nebulizers immediately upstream from the humidification chamber is the most efficient position (8). Placement of aerosol devices between the humidifier and the patient results in a greater aerosol deposition in the tube that can occlude the nasal prongs (24).

This study has some limitations. The experimental setting was restricted to a fixed flow and one size of prongs. Perry et al showed that the inspired dose of salbutamol decreased with smaller sized cannulas (11). The use of different flows and of prongs with other sizes will influence the deposition of medication, as might the type of circuit used. As such, results of this in vitro study can not be generalized to all types of circuits and all flow settings. Therefore, each neonatal unit practicing nebulization in high flow circuits should measure the efficacy of deposition of medication with their own set-up. The in vitro setting excludes the influence of the patient, whose breathing efforts might influence the quantity of medication that effectively reaches the respiratory system. In adults with "quiet" breathing patterns, the inhaled dose seems to increase with lower flow rates while in a "distressed" breathing pattern, the aerosol delivery is higher when gas flow reaches approximately 50% of the inspiratory flow (19). If the same would be applicable in (preterm) neonates, in whom the inspiratory flow is low (ranging from 0.8 L/min to 3.5 L/min), lowering the flow rate to less than 50% of the inspiratory flow might compromise some physiologic benefits of HFNC (19,25). Finally, in the second experiment the nasal prongs were submerged into a sealed test tube. Additional pressure built up in the test tube during the experiment may have affected the final deposition of medication. To verify this, the experiment should be repeated with components for which total cannula output is known. Unfortunately, knowledge about this is currently lacking.

Conclusion

This in vitro study showed that nebulizing budesonide, ipratropium bromide and salbutamol using a jet nebulizer through a humified and heated (37˚C) Optiflow™ nasal cannula system with a flow of 6L/min, does not result in clinical relevant deposition of these drugs at the nasal interface. Therefore, routine use of that specific set-up in neonatal units should not be recommended. However, in vitro studies miss several important patient factors, underscoring the need for more anatomically accurate models. Validated deposition models using the airway geometry of children of different ages do not exist to date. Therefore, well-designed studies in neonatal patients are necessary to determine how nebulizing conditions can be optimized in order to result in a therapeutic amount of drugs delivered through an Optiflow™ nasal cannula system, enabling delivery of oxygen and medication simultaneously without patient manipulation.

Conflicts of interest

The authors have no conflicts of interest to declare.

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How to clean and care for baby's skin

The power of Pampers® wipes

Nothing is as plump and perfect as a baby's skin, but, not all is as perfect as it seems. From the moment a baby is born, this soft and squishy barrier is hard at work, protecting them from infection, irritants and much more.[1,2] All whilst still being delicate and vulnerable!

Did you know that at birth, the stratum corneum is up to 30% thinner than adult skin? And that baby's skin continues to develop even beyond the first 3 years of life![3,4,5,6]

That's not all; for roughly the first two and half years of their life, babies' bottoms are covered 24 hours a day by a diaper, where the skin is exposed to humidity and irritants like pee and poo... **This is why it's up to all of us to protect babies' delicate skin from day one!**

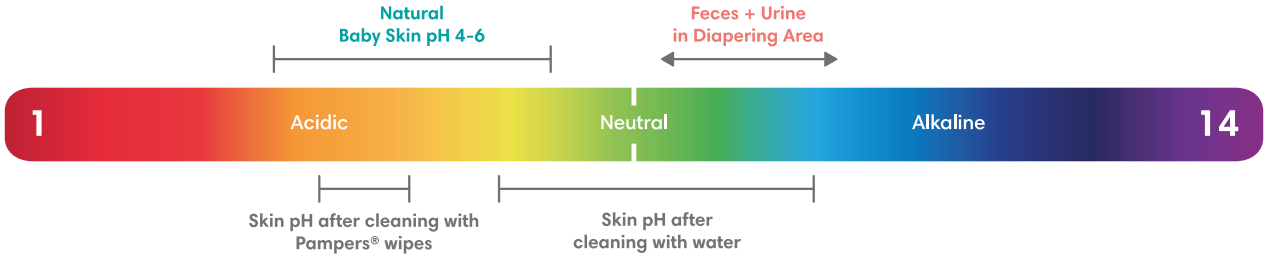
Understanding pH Balance for Healthy Baby Skin

Balanced skin pH (between 4-6)

- Healthy baby skin surface is naturally acidic
- During the first days of life, baby's skin develops a protective layer - an acid mantle - which helps healthy development of stratum corneum and protects against infection[7]

Elevated skin pH (above 6.0)

- Increases the activity of fecal enzymes that break down the skin barrier
- Damages the stratum corneum barrier, changes the microbial flora and increases the risk of infection[8]



Why water and cotton might not be enough?

Cleaning method is important in helping to restore natural skin pH

Pampers® baby wipes are made of a soft, cloth-like substrate, with **a unique blend of fibre shapes and sizes** which keep them **absorbent, and flexible to pick up mess from every crease and curve** of the skin while staying gentle. Intentionally designed wipe lotion - such as Pampers® baby wipes - has a number of ingredients that help to **clean skin, and help restore healthy skin pH.**[8,12] While water is a foundational component of baby wipes, water alone is not optimal to support baby's skin.

Ingredients in Pampers® Wipes

pH Buffering System
Helps restore natural skin pH

Emulsifiers
Efficiently remove urine and stool

Conditioners
Help restore skin appearance and improves feel

Preservatives
Inhibit the growth of germs

Include citric acid based buffering system that helps restore skin's natural acidic pH and help inactivate fecal enzymes

Contain water and emulsifiers to remove both water-soluble and oily mess

Soft with conditioners to gently glide across skin

Inclusion of a mild preservative to help prevent the growth of germs

Water has a poor pH-buffering power and neutral pH. It cannot restore skin's natural pH and decrease fecal enzyme activity[3,9,10]

Poor cleaner, especially of oily substance found in stool and on skin[3,9,11]

Washing with water alone can have a drying effect on infant skin[3,10]

Cannot stop germs from growing

Pampers® Wipes - everyday safe and high performing products

Over the past decades at Pampers®, we have been innovating to provide everyday safe & high performing products that can be used confidently.

We not only intentionally design products to protect your little ones skin, all of Pampers® baby wipes and their ingredients undergo rigorous testing to ensure they are safe, effective and gentle for babies' delicate skin. Every product we make must live up to the most demanding standards of all – yours.

What is NOT in Pampers® Harmonie Aqua

- Parabens
- Dye
- Ethanol/Rubbing Alcohol
- Natural Rubber Latex
- Methylisothiazolinone
- Sulfates
- Fragrances
- Phenoxyethanol

Gentle Skin Protection

Helps restore natural skin pH, made with 99% water

Dermatologically tested

100% Plant-Based Fibres and **10%** Premium Cotton

Suitable from **Day One**

Recommended by SHA dermatologists

Tested for impurities

We are accelerating our journey towards plastic free wipes

Our Harmonie wipes **are now fully plastic-free**

And we will not stop there!

Progressing towards **70% recycled plastic** from industrial residues in our lids and outer bags

We remain committed to **correct disposal**

With clear "Do not flush logo" across our portfolio, and SUP logo on plastic SKU, in compliance with the EU regulation

Why do we believe biodegradability for wipes can be misleading?

Regardless of their composition...

A used wipe is typically wrapped inside a used diaper and then disposed of in normal household waste, which is usually incinerated or landfilled where biodegradability makes no sense

Many authorities don't accept human waste in the organic bin in Europe

Baby wipes are used to clean baby's bottom, meaning that they contain human waste (pee and poo), and therefore pathogens, creating a biohazard in home composting

Biodegradability claims can be perceived as a 'license to litter' plastic into the environment for consumers[13]

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Caudal regression syndrome: 2 Case reports and literature review

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Keywords

Caudal regression syndrome ; caudal dysplasia syndrome ; caudal agenesis ; sacral agenesis ; sacral dysgenesis ; sacral regression ; nervous system malformations ; spine ; sacrum ; congenital ; anorectal malformation ; imperforated anus ; musculoskeletal ; VACTERL ; vertebral defects ; renal agenesis ; vesico-ureteral reflux ; neurogenic bladder ; neurogenic bowel

Abstract

Caudal regression syndrome (CRS) is a rare congenital disorder in which there is abnormal fetal development of the caudal partition of the spine. CRS has a broad clinical spectrum with variable anomalies of the lumbosacral spine, lower limbs, anorectal complex and genitourinary tract. Patients present with a variety of symptoms or features. We report two clinical cases, describing the clinical manifestations and diagnosis of these patients. We discuss the importance of screening for additional anomalies, early intervention and multidisciplinary follow-up.

Introduction

Caudal regression syndrome (CRS) is a rare congenital disorder in which there is an abnormal fetal development of the caudal partition of the spine. CRS encompasses a broad clinical spectrum with variable anomalies of the lumbosacral spine, lower limbs, anorectal complex, and genitourinary tract (1).

We present two clinical cases describing the clinical manifestations and diagnosis of these patients. We discuss the importance of screening for additional anomalies, early intervention, and multidisciplinary follow-up.

Case report 1

A 6-month-old girl was referred to the pediatric neurological department for evaluation of constipation associated with a sacral dimple. Since the introduction of solid foods, she had difficulty passing stools with a frequency of 2 to 3 bowel movements per week. Frequent enemas and laxatives were necessary. Sometimes even manual evacuation was required.

She was born at term but small for gestational age. Her birth length was 45 cm (-2.1 SD) and birth weight was 2660g (-1.6 SD). However, her head circumference was within the normal range. The pregnancy was complicated by gestational hypertension, which was treated with labetalol. There were no other chronic maternal conditions, infections, or drug use reported during pregnancy. In particular, the mother did not suffer from diabetes. Prenatal ultrasound showed no anomalies.

On clinical examination she presented with a sacral dimple and an abnormal intergluteal cleft, with the anus positioned more ventrally. The lower limbs appeared shorter compared to the rest of the body. She had no motor or sensory deficits and normal lower limb reflexes. She achieved expected motor and cognitive milestones. Additional imaging revealed sacral and coccygeal dysgenesis, a dysplastic lumbar vertebra with a neural cleft and a hemivertebra at Th9. These anomalies contributed to the development of a secondary S-shaped thoracolumbar scoliosis. In addition, partial fusion was observed between the right 6th and 7th ribs and the left 2nd and 3rd ribs (Fig. 1a). Magnetic resonance imaging also showed a tethered cord, tight filum terminale and a dilated ventriculus terminalis (Fig. 1b). Ultrasound and voiding cystourethrogram examinations revealed a crossed fused renal ectopia with hydronephrosis, a small overactive bladder, and a Mullerian duct anomaly, with agenesis of the right adnex and suspicion of a unicornuate uterus (Fig. 1c).

She is currently 18 months old and requires frequent enemas, laxatives and manual evacuation of stools. She receives a low dose of anticholinergic drugs and prophylactic antibiotics for her neurogenic bladder dysfunction and vesicoureteral reflux. She had one urinary tract infection (UTI) before being diagnosed and treated.

Case report 2

A newborn with CRS was referred to our institution at 14 days of age for further diagnosis and management. He was born with an imperforate anus and immediately underwent colostomy. X-ray examination showed sacral agenesis. On day 12 he had hydronephrosis and experienced suboptimal bladder emptying, which necessitated a bladder catheterization. Other clinical features included a sacral Mongolian spot, bilateral rocker bottom feet, moderately limited hip extension, and hypotrophy of the lower legs, particularly on the left side. Lower limb and anocutaneous reflexes were weak, while plantar reflexes were absent. Sensation appeared normal, although objective testing is not feasible in a newborn at two weeks of age. He was born at term to a non-diabetic mother.

Further magnetic resonance imaging revealed a sacral agenesis without no other vertebral anomalies. The conus medullaris ended bluntly with a normal position at the L1 vertebral level. Abdominal ultrasound showed a left renal agenesis with hypertrophy of the right kidney. A micturating cystourethrogram showed a small bladder and urinary dribbling. The bladder neck was open, and the urethra was dilated due to a hypercontractile external sphincter. This sphincter dyssynergia required early catheterization. He had a febrile UTI at the age of 10 days after cystography, which was treated with therapeutic antibiotics. Prophylactic antibiotics were started after this UTI. Intermittent catheterization and oxybutynin were instituted to treat the overactive neurogenic bladder with hydronephrosis.

Figure 1: **(A)** RX full spine; **(B)** MRI showing tethered cord, tight filum terminale, dilated ventriculus terminalis; **(C)** Voiding cystourethrogram showing a small oval shaped bladder, dilated ureter, and overflow of contrast in Mullerian duct.

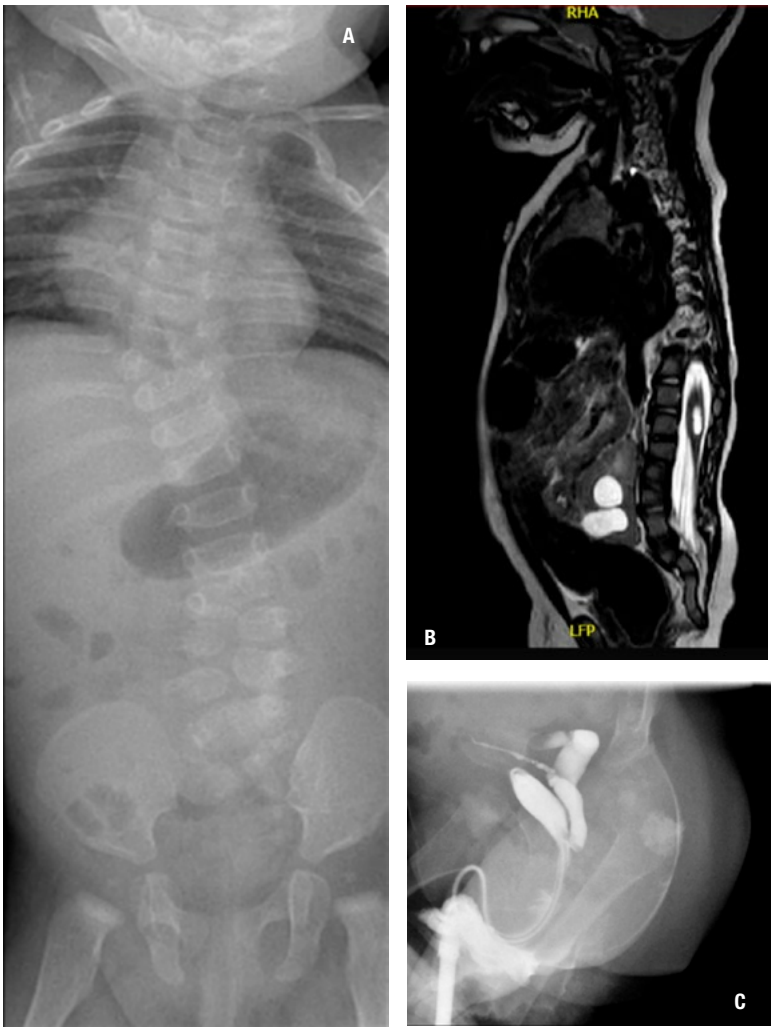
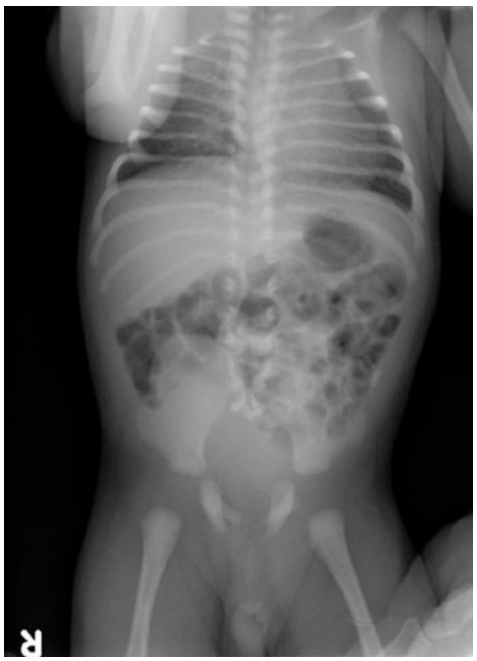


Figure 2: Sacral agenesi.



A laparoscopic pull through procedure was performed at 4 months of age with colostomy removal 6 months later. He is currently 10 years old and has regular follow-up visits in the departments of pediatric neurology, gastroenterology, nephrology, urology and orthopedics. He walks with orthoses. He performs regular enemas to establish fecal continence. He has continued intermittent catheterization, had multiple intravesical Botox injections, a detrusorectomy and a bladder augmentation without achieving full urinary continence. He has a normal renal function.

Discussion

CRS is also known as caudal dysplasia syndrome, caudal agenesis, sacral agenesis, sacral dysgenesis or regression. Duhamel was the first to use the term CRS to describe this entity in 1961(1). The incidence is estimated to be 1-5/100.000 live births (2).

Pathoembryogenesis and Etiology

CRS is caused by a developmental failure in the secondary neurulation during the early stages of gestation. Secondary neurulation comprises further neural development of the caudal cell mass occurring distal to the caudal neuropore after completion of primary neurulation. The caudal cell mass gives rise to the caudal spinal cord distal to S2 (conus medullaris), the filum terminale and the distal nerve roots by canalization and retrogressive differentiation in the fifth week of gestation. Besides the formation of the caudal spinal cord, the caudal cell mass is also involved in the formation of the sacrum and the development of the primitive cloaca into the genitourinary tract and anorectal organs (3,4).

If also part of the true notochord fails to develop, both the primary and secondary neurulation processes are affected (5). Depending on the severity of the original damage, the final degree of vertebral aplasia will range from absence of the coccyx to aplasia of all coccygeal, sacral, lumbar, and lower thoracic vertebrae (2,5,6).

The exact cause of the insult is unclear but maternal diabetes is the most associated environmental factor (3). The prevalence of CRS is reported to be 200 times higher in diabetic pregnancies (7,8). Most cases are sporadic but Currarino syndrome, a dominantly inherited sacral agenesis, is often associated with mutations within the HLXB9 gene (9,10). Other associated factors include teratogens, such as retinoic acid, and vascular anomalies that alter blood flow (3,11).

Clinical manifestations

Patients with CRS present with a broad range of symptoms or features. This is illustrated in Tables 1 and 2 by the presenting features of CRS patients found in the literature. Classic external features consist of shortened intergluteal cleft, small gluteal masses, flattened buttocks, bilateral buttock dimples, narrow hips, distal leg atrophy, and talipes deformities, with or without proximal joint deformities and contractures (3). Other orthopedic anomalies include caudal vertebral agenesis (usually sacrococcygeal), vertebral dysplasia or agenesis, hip dysplasia, popliteal webbing, frog leg position and in extreme cases, sirenomelia (3).

Although the neurological manifestations include both motor and sensory deficits, motor impairment is usually predominant with relative sparing of the sensory function (2). Patients with CRS present with a a broad spectrum of disability, ranging from individuals who can walk to complete limb hypotrophy. Several reports show that the motor level corresponds well with the level of the vertebral defect (3,6). High sacral defects correlate with more severe motor deficits and short conuses that are blunted, club or wedge shaped and have lost their usual taper, as if the caudal portion is missing (3,12). Low sacral malformations are associated with conuses that are extremely elongated to well below L1 and are variously tethered by thick filums or distended by large terminal hydromyelia (3). Neurological symptoms may be progressive in case of an associated tethered cord (6).

The incidence of genitourinary anomalies is reported to be approximately 72% (13). The most common anomalies include neurogenic bladder, renal dysplasia or agenesis and impaired renal function. Hydronephrosis, dysplasia or agenesis of other parts of the genitourinary system and renal ectopia have also been described (13,14). Urinary incontinence

Table 1: Presenting features of patients with caudal regression syndrome published in the last five years. (NR: Not reported, M: male, F: Female).

Cases	Age at diagnosis	Sex	Main presenting feature(s)	Spinal anomalies	Other anomalies present?
Ferreira et al., 2021	Newborn	F	Prenatal suspicion of spina bifida occulta: meningocele with lowered medullary cone. Neonatal diagnosis Currarino syndrome with recto-sacral mass	Partial sacral agenesis, anterior myelomeningocele, spinal cord tethering, cone in L4	Gastro-intestinal
Soltani et al., 2018	Newborn	M	Paraplegia, atrophic legs, and flexion contracture both knees	Vertebral column ending to dysplastic L2 vertebra. Club shape conus T12 level.	Limb, genitourinary
Mehdi et al., 2021	Newborn	M	Widely spaced nipples, slanting eyes, low set ears, underdeveloped genitals and lower limbs. Curved spine with thoracolumbar dimple and hair growth.	Total sacral and partial lumbar agenesis. Not further reported.	Limb, genitourinary, cardiac
Bevanda et al., 2020	Newborn	M	Anus atresia and rectovesical fistula	Sacral agenesis below S2, Cone ending T11-12 level.	Limb, genitourinary, gastro-intestinal, cardiac
Ponde et al., 2021	3 days	M	Anorectal malformation	Sacral agenesis below S3. Not further reported.	NR
	14 months	M	Congenital talipes equinovarus deformity	Total sacral agenesis. Not further reported.	Limb, other not reported
Mwamanenge et al., 2023	2 months (born 30 weeks gestation)	M	Respiratory distress syndrome due to transposition of great arteries with large VSD, bilateral hip and knee flexion contracture, dimples femoral trochanter area, short neck, low-set ears, undescended testes and microphallus	Complete agenesis lumbar, sacral and coccygeal spine. Not further reported.	Limb, genitourinary, gastro-intestinal, cardiac
Khandelwal et al., 2020	2 months	NR	Bilateral talipes equinovarus	Complete sacral agenesis. Wedge-shaped cone ending T12 level.	Limb, genitourinary
Dayasiri et al., 2020	2 months	M	Narrow pelvis, dimpled buttocks, bilateral knee flexion contractures, leg muscle atrophy, congenital talipes equinovarus, microphallus, displaced patulous anus, and constant leakage of urine and stools	Agenesis L5 and below. Thickened cone ending L1 level.	Limb, genitourinary, gastro-intestinal
Diallo et al., 2022	5 months	M	Chronic constipation	Agenesis L3 and below. Squared cone ending T11 level, with tapering ending L2 level. Syrinx T11-L1 (17 x 1 mm)	Limb, gastro-intestinal
Khanna et al., 2019	8 months	M	Anal imperforation and superior vesical fissure	Sacral agenesis, not further specified.	Genitourinary, gastro-intestinal
Karthiga et al., 2021	8 months	M	Reduced movement of lower limbs	Dysplastic L5 and S2 vertebra, Sacral agenesis S3-S5. Low lying conus with thickened filum terminale and tethered cord, dorsolumbar syringohydromelia.	Limb
Hage et al., 2020	13 months	F	Chronic urinary bladder infections	Sacral agenesis S3-5. Drumstick-shaped cone ending L1 level.	Limb, genitourinary
Ali Akhaddar, 2020	2 years	M	Walking disability and sphincter incontinence (hypoplastic and akinetic lower extremities)	Agenesis below T9. Abrupt termination cone at T6 level.	Limb
Kang et al., 2021	31 months	M	Chronic constipation	Agenesis distal sacrum. Club-shaped cone ending at T12/L1 level, thickened filum terminale.	Gastro-intestinal, genitourinary, hearing impairment
Graul et al., 2019	18 years	F	Scoliosis and back pain	Partial sacral agenesis below S2, only 4 lumbar vertebrae, cone ending at S1/S2 level	No
Shin et al., 2019	29 years	F	Pelvic mass identified during a routine gynecological examination, chronic constipation	Asymmetrical sacral agenesis below S2 level right, below S4 level left. Anterior sacral meningocele.	Genitourinary, gastro-intestinal
Rebelo et al., 2020	48 years	M	Chronic constipation after anal imperforation correction surgery	Right partial sacral agenesis. Not further reported.	Gastro-intestinal

Table 2: Radiographic features in prenatal diagnosis of caudal regression syndrome published in the last five years. (NR: Not reported, M: Male, F: Female).

Cases	Age at diagnosis	Sex	Radiographic features
Taylor et al., 2019	21 weeks gestation	NR	Complete sacrococcygeal agenesis, abnormalities lumbar vertebrae at L4-L5, atrophic lower limbs, mild bilateral talipes.
Mahmoud et al., 2023	24 weeks gestation	NR	Sacral agenesis and abrupt termination of lumbar spine at T12/L1 level. Spinal cord stops at the mid-thoracic level.
	29 weeks gestation	NR	Malaligned spine with mild thoracic kyphosis, absent lumbar lordosis and absent sacral spine. The spinal canal appears wide and ends abruptly. Termination spinal cord just below level of fetal kidneys. Ventricular septal defect, and two vessels umbilical cord.
Zhang et al., 2019	26 weeks gestation	NR	Shorter spine, partial agenesis lumbar and sacrococcygeal vertebrae. Flexed lower limbs without movement, left-sided talipes varus, situs ambiguous with levocardia, complex congenital heart defect (heterotaxy syndrome).
Kylat & Bader, 2020	30 weeks gestation	F	Hypoplastic lower limbs with bilateral clubfoot, low vertebral and sacral anomalies, polyhydramnios.
Charach et Yagel, 2021	30 week gestation	NR	Polyhydramnios, horseshoe kidney, a missing lumbar and sacral vertebral column.

and/or constant dribbling are the most frequent urological symptoms among children aged four and older (85%) (6). Recurrent urinary tract infections are also common (74%), sometimes leading to end-stage renal disease (6).

Gastrointestinal anomalies include imperforate anus, anorectal atresia, fistulas, esophageal or duodenal atresia, bowel incontinence, or obstipation, with a reported overall incidence of approximately 42% (13). CRS occurs in approximately 13 to 54% of patients with imperforate anus, necessitating a thorough assessment of neonates with imperforate anus (6).

In 24% of patients, CRS may be associated with pulmonary hypoplasia or dysplasia and congenital cardiovascular anomalies, such as patent ductus arteriosus, ventricular septal defect, atrial septal defect, vascular anomalies of the pulmonary artery and aorta and its branches (13).

Because multiple systems are often involved, CRS may be a component of complex syndromes, including VACTERL (vertebral anomaly, anal atresia, cardiac anomaly, tracheoesophageal fistula, renal anomaly, limb anomaly), OEIS (omphalocele, cloacal exstrophy, imperforate anus, spinal defects), and Currarino triad (caudal agenesis, presacral mass, anorectal anomalies) (2).

Diagnostic workup

Prenatal ultrasound is a sensitive tool for the diagnosis of major defects. Diagnostic features are most commonly a sudden interruption of the spine due to the absence of vertebrae, disproportionately smaller lower extremities, and a froglike position of the lower limbs. Transvaginal ultrasound has proven to be an effective tool for earlier prenatal detection of CRS (15). In the first trimester CRS can be suspected by observing of a short crown-rump length or an increased nuchal translucency measurement (15,16). Prenatal magnetic resonance imaging is valuable to assess the degree of vertebral body dysgenesis and genitourinary, gastrointestinal, and musculoskeletal anomalies.

As in our patients CRS is often diagnosed postnatally in cases with more subtle clinical signs at presentation. Postnatal investigations were performed in the first case because of obstipation with a sacral dimple and, in the second case because of an imperforate anus with a neurogenic bladder.

Postnatal evaluation for CRS should include plain abdominal radiographs and ultrasound of the spine and kidneys. MRI of the spinal cord is indicated in all cases with signs of spinal dysraphism or CRS, such as vertebral or midline cutaneous abnormalities, imperforate anus, neurogenic bladder or other urogenital anomalies (6). In the presence of urinary tract abnormalities, a thorough urological evaluation is recommended to prevent irreversible renal damage secondary to urinary incontinence and urinary tract infections. A voiding cystourethrogram is needed to rule out vesicoureteral reflux.

A classification system described by Pang et al. depends on the amount of remaining sacrum and the articulation between the pelvis and the spine (3). Notably, the motor level closely aligns with the level of the vertebral defect (3,6). This structured framework serves as a valuable tool for consistent documentation, outcome prediction and effective treatment planning. Pang's classification divides CRS into five types (3). It identifies the complete absence of the sacrum with or without lumbar vertebrae agenesis as type I and II respectively. Type I and II are further divided into type Wide (W) and Narrow (N) based on the position of the ilia. In type W the ilia articulate with the lateral sides of the lowest vertebrae, whereas in type N the caudal endplate of the lowest vertebrae is resting above the articulate or fused ilia. In type III, S1 is present but the lower sacral segments are missing to varying degrees. Type IV consists of various forms of hemisacrum. Type V includes total to subtotal coccygeal agenesis (2,3).

Treatment and Prognosis

Prognosis depends on the severity of spinal involvement and associated malformations. If vital systems are unaffected, infants with CRS are expected to survive and they usually have a normal mental function (6,17). Although patients with CRS patients face many challenges, most have a good quality of life (14). Most children are ambulatory (18). Early diagnosis and supportive management of the associated anomalies are very important to prevent further consequences. For example, neurogenic bladder was present in both our cases. Early intervention with catheterization or anticholinergic drugs to prevent renal damage is warranted. These cases corroborate the importance of a multidisciplinary approach and long-term follow-up.

Conclusion

Caudal regression syndrome is a rare congenital disorder with a variable presentation. Various anomalies of the lumbosacral spine, nervous system, lower limbs, anorectal complex and genitourinary tract can be present. This entity should be considered when a child presents with anomalies of the sacrum, lower limbs or suffers from chronic constipation or neurogenic bladder. Early diagnosis and multidisciplinary follow-up may prevent further complications.

Conflicts of interest

The authors declare no conflict of interest.

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Severe hypotonia and developmental delay due to an *EBF3* pathogenic variant. Clinical implications of a molecular defect and narrative review.

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Keywords

Hypotonia ; Ataxia ; Developmental delay ; HADDS ; EBF3 gene ; Rare diseases ; Child.

Abstract

Hypotonia Ataxia and Delayed Development Syndrome (HADDS) is a neurodevelopmental syndrome due to missense pathogenic variants of the *EBF3* gene, located on chromosome 10q26.3. In most cases, these variants appear de novo and the transmission is autosomal dominant. HADDS would affect about 200 people worldwide and is characterized by a high clinical variability in the expression of these different symptoms : severe hypotonia, failure to thrive, psychomotor delay, digestive and feeding disorders, vesicoureteral anomalies, strabismus, and moderate facial dysmorphia. Although our knowledge is still limited, the significance of these symptoms seems to depend upon the *EBF3* expression during embryogenesis. Animal studies suggest that *EBF3* plays a critical role in neuronal migration and differentiation and interacts with *CDKN1A*, *NeuroD*, and *ARX* regulation pathways. With respect to diaphragmatic and vesicoureteral dysfunction and hypotonia, *EBF3* appears to be involved in myocyte calcium metabolism. In addition, *EBF3* has recently been identified as a novel tumor suppressor gene in some cancers. Further research on the *EBF3* gene and the associated pathological pathways is needed to improve our understanding of HADDS and to provide appropriate care for such rare diseases.

Introduction

Worldwide, several million children are born each year with neurological disturbances or with congenital neurodevelopmental disorders. Historically, their diagnosis relied on clinicians' ability to recognize and associate clinical signs and compare them with previously reported cases in the literature. The development of genetic techniques has made it possible to associate certain clinical signs based on the detection of chromosomal aberrations, and more recently, through the detection of pathogenic variants at the molecular level, thus becoming diagnostic markers. Over the last two decades, advances in molecular biology have focused on studying the disorders associated with these pathogenic variants. The intention has been to study their consequences in order to understand the biochemical mechanisms behind the expression of specific clinical and biological signs specific to these syndromes.

The case we report concerns a child with a significant developmental delay and clinical signs indicative of a rare syndrome : Hypotonia Ataxia Delayed Development Syndrome (HADDS). The discovery of a pathogenic variant in molecular biology allowed us to define the diagnostic marker. Beyond the identification of this anomaly and the gene whose expression is disturbed by it, it is interesting to analyze the neurobiological disturbances susceptible to explain the different symptoms.

Case report

A Caucasian girl was born by cesarean section at 36 weeks to non-consanguineous parents with no significant medical history. Her birth weight was 2.605 kg. She was born with mild respiratory distress requiring short-term non-invasive respiratory support, followed by a few hours of monitoring in the neonatal intensive care unit (NICU). The Guthrie test was negative.

Since her birth, she has been described by her parents as a rather quiet child, not very mobile and lacking energy. Not very reactive, she does not smile or cry vigorously. In spite of a very intense psychomotor rehabilitation program, her evolution remained very slow. She was able to develop eye contact and visual exchange with smiling. Archaic and osteotendinous reflexes were present, and no acute neurological events, such as seizures, were described. Her evolution was characterized by severe hypotonia, slow weight gain and significant failure to thrive (Figure 1), pathological gastroesophageal reflux and severe feeding difficulties leading to dehydration episodes requiring hospitalization, and chronic constipation resistant to conventional treatments. No swallowing problems were reported. She was initially fed through a nasogastric tube. However, this method was quickly proved to be insufficient and justified gastrostomy placement at 18 months

Figure 1: Weight curve showing an important slow weight gain and a significant failure to thrive < P3. She was initially fed by nasogastric tube. This method quickly proved to be insufficient and justified the gastrostomy placement at the age of 18 months.

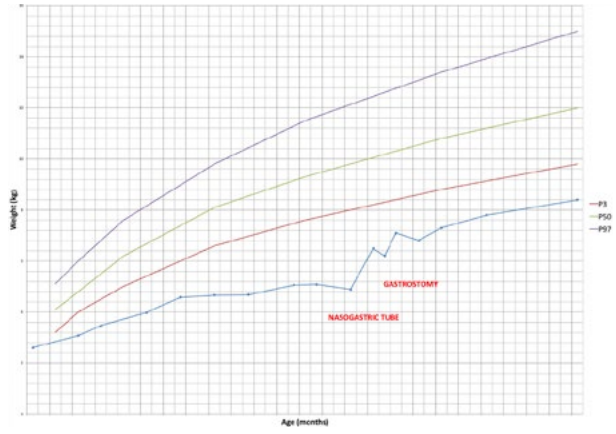
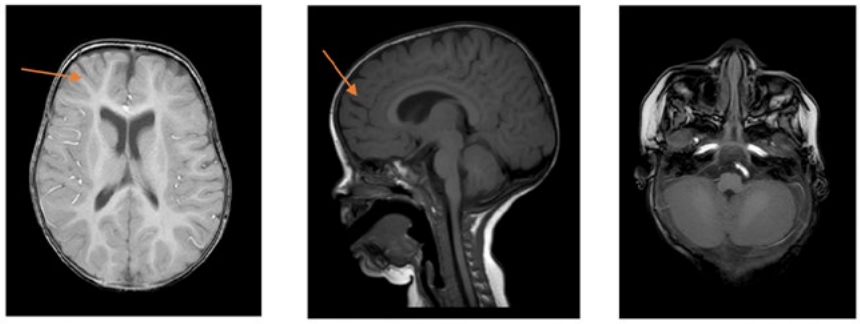


Figure 2: Brain MRI shows a discrete alteration of the cerebral gyration made of deeper sulci in the frontal area.



of age (Figure 1). She also had grade II left vesicoureteral reflux, which was responsible for recurrent urinary tract infections. Cardiac check-up was normal. A comprehensive workup was performed which allowed to rule out neuromuscular pathology, gastrointestinal pathology, malabsorption, endocrine or metabolic disorders. Her brain MRI showed a discrete alteration of the cerebral gyration consisting of deeper sulci in the frontal area (Figure 2). Routine genetic studies were also inconclusive, both fort the molecular karyotype and for any other syndromic research.

Despite a multidisciplinary rehabilitation program, her follow-up was still characterized by severe hypotonia and psychomotor retardation. At the age of 20 months, she could turn around and sit up by herself for shorts periods of time. She couldn't walk, even with assistance, but could crawl only on short distances. She had eye contact and eye tracking but did not speak. She could make only a few cries and babbles. Eight months later, she begins to say a few words such as mom and dad. She can now stand without help and presents with ataxia ; she can also take a few steps with a walker. Some dysmorphism was reported with a broad forehead and low implanted ears. She also presented with right convergent strabismus. Finally, a whole-body x-ray revealed scoliosis.

Ultimately, the association of the symptoms led to perform a whole exome sequencing. This revealed a de novo missense *EBF3* pathogenic variant c.626G>A (p.Arg209Gln).

Discussion

Hypotonia Ataxia Delayed Development Syndrome (HADDS) is characterized by the association of several major symptoms albeit of variable expression : severe hypotonia, ataxia, psychomotor delay, failure to thrive, digestive and feeding disorders, vesicoureteral anomalies, strabismus, and moderate facial dysmorphia. It was first described in Texas in 2016 (1). Specifically, HADDS is a neurodevelopmental syndrome caused by missense pathogenic variants of the *EBF3* gene located on chromosome 10q26.3.

Based on available information from the HADDS Foundation, *EBF3* pathogenic variants affect approximately 200 people worldwide. The incidence of *EBF3* pathogenic variants is estimated to be approximately 3 per 100 million people and affect both sexes equally (1). The *EBF3* gene is located on chromosome 10 at position 10q26.3. Each structural protein of *EBF3* is composed of a DNA binding domain (N-terminal), a transcript factor/Ig-like/plexin domain of unknown function, a helix-loop-helix domain (critical for homo- and hetero-formation), and a C-terminal transactivation domain (2-5). According to the literature, the most commonly described pathogenic variants are missense variants are the most frequently described (54% of cases). Duplications (18% of cases), nonsense mutations (15% of cases), frameshifts (8% of cases), and splice-site (5% of cases) have also been described. In most cases, these variants appear de novo and result in loss of gene function. Transmission is autosomal dominant. A literature review is provided in Table 1.

According to Gene Reviews, only 42 cases of HADDS from 39 unrelated families have been identified (6). Their phenotypes are extremely variable because HADDS is characterized by a wide clinical variability with each symptom (Table 2). Moreover, no correlation could be established between the position of the affected amino acids and the clinical signs. Nevertheless, moderate facial dysmorphia, hypotonia, and ataxia were observed in 88.2%, 82.9%, and 81.5% of these patients respectively. Strabismus was described in 81% of the cases. Developmental delay was reported in 95.1% of the cases. This includes learning difficulties in reading and writing, as well as a speech delay, some children remain nonverbal. In addition, most of the time a pronunciation defect persists. Developmental delay also includes delayed motor development. MRI abnormalities were found in only 35.3% of the patients. Genitourinary anomalies and digestive disorders are described in 34-51% of the cases. Failure to thrive and/or short stature affect approximately half of the patients. Additional clinical signs such as autistic features, behavioral disorders, epilepsy, high pain tolerance, or musculoskeletal anomalies, are described in only 24-41% of the cases. Finally, it is important to note that there is a significant phenotypic overlap between patients with an *EBF3* pathogenic variants and patients with larger microdeletions in the terminal portion of chromosome 10 (7, 8).

The pathophysiology of HADDS is summarized on Figure 3. *EBF3* interacts with several cofactors involved at different stages of brain development such as *CDKN1A*, *NeuroD* and *ARX* (2, 4, 9-13). It is involved in the Cajal-Retzius migration process, the regulation of the cell cycle within the ventricular zone and their migration to the cortex as well as the differentiation of some classes of neurons. This does not lead to spectacular malformations but to subtle disturbances of neuronal organization and intracortical relations (10). The ultimate consequence is an intellectual disability and a mental retardation (14, 15). As in the central nervous system, *EBF3* interacts at muscular level with a few factors and peptides, such as myoD protein, *ATP2a1*, and *SERCA1*. These proteins are essential to maintain an proper contractility of the sarcolemma and influence Ca^{2+} transport within the muscle fibers (16). The role of *EBF3* in urinary disorders remains unclear. It appears to influence similar molecular and cellular processes in sphincter contractility as they do in muscle tissue (4, 10, 11). It may involve dysregulation of several cofactors such as *ARX*, *HPSE2* and *LRIG2*, which are also involved in the Uro-Facial Syndrome (11). Disturbances in muscle contractility may also be hypothesized to explain intestinal dyskinesia and constipation. In addition, *EBF3* has recently been identified as a novel tumor suppressor gene in some cancers by inducing apoptosis (2, 4, 5). Notably, none of the HADDS cases reported to date have been associated with oncologic disease.

Figure 3: Pathophysiological mechanism of *EBF3* gene. The significance of the different symptoms of HADDS seem to rely upon the *EBF3* expression in different tissues during embryogenesis.

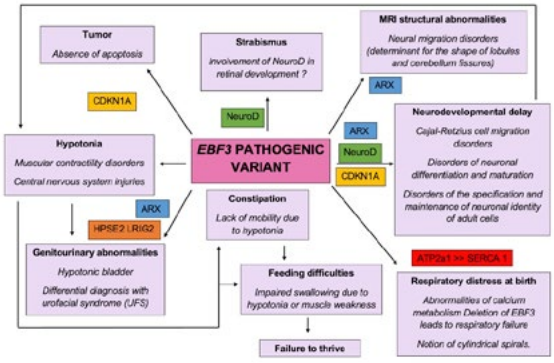


Table 1: Literature review (2-5, 7, 9-11, 13, 16-21). ***Part 1:*** EBF3 gene mutation and a maximum 4 non evaluated clinical features (included in table 2).

Ref Nr.	Individuals	Pathogenic variant	Growth	Developmental Delay	Hypotonia	Ataxia	Epilepsy	Dysmorphia	MRI	View	Genitourinary	Gastrointestinal	Others
2	**Girl** 9 years, 3 months	**c.625C>T (p.Arg209Trp)** Missense (inherited)	22kg (P3) 119 cm (<P3) HC 50 cm (P3)	Intellectual disability Motor delay Speech delay	-	+	+	+	Normal	Strabismus	-	-	-
2	**Boy** 3 years, 4 months	**c.625C>T (p.Arg209Trp)** Missense (inherited)	11 kg (<P3) 91 cm (<P3) HC 48,3 cm (<P3)	Intellectual disability Motor delay Speech delay	-	+	+	+	NE	Strabismus	-	-	-
2	**Boy** 5 years, 9 months	**c.913C>T (p.Gln305*)** Nonsense	21 kg (P50-75) 108 cm (P25) HC 51.5 cm (P25)	Intellectual disability Motor delay Speech delay	Normal with increasing age	+	-	-	Normal	Strabismus	-	Inguinal hernia	2nd and 3rd toe syndactyly
2	**Boy** 16 years, 6 months	**c.196A>G (p.Asn66Asp)** Missense	45.8 kg (P3) 168 cm (P25-50) HC 57 cm (P50-75)	Intellectual disability Motor delay Speech delay Dysarthria	-	+	-	+	Vermis hypoplasia	Strabismus	-	Gastroesophageal reflux Esophagitis	Behavioral disorders
2	**Boy** 4 years, 6 months	**c.1101-1G>T** Splice site	25,67 kg (>P97) 110,5 cm (P75)	Intellectual disability Motor delay Speech delay	+	NE	-	NE	Normal	Strabismus	-	-	-
2	**Girl** 2 years, 7 months	**c.530C>T (p.Pro177Leu)** Missense	13,3 kg (P50) 90,2 cm (P50) HC 49,7 cm (P70)	Intellectual disability Motor delay Speech delay	+	+	-	+	Normal	Strabismus	-	-	-
2	**Boy** 23 months	**c.422A>G (p.Tyr141Cys)** Missense	10,6 kg (P10) NE HC 49,7 cm (P70)	Intellectual disability Motor delay Speech delay	+	-	-	-	Normal	Strabismus	-	-	Congenital heart disease
2	**Girl** 13 years	**c.512G>A (p.Gly171Asp)** Missense	42,2 kg (P25) NE HC 51,9 cm (P10)	Intellectual disability Motor delay Speech delay	+	+	NE	+	Normal	NE	Neurogenic bladder Bilateral vesicoureteral reflux	Constipation Feeding difficulties	2nd and 3rd toe syndactyly Moderate scoliosis
2	**Girl** 25 years	**c.907C>T (p.Arg303*)** Nonsense	55 kg (P50) 167 cm (P50)	Intellectual disability Motor delay Speech delay	-	-	-	+	NE	Normal	-	-	-
2	**Boy** 3 years, 5 months	**c.469_477dup (p.His157_Ile159dup)** 9pb duplication	12,4 kg (P3) 95 cm (P25) HC 51 cm (P50)	Intellectual disability Motor delay Speech delay	+	NE	-	+	Vermis hypoplasia	Strabismus	Recurrent urinary tract infection Phimosis	Constipation	-
9	**Boy** 7 years	**c.488G>A (p.Arg163Gln)** Missense	NE	Developmental delay Dysarthria	+	+	NE	+	Vermis hypoplasia, small cerebellar lobes	Strabismus	Micropenis Cryptorchidism	Dysphagia Gastroesophageal reflux	Decreased fetal movements
9	**Girl** 5 years	**c.488G>A (p.Arg163Gln)** Missense	NE	Developmental delay Dysarthria Apraxia	+	+	NE	+	Vermis hypoplasia	Strabismus	-	Feeding difficulties	Decreased fetal movements High pain tolerance
9	**Girl** 3 years	**c.488G>T (p.Arg163Leu)** Missense	NE	Developmental delay Dysarthria	+	NE	NE	+	Normal	NE	-	Dysphagia	High pain tolerance Motor stereotypes
4	**Boy** 2 years, 6 months	**c.191A>C (p.Lys64Thr)** Missense	10.890 kg (P3) HC 47 cm (P10)	Sitting at 18 months Stands on its own, do not walk. Nonverbal, he understands his parents	+	+	-	+	NE	NE	Micropenis	-	High pain tolerance No social contact Pectus excavatum Laryngomalacia
4	**Girl** 24 years	**c.244delG (p.Val82TrpfsX50)** Frameshift	68,5 kg (P85) 149,5 cm (<P3) HC 56 cm (P75)	Sitting at 9 months Walking at 2 years Speaks normally, dysarthria	+	-	-	+	Normal	Strabismus	-	-	autistic features with tics and hallucinations Hypothyroidism Scoliosis ++
4	**Girl** 10 years	**c.471C>A (p.His157Gln)** Missense	27,2 kg (P10) 131,5 cm (P10) HC 52,5 cm (P50)	Sitting at 12 months Walking at 3 years Speaks at 5 years, dysarthria, fine motor difficulties	+	NE	-	+	NE	Strabismus	Bilateral vesicoureteral reflux Neurogenic bladder Renal duplication	-	Behavioral difficulties, autism, 2nd and 3rd toe syndactyly, sleeping disorders
4	**Girl** 11 years	**c.486-1G>A (IV55-1G>A)** Splice site	30,2 kg (P10) 129 cm (<P3)	Walks with help only Nonverbal	+	+	-	+	Vermis hypoplasia	Strabismus	-	Constipation Nasogastric tube	Autistic features Headaches
4	**Girl** 11 years	**c.616C>T (p.Arg206X)** Nonsense	51,6 kg (P95) 131,4 cm (P3) HC 54,2 cm (P75)	Sitting at 4 months Walking at 14 months Speaks at 10 months, dysarthria	+	+	-	+	Delayed myelination at 2 years	Refraction error	Recurrent urinary tract infections, hydronephrosis	-	Obesity
4	**Boy** 15 months	**c.626G>A (p.Arg209Gln)** Missense	8 kg (<P3) 72,2 cm (P3)	Sitting at 9 months No walking at 12 months, babbling at 8 months, but no words at 12 months	+	+	+	+	Abnormal	Strabismus	Micropenis	-	No social smile Decreased fetal movements
4	**Girl** 4 years	**c.1402_1414del13 (p.Thr46Profs*10)** Frameshift	14,7 kg (P50) 104 cm (P50) HC 47,2 cm (P10)	Sitting at 8 months Walking at 2 years Speaks at 4 years (begins to say words at 2 years)	-	+	-	-	Normal	-	Recurrent urinary tract infection	-	Hypertonia of the hips
3	**Girl** 2 years	**c.487C>T (p.Arg163Trp)** Missense	Height (< P3) Weight & HC (P25)	Developmental delay Sitting at 12 months Do not walk at 2 years 2-3 word's sentences at 2 years	+	-	NE	+	Normal	Strabismus	Urethra stenosis Bicornuate uterus	-	Pectus excavatum
5	**Boy** 13 years	**c.488 G>C (p.Arg163Pro)** Missense	Height (< P3) HC (P75-90)	Stands with support at 2 years Walking at 5 years and 8 months Speech = 50 words at 6 years ½ Dysarthria Intellectual disability (IQ 71) – special school	+	+	-	+	Vermis atrophia	Strabismus	Left cryptorchidism	-	High-pitched voice, pectus excavatum
5	**Boy** 7 years	**c.530 C>T (p.Pro177Leu)** Missense	Normal height Normal weight HC (P50-75)	Sitting at 9 months Stands with support at 19 months Walking at 2 years Speaks at 20 months, (speech delay), dysarthria Normal school	+	+	-	+	Normal	Strabismus	-	-	High pain tolerance Behavioral difficulties
5	**Boy** 8 years, 4 months	**c.355 + 1 G>C** Unknown pathogenic variant	Height & Weight (<P3) Microcephaly	Stands with support at 2 years Walking after 4 years Speaks at 3 years (speech delay) Normal school	+	+	NE	+	Normal	Strabismus	-	-	Smalls toes and fingers
5	**Girl** Unknown age	**c.579 G>T (p.Lys193Asn)** Missense	Short stature Normal HC	Head support at 2 years Sitting at 30 months Stands with support at 4 years, do not walk Speech : < 20 words at age 10 Special school	+	-	+	+	Normal	Strabismus	Bilateral vesicoureteral reflux	Feeding difficulties	-
5	**Girl** 8 years, 5 months	**c.280_283del (p.Glu94Lysfs*37)** Frameshift	Short stature Small weight Small HC	Sitting at 12 months Waking at 2 years, 8 months Speech : a few sentences, echolalia and dysarthria Special school	+	+	Febrile seizures	+	Subtle cortical dysplasia	Strabismus	Neurogenic bladder, bilateral vesicoureteral reflux Recurrent urinary tract infections	Constipation Feeding difficulties	-

5	**Girl** 4 years, 8 months	**c.554 + 1 G>A**	Normal weight Normal height Microcephaly	Head support at 18 months Sitting at 2 years Do not stand up Do not walk Do not speak Special school	+	+	+	-	Normal	Nystagmus	Bilateral vesicoureteral reflux Renal dysplasia Recurrent urinary tract infections	-	-
5	**Boy** 14 years	**c.616 C>T (p.Arg206*)** Nonsense (inherited)	Normal weight Normal height Normal HC	Sitting at 8 months Stands with support Walking at 18 months Speech : first words at 19 months Normal school	+	+	-	+	Normal	Normal	-	-	Behavioral difficulties
5	**Girl** 9 years	**c.616 C>T (p.Arg206*)** Nonsense (inherited)	Normal weight Normal height Normal HC	Sitting at 8-9 months Walking at 16 months Speech : first words after 2 years, ten words after 2 years ½ Normal school	+	+	-	+	Normal	Normal	-	-	Behavioral difficulties
11	**Girl** Died at 17 years old	**c.626 G>A (p.Arg209Gln)** Missense	Short stature ++ Microcephaly	Developmental delay Do not walk Speech : 2 words at 3 years	+	NE	NE	+	Normal	NE	Bilateral vesicoureteral reflux Neurogenic bladder Recurrent urinary tract infections Died from acute renal failure	Constipation	2nd and 3rd toe syndactyly, Atrioventricular defect DD with orofacial syndrome (UFS)
16	**Boy** 18 years	**c.616C>T (p.Arg206*)** Nonsense (inherited)	NE	Developmental delay Intellectual deficiency Sitting at 13 months Walking at 27 months Speaks normally at 18 years, no mental retardation	+	+	-	+	NE	Strabismus	Neurogenic bladder	Feeding difficulties	Laryngomalacia Recurrent otitis Autistic features Scoliosis Muscle cramps Muscle biopsy at the age of 3 (cylindrical spirals)
7	**Girl** 34 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (de novo)	Normal height Normal HC	No development delay but clumsy Walking at 15 months No ID	+	-	NE	+	Normal at 34 years	Strabismus	Vesicoureteral reflux Recurrent urinary tract infections	-	Tremor Behavioral difficulties Vertigo
7	**Girl** > 16 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 24 months No ID	+	+	NE	+	Normal	Strabismus	-	-	Tremor Behavioral difficulties Congenital calcaneovalgus Pes planus
7	**Girl** > 16 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	No motor delay (walking at 14 months) but clumsy Speech delay No ID	-	+	NE	NE	NE	Strabismus	Renal cyst Recurrent urinary tract infections	-	Tremor Behavioral difficulties Vertigo
7	**Girl** 5-15 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 21 months No ID	+	+	NE	NE	NE	Strabismus	-	-	Tremor Behavioral difficulties Pes planus
7	**Girl** 5-15 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Normal height Normal HC	Developmental delay Walking at 20 months No ID	-	+	NE	+	Normal	Strabismus	Smaller right kidney Recurrent urinary tract infections	-	Tremor Pes planus Proximal radius abnormalities
7	**Girl** 1-5 years	**c.622dup (p.Met208AsnfsTer56)** Duplication (inherited)	Short stature Normal HC	Motor delay No speech delay No ID	+	+	NE	NE	Normal	Strabismus	Recurrent urinary tract infections	-	Tremor Pes planus
7	**Girl** 5-15 years	**c.625C>T (p.Arg209Trp)** Missense	Normal height Normal HC	Developmental delay Walking at 22 months No ID	+	+	NE	NE	Vermis hypoplasia	Strabismus	-	-	Tremor Pes planus
7	**Girl** 5-15 years	**c.1183C>T (p.Arg395Ter)** Missense (inherited from mosaic mother)	Normal height Normal HC	Motor delay Walking at 18 months No speech delay No ID	+	+	NE	NE	Normal	Strabismus	-	-	Tremor Pes planus
7	**Boy** < 2 years	**c.530C>T (p.Pro177Leu)** Missense	Normal height Normal HC	Developmental delay No walking at 17 months	+	+	NE	NE	Abnormal	-	Hydrocele testis	Feeding difficulties Vomiting	Respiratory distress at birth Weak cry
GY	**Girl** 2 years, 4 months (may 2021)	**c.626 G>A (p.Arg209Gln)** Missense	8,800 kg (< P3) 78 cm (< P3) HC 49 cm (P85)	Speech : few words Sits, moves on all fours, stands while holding on a chair, can take a few steps with a walker, thumb-index grasp, turns pages in a book	+	+	-	+	Large sulci Vermis atrophia	Strabismus	Bilateral vesicoureteral reflux Neurogenic bladder Recurrent urinary tract infections	Feeding difficulties Nasogastric tube, gastrostomy Constipation Gastrointestinal reflux	Sleeping disorders Hyperacusis

Table 1: Literature review (2-5, 7, 9-11, 13, 16-21). ***Part 2:*** EBF3 gene mutation with less than 4 evaluated clinical features.

Ref Nr.	Individuals	Pathogenic variant	Growth	Developmental Delay	Hypotonia	Ataxia	Epilepsy	Dysmorphia	MRI	View	Genitourinary	Gastrointestinal	Others
10	**Boy** Unknown age (first visit at 5 months)	**c.512 G>A (p.G171D)** Missense	NE	Developmental delay	+	+	NE	+	Abnormal cerebellum	NE	NE	NE	NE
17	**Boy** 4 years, 8 months	**c.872 T>A (p.L291*)** Nonsense	NE	Motor delay Speech delay, dysarthria Do not go to school	NE	+	-	-	NE	NE	-	Feeding difficulties	-
18	**Unknown gender** Unknown age	**c.232 C>T (p.Gln78*)** Nonsense	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	Autistic features
16	**Girl** 31 years (mother of individual 31)	**c.616C>T (p.Arg206*)** Nonsense	NE	Developmental delay Walking at 2,5 years Speech delay	+	NE	NE	+	NE	NE	NE	NE	Scoliosis Muscular weakness with cramps Muscle biopsy at the age of 31 (cylindrical spirals)
19	**Girl** 6 years	**c.318C>G (p.Asn106Lys)** Missense Consanguineous family	NE	Developmental delay Intellectual deficiency Speech delay	NE	+	NE	NE	NE	NE	NE	NE	NE
20	**Unknown gender** Unknown age	**Unknown mutation** Missense	NE	Developmental delay Intellectual deficiency	NE	NE	NE	NE	NE	NE	NE	NE	Autistic features
13	**Girl** 11 years	**De novo 600 kb deletion at 10p26.3** 3 genes : MGMT, EBF3 & GLRX	NE	Developmental delay Head control at 12 months, sitting at 18 months, walking at 30 months No words at 3 years	+	NE	Suspicious	+	Normal	Strabismus	No renal abnormalities Urinary tract infection	Gastro-intestinal reflux	Small weight birth (< P3) Pes planus Recurrent otitis Autistic features
21	**Girl** 5-15 years	**Deletion ?**	Normal height Normal HC	Developmental delay No walking at 17 months No ID	+	+	NE	NE	Superior part of vermis dysplasia	-	-	NE	Tremor Behavioral difficulties Pes planus

Table 2: Prevalence in the literature of clinical signs observed in HADDS.

	Prevalence in the literature
Hypotonia	82,9%
Ataxia	81,5%
Developmental delay - Intellectual deficiency - Motor delay - Speech delay	95,1%
Moderate dysmorphia	88,2%
Epileptic seizures	24%
Autistic features and/or behavioral disorders	29,2%
Abnormal RMI	35,3%
Strabismus	81%
Failure to thrive and/or short stature	51,4%
Genito-urinary abnormalities - Recurrent urinary tract infections - Vesicoureteral reflux - Neurogenic bladder - Renal disorder - Micropenis - Phimosis - Cryptorchidism - Bicornuate uterus	51,2%
Gastrointestinal disorders - Gastro-esophageal reflux/dysphagia - Feeding difficulties - Constipation - Inguinal hernia	34,1%
Musculoskeletal abnormalities - Syndactyly 2nd/3rd toe - Scoliosis - Pectus excavatum - Muscle weakness/cramps - Pes planus	41,5%
Heart defects	<5%
Pathogenic variants - Missense - Nonsense - Duplication - Frameshift - Splice-site	 54% 15% 18% 8% 5%

Currently, there is no cure for HADDS. Only symptomatic treatments can improve the quality of life. Multidisciplinary care involving psychologists, speech therapists, physical therapists, and occupational therapists is essential. Assessing the prognosis of HADDS patients remains challenging due to the recent discovery of this syndrome (1).

Conclusion

HADDS is an extremely rare genetic syndrome in which the principal symptoms of severe hypotonia, ataxia, global developmental delay, strabismus, failure to thrive, and muscular dysfunction appear to be linked to a pathogenic variant of the *EBF3* gene. Other clinical manifestations have been reported with a large inter-individual variability. Further research on the *EBF3* gene and the associated pathological pathways is needed to improve our understanding of HADDS and provide appropriate care in such rare diseases.

Conflict of interest

All authors declare no conflicts of interests.

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

qui le fera ?

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

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

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

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

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

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Ramsay-Hunt Syndrome in an 8-Year-Old Girl, Case Report and Literature Review

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Keywords

Ramsay-Hunt syndrome ; facial paralysis ; acyclovir ; varicella-zoster virus.

Abstract

Ramsay-Hunt syndrome results from reactivation of latent varicella-zoster virus and subsequent spread to the seventh (and sometimes eighth) cranial nerve. The syndrome results in unilateral painful vesicular lesions on the external ear with ipsilateral facial weakness or paralysis. Other symptoms may include generalized malaise, altered taste, lacrimation, paroxysmal neuralgic ear pain, and hearing abnormalities. Due to its rare occurrence in young children and the inconsistent co-occurrence of pathognomonic vesicles and peripheral facial paralysis, diagnosis may be delayed or missed. As a result, many affected pediatric patients do not receive appropriate therapy with high-dose corticosteroids in combination with acyclovir.

Introduction

Varicella-zoster virus (VZV) is a pathogenic human herpesvirus responsible for the induction of chickenpox during primary infection. Subsequently, the virus establishes latency in neuronal cells within ganglia, including cranial nerve ganglia such as the geniculate ganglion. Reactivation of the virus primarily affects the facial nerve and often involves the vestibulocochlear nerve, resulting in Ramsay-Hunt syndrome (RHS). The annual incidence of RHS is approximately 5 per 100,000 people, with only 14% of reported cases occurring in children under the age of 16 (1).

The characteristic clinical triad includes facial paralysis, painful erythematous vesicular lesions on the external ear, and vestibulocochlear dysfunction. Other variable features may include nausea, vomiting, altered taste, lacrimation, and paroxysmal neuralgic ear pain. Typically, the disease manifests unilaterally, although rare cases of bilateral facial paralysis have been documented.

The annual incidence of facial nerve palsy in children is estimated to be 21 per 100,000. Common etiologies include idiopathic peripheral facial nerve palsy (Bell's palsy), acute otitis media, and Lyme disease, with RHS accounting for only 2.8% of all cases (2).

James Ramsay Hunt first described the syndrome in 1907, but there is little published large-scale research on its treatment. The recommended approach is a gold-standard combination of systemic acyclovir and high-dose corticosteroids.

Case presentation

An 8-year-old girl presented to the emergency department with drooping of the right corner of her mouth and inability to close her right eye. In addition, she reported pain in her right ear for the previous 3 days, accompanied by excessive tearing in her right eye, for which her general practitioner had previously prescribed an eye ointment. On admission to the emergency department, the patient presented with right-sided lagophthalmos and general malaise, leading to two episodes of vomiting. There were no complaints of tinnitus, hearing loss, dizziness, loss of taste or sensitivity, and no fever. Her medical history revealed no evidence of significant prior varicella infection, tick bite, or erythema migrans. In addition, there was no mention of a possible traumatic cause related to oral, maxillofacial, or nose-throat-ear surgical procedures. Subsequent clinical examination of the ear, nose, and throat revealed acute peripheral facial palsy on the right side. There were no symptoms or clinical findings of nystagmus or meningeal excitation. The severity of facial paralysis was graded according to the House-Brackmann scale (Table 1), with a grade IV status at the time of admission. Laboratory tests, including a complete blood count, C-reactive protein, and erythrocyte sedimentation rate, were within normal limits. Additional serologic testing was performed to identify an underlying viral or bacterial etiology of the facial nerve disorder.

Given the acute vomiting, a lumbar puncture was conducted to exclude central nervous system involvement. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans were not performed due to the patient's young age, the sudden onset of nerve paralysis, and the absence of a previous affliction.

Table 2 provides a chronological overview of the main symptoms and associated treatments. Intravenous corticosteroid therapy (60 mg/day) and ceftriaxone (100 mg/kg/day) were initiated. The anti-inflammatory properties of corticosteroids were expected to reduce the acute facial nerve swelling within the bony canal, thereby reducing the likelihood of residual symptoms. The administration of antibiotics was prompted by the possible occurrence of Lyme borreliosis, given the endemic prevalence of *Borrelia burgdorferi* in the geographical area, the seasonal context of

Table 1: House-Brackmann scale for assessing nerve damage in facial paresis.

Grade	Description	Characteristics
I	Normal function	Normal mimicry in all regions
II	Mild dysfunction	Mild asymmetry of mouth and forehead, complete eye closure with minimal effort
III	Moderate dysfunction	Mild asymmetry of the mouth, full eye closure with effort, slight movement of the forehead
IV	Moderate to severe dysfunction	Asymmetric mouth, incomplete eye closure, no forehead movement
V	Severe dysfunction	Slight mouth movement with effort, incomplete eye closure
VI	No movement	No movement

Table 2: Timeline of symptoms and associated treatments

	Day -3	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 13
Symptoms	Right-sided earache, lacrimation	Right-sided facial paralysis, vomitus		Right-sided auricular herpetic vesicles			Dismissal	Control
HB grade		IV					II	I
Therapy		CS (60 mg p.o.) + ceftriaxone (100 mg/kg i.v.)	CS (60 mg p.o.) + ceftriaxone (100 mg/kg i.v.)	CS (60 mg p.o.) + aciclovir (100 mg/kg i.v.)	CS (60 mg p.o.) + aciclovir (100 mg/kg i.v.)	CS (60 mg p.o.) + aciclovir (100 mg/kg i.v.)	CS in 4-day tapering schedule + valaciclovir (60 mg/kg p.o.)	Stop treatment

CS = corticosteroids; HB = House-Brackman scale.

spring at the time of admission, and the conceivable pathogenic extent of such an infection (3). To protect the cornea of the affected eye, artificial tears were applied during the day and eye ointment and an eye patch were applied at night. No additional reports of nausea or vomiting were documented during the course of the admission.

On the second day after admission, the patient developed herpetic vesicles on the right auricle. CSF PCR was positive for VZV, confirming RHS. Intravenous aciclovir (100 mg/kg/d) was added to the corticosteroids for five days. Ceftriaxone was discontinued because of negative *Borrelia* serology and CSF PCR. The patient was discharged on day 6 with significant clinical improvement of facial paralysis, graded II on the House-Brackmann scale, and desiccation of the vesicular lesions.

Gradual tapering and discontinuation of corticosteroid therapy was achieved over a four-day period. Subsequently, the patient was started on oral valaciclovir (60 mg/kg/day), which was prescribed until the next follow-up visit 8 days later. During this follow-up, mild and limited asymmetry persisted at the ocular and oral levels. A follow-up visit 4-6 weeks after discharge revealed further resolution of symptoms.

Table 3: Most described medical condition associated with acute peripheral facial paresis in children

Medical condition	Disease or pathogen
Idiopathic	Bell's palsy
Infectious - Bacterial - Viral	 Lyme disease Herpes simplex virus/ Varicella zoster virus/ Coxsackievirus/ Epstein-Barr virus/ Cytomegalovirus/ Mumps virus/ Adenovirus/ Rubella virus/ Influenza B
Neoplastic	Acute leukemia/ Schwannoma/ Cholesteatoma
Traumatic & iatrogenic	
Others	Acute otitis media

Discussion

Acute peripheral facial paralysis in pediatric patients presents with a variety of potential etiologies, including infectious, neoplastic, traumatic, or idiopathic, as outlined in Table 3. Since idiopathic causes account for approximately half of all cases, and given the lack of a clear infectious focus on initial presentation, Bell's palsy initially emerged as the preferred diagnosis in our patient. Despite the negative history and clinical examination, Lyme disease could not be completely excluded, given the endemicity of *Borrelia burgdorferi* in the patient's home area and the temporal context of spring at admission. Notably, VZV, Epstein-Barr virus, and Coxsackievirus are the most commonly documented viral pathogens associated with peripheral facial paralysis.

RHS is a neurological disorder that may result from reactivation of VZV. The diagnosis of RHS is primarily based on clinical manifestations, as serologic testing is limited to the detection of antibodies to VZV, the presence of which does not unequivocally indicate ongoing infection. Confirmatory tests can be performed on cerebrospinal fluid or specimens obtained from herpetic vesicles, and sometimes tear fluid. In addition, MRI scans are used to rule out other conditions and may show swelling of the seventh cranial nerve, which is stained by contrast.

The timing of herpetic vesicles in relation to facial paralysis varies between children and adults. In children, these vesicles typically appear several days after the onset of facial paralysis, while in adults they often occur simultaneously (4). This observation underscores the importance of close and vigilant monitoring of children suspected of having RHS.

While spontaneous remission with complete recovery occurs in only about 20% of VZV infections resulting in facial paralysis, numerous case series and cohort studies have shown that a combination of antiviral therapy and corticosteroids can improve the overall prognosis and reduce the risk of complications such as permanent facial paralysis and deafness (5). In addition, antiviral therapy may have a significant beneficial effect on subjective hearing loss and vestibulocochlear nerve excitability testing (NET). A combination of aciclovir and corticosteroids is recommended to improve the rate of recovery of seventh and eighth cranial nerve function (6). Treatment should be initiated within 72 hours of symptom onset to take advantage of the narrow therapeutic window (7). However, the lack of pathognomonic vesicles and reliable early detection tests for VZV infection often leads to delayed diagnosis, especially in cases of zoster sine herpete, where an initial misdiagnosis as Bell's palsy leads to monotherapy with high-dose corticosteroids (8). While acyclovir is traditionally considered the drug of choice, valaciclovir may be used as a maintenance treatment due to its lower dosing frequency and better adherence.

Varicella vaccination is considered an effective approach to prevent RHS in children, although vaccinated individuals are not completely immune to varicella and its associated complications. Although the incidence of VZV reactivation appears to be lower in vaccinated children than in those who contract natural varicella infection, further studies are needed to prove the effectiveness of vaccination in preventing RHS (9).

Conclusion

RHS is a rare complication of latent VZV infection involving the facial nerve and occasionally the vestibulocochlear nerve. Despite its rarity, RHS can manifest in young children whose history of varicella infection is not always well documented. Clinicians must be aware that the hallmark symptoms of RHS, including peripheral facial palsy, vesicular rash, and otalgia, may not occur simultaneously. While the diagnosis is primarily based on clinical features, confirmatory testing can aid in accurate identification. Prompt initiation of treatment with a combination of antiviral and corticosteroid therapy within 72 hours of symptom onset is essential to improve prognosis and minimize neurologic dysfunction. Vigilant monitoring is essential for children with facial paralysis, with the nerve excitability test and the House-Brackmann scale serving as tools to assess the impact of the disease. Varicella vaccination has the potential to prevent RHS, although further research is needed to determine its efficacy in this regard.

Conflict of interest

The authors mention no conflict of interest.

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Pyometra in an 8-year-old prepubertal girl without congenital malformities, a case report

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Keywords

Pelvic inflammatory disease ; Pyometra ; Child ; Pediatric gynecology.

Abstract

Pelvic inflammatory disease is an inflammation of the upper genital tract, mostly presenting in sexually active woman. Pyometra, a pus collection in the uterine cavity which cannot be drained, can occur in woman with PID. An 8-year-old girl presented with persisting fever, weight loss and abdominal pain. Clinical examination showed an abdominal mass. Computed Tomography suggests a pyometrocolpos. Gynecological infections should be included in the differential diagnosis of abdominal pain with fever in young girls. Thorough clinical examination, sampling and sufficient imaging should be included. Treatment of Pyometra exist off parenteral broad-spectrum antibiotics and if necessary chirurgical drainage.

Introduction

Pyometra, or the accumulation of pus in the uterus due to cervical occlusion or stenosis is a rare condition, primarily affecting postmenopausal women. In younger women and children, factors such as hypoestrogenized endometrium, cervical stenosis, and exposure to transient bacteremia are more likely to cause obstruction and accumulation of pus (1) . The incidence of pyometra in the general population is 0,2% (1).

Pelvic inflammatory disease (PID) is, by definition, an inflammation of the upper genital tract involving any or all of uterus, fallopian tubes or ovaries and the term is by convention reserved for sexually transmitted micro-organisms.

Although pyometra is a form of PID, it can be caused by non-sexually transmitted organisms (2). In 85% of PID cases, sexually transmitted bacteria, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, are responsible. The remaining 15% are caused by other cervical (e.g. *Mycoplasma genitalum*), respiratory (e.g. *Streptococcus pneumoniae*), or gastrointestinal (e.g. *Esschericia coli)* pathogens (2). PID is most common in sexually active adolescent females, particularly in the 15-25 age group (2).

In 2015, one case was published by Barry et al.,together with a review of 12 other cases from 1948 to 2015 (1). The average age of these patients was 9 months, except for one 12-year-old with anorexia nervosa. In only 4 cases could the causative pathogen be identified. Three infants had an E. coli infection and one had a *Pseudomonas infection* (1). Since 2016, only two cases have been found in the literature: a prepubertal girl with pyometrocolpos due to congenital vaginal agenesis and another 8-month-old African girl with recurrent pyometra (3, 4).

Thus, there are only 15 published cases of pyometra in children since 1948 (1, 3, 4). The present case represents the first Belgian prepubertal girl diagnosed with pyometra without congenital anomalies.

It is essential to diagnose pyometra promptly, as increased intrauterine pressure can cause pus to be drained through the fallopian tubes, potentially leading to peritonitis (1).

Case

An 8-year-old prepubertal girl with no significant family or personal medical history was admitted to the pediatric ward after experiencing fever for nine days, a 12% weight loss, and abdominal pain for 11 days, accompanied by occasional vomiting and bloody diarrhea. The girl had initially consulted her general practitioner after two days of fever, where a urine dipstick revealed hematuria. The diagnosis of urinry tract infection was withheld and she was subsequently treated with oral amoxicillin. However, despite the antibiotic therapy, her fever persisted for another seven days. She then consulted the pediatrician.

On admission, clinical findings revealed an uncomfortable, prepubertal girl with a tender, swollen abdomen and a palpable mass in the hypogastric region. External vaginal examination showed no signs of trauma or infection. No significant cardiac, respiratory, or neurological findings were noted, and vital parameters were stable, except for the persistent fever.

Laboratory tests showed elevated inflammatory markers with a C-reactive protein of 425 mg/l (<5 mg/l) and a mild leukocytosis of 16,83 x 10*9th /L leucocytes (4-10 x 10*9th /L) with 12,96 x 10*9th/L neutrophils (1-9 x 10*9th/L). Platelets were also elevated to 647 x 10*9th/L (150-350 x

Figure 1: CT scan of the patient at presentation.

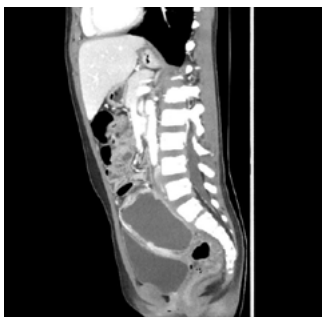
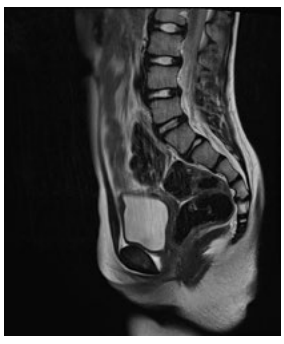


Figure 2: MRI of the patient three months after treatment



10*9th/L). Kidney and liver function were normal. Empirical intravenous cefotaxime was started admission after urine and stool cultures were obtained.

An abdominal CT scan revealed an enlarged, fluid-filled uterus measuring 8,6 cm x 4,8 cm with no other abdominal abnormalities (Figure 1).

On the second day of admission, a hysteroscopy and vaginal examination under general anesthesia revealed a narrow cervix with drainage of a small amount of pus, confirming the diagnosis of pyometra. No congenital malformations or clinical signs of sexual abuse were found during the examination. Pus samples and cervical and vaginal swabs were taken. No uterine lavage or continuous drainage catheter was used during the hysteroscopy.

Given the differential diagnosis of sexual abuse, our approach in this case involved multiple discussions with both the patient and her parents. It is noteworthy that the parents demonstrated a high degree of understanding and cooperation throughout this process. In particular, the absence of any concerning indicators, coupled with a consistently consistent narrative from the patient and a reassuring vaginal examination, led to the decision to forego further investigative measures, until cultures were known.

Treatment included intravenous amoxicillin-clavulanic acid (100 mg/kg/day) and metronidazole (30 mg/kg/day)., with metronidazole discontinued after five days. Clinical findings progressively improved,

and follow-up included systematic blood sampling and ultrasound, which revealed a reduction in infectious parameters and collection volume.

Pus culture showed presence of *Escherichia coli* and *Streptococcus anginosus*, both susceptible to amoxicillin-clavulanic acid.

Urine, stool, cervical and vaginal cultures remained sterile, possibly because antibiotic therpay was administered prior to culture collection or possibly because of nonspontaneous drainage of pus due to stenosis.

After ten days of intravenous antibiotic treatment, the C-reactive protein level decreased to 16 mg/L, and the volume of the pus collection on ultrasound decreased to 3.3 cm x 0.9 cm.

After discharge, oral amoxicillin-clavulanic acid was continued for four days. The medication was well tolerated and no side effects or complications were observed.

One week after discharge, a blood sample showed a negative CRP and an ultrasound showed no residual intrauterine fluid.

A follow up MRI was performed one month after discharge to rule out residual collections and possible post-infection sequelae such as hydrosalpinx or post-inflammatory peritoneal adhesions (Figure 2). These post-inflammatory complications are easily detected by MRI (3). Fortunately, in this case MRI showed no evidence of residual fluid, hydrosalpinx or peritoneal adhesions.

(Figure 2) (3).

There were no further clinical or anamnestic signs of child abuse at these follow-up visits, so this differential diagnosis was abandoned.

Discussion

Abdominal pain and fever in children are commonly associated with urinary tract infections, but other causes such as gastroenteritis, appendicitis, and pyometra should be considered. A comprehensive clinical examination is essentiall for diagnosis (5-7). In young children with unexplained fever above 38°C, a urinanalysis is essential and urine culture is critical for the diagnosis of urinary tract infection. Empiric broad-spectrum antibiotics can be initiated if the urine sediment is positive, taking into account local antibiotic resistance patterns (4-7). Of note, resistance rates fto amoxicillin are high in Belgium, and its use should be based on antimicrobial susceptibility (7).

Radiological investigations may be useful, with ultrasound recommended before CT to exclude gynecologic causes (8).

In the review of published cases by Barry et al., many patients had a history of previous acute gastroenteritis (AGE) (1). In this case, the patient also experienced gastroenteritis symptoms, such as fever, vomiting, and diarrhea, suggesting a possible ascending infection as the cause of pelvic inflammatory disease or urinary tract infection (UTI) (1). Hygiene practices in this age group, such as wiping from back to front, may have contributed to this condition, highlighting the importance of personal hygiene education. These hygiene practices are often suboptimal, because at this age they may no longer seek parental assistance for perianal hygiene (8, 9). After a secondary anamnesis it appeared that the patient wiped her bottom from the back to the front.

The article by Barry et al. hypothesized that ovarian steroids and an estrogenized endometrium may provide protection against ascending infections. Young women who have not yet reached puberty do not have this protection and are therefore more at risk for ascending genital infections (1). The possibility of sexually transmitted diseases and pathogens must be considered in the differential diagnosis of pyometra, in all children, given the pathogenesis of PID in adults. Therefore, child abuse should be considered in all pediatric cases of pyometra.

Conclusion

Pyometra and gynecologic infections should be considered in the differential diagnosis of abdominal pain with fever in young girls, especially in the absence of other abdominal focus of infection such as UTI, or AGE. A comprehensive clinical examination, specimen sampling, and imaging are crucial when there is a history of persistent fever, abdominal pain, and weight loss. Emirical initiation of antibiotics prior to obtaining cultures can complicate the diagnosis and mask certain pathogens and infection parameters. Tretament should include broad-spectrum parenteral antibiotics, with surgical drainage if necessary.

Conflicts of interest

There was no conflict of interest in this case report.

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Varicella Zoster Virus reactivation causing meningitis in a 12-year-old immunocompetent girl, a case report

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Keywords

Varicella-zoster virus ; meningitis ; child.

Abstract

Varicella-zoster virus (VZV) presents as chickenpox during primary infection. The virus becomes dormant in the dorsal root ganglia and can reactivate. Neurological complications of VZV reactivation have been described and may present without the typical herpes zoster rash. We present a case of a 12-year-old girl with persistent headache, photophobia, nausea, and vomiting. Cerebrospinal fluid showed lymphocytic pleocytosis and positive PCR for VZV. VZV meningitis is a rare diagnosis in immunocompetent children. However, our case suggests that sudden onset and persistent headache may rarely be caused by reactivation of VZV, even in the absence of a typical rash.

Introduction

Varicella-zoster virus (VZV), along with herpes simplex viruses 1 and 2, is a member of the alphaherpesvirinae subfamily. VZV can be spread by droplets from the upper respiratory tract or by direct contact and causes chickenpox as a primary infection. After primary infection, the virus becomes dormant in the dorsal root ganglia and cranial nerve ganglia. VZV can reactivate and the most commonly described disease is shingles (herpes zoster), a (painful) vesicular dermatomal rash. Reactivation of VZV is most common in elderly or immunocompromised patients (1).

Neurological complications have been described in both primary infection and reactivation of VZV. Possible neurologic complications of VZV reactivation include meningitis, encephalitis, transverse myelitis, large vessel encephalitis, and cranial nerve palsies. VZV reactivation can occur without the typical shingles rash, making PCR testing an important diagnostic tool (2).

Central nervous system infection from VZV reactivation can be difficult to recognize, especially if the disease presents without the typical shingles rash. In addition, VZV is often not recognized as a possible pathogen in an immunocompetent child or young adult. We present a case of a 12-year-old girl who presented with acute headache without rash or fever. A lumbar puncture revealed signs of meningitis, and PCR testing confirmed VZV as the causative agent.

Case

A 12-year-old girl presented to the emergency department with a 3-day history of persistent headache. There was no significant past medical history. She described the pain as throbbing and localized it to the frontal region. The pain was associated with nausea, vomiting, sonophobia and photophobia. She was afebrile, had a normal neurological clinical examination and no nuchal rigidity. There were no skin lesions present. Laboratory values showed no elevated markers of infection.

She was admitted for observation and symptomatic treatment of her headache. Intravenous tramadol hydrochloride, acetaminophen, ketorolac and alizapride had little effect. Because she did not respond to any of the medications, further investigations were indicated. The ophthalmologic examination with fundoscopy and the CT scan of the brain were both normal and showed no evidence of increased intracranial pressure. A lumbar puncture was performed because of persistent symptoms without a known cause and to rule out a treatable infection. Measurement of the opening pressure showed an increased intracranial pressure of more than 50 cmH2O (N < 28 cmH2O). Cerebrospinal fluid (CSF) cell count showed a lymphocytic pleocytosis (589 WBC/µL and 86% lymphocytes), elevated protein (0.71 g/dL, reference rang 0.15-0.45 g/dL) and low glucose (47 mg/dL N 40-80 mg/dL). PCR meningitis-encephalitis panel identified Varicella-zoster virus as the cause of meningitis. Brain MRI scan with angiography and EEG were normal. Additional serologic tests showed the presence of varicella zoster virus IgG, but no IgM. In depth history revealed that she had a primary infection with VZV when she was two years old.

Acyclovir was started for a period of 12 days and a good clinical response was seen after a few days. A repeat lumbar puncture on day 10 showed negative PCR for VZV, but the opening pressure measurement was not repeated. Follow-up at 6 months showed no sequelae.

Discussion

We present the case of a 12-year-old immunocompetent girl with persistent and debilitating headache, in whom VZV reactivation was surprisingly found in the central nervous system. Central nervous system complications of VZV reactivation in immunocompetent children and adolescents have been described in the literature, but are uncommon (3-8). The best known presentation of VZV reactivation is shingles with the typical (painful) vesicular dermatomal rash. Central nervous system complications may occur without the typical rash. A recent review of 25 cases shows that 24% of these children with VZV reactivation meningitis presented without the typical rash (9). This review included both VZV reactivations after natural infection as well as after vaccination. Our patient presented without nuchal rigidity. In a retrospective case series describing 11 patients with central nervous infection due to varicella reactivation were described, only 27% of the patients had nuchal rigidity (10).

Studies estimating the prevalence of VZV meningitis and encephalitis have been performed in recent years, but most have been conducted in an adult patient population and include immunocompromised patients. In a prospective Finnish study, 8% of the cases of aseptic meningitis or encephalitis were positive for VZV (11). A retrospective study of adult patients with a clinical diagnosis of viral meningitis or encephalitis showed that 2.1% of the CSF samples were positive for VZV(10). Both

studies were conducted in an adult patient population and one of the studies included only immunocompetent patients (11). Data on pediatric patients are scarce and the prevalence cannot be estimated.

VZV central nervous system infections are mostly seen in the elderly with declining cell-mediated immunity or in immunosuppressed patients. With recent advances in PCR diagnostic testing, VZV central nervous system infections due to reactivation are also seen in immunocompetent patients and even children. One known risk factor for the development of childhood zoster is a varicella infection during the first year of life, but our patient had chickenpox at the age of 2 years (12). Although new insights have been gained into the latency and reactivation of VZV, more needs to be discovered to fully understand why the virus reactivates (13).

Vaccination against VZV is performed with a live attenuated vaccine and after vaccination, the vaccine strain of VZV also becomes dormant in the dorsal root and cranial nerve ganglia. A study conducted in California from 2000 to 2006 reported a decreased risk of herpes zoster in vaccinated children (14). However, VZV reactivation can still occur after vaccination. An article reviewing vaccine safety in the United States with data from 1995 to 2005 reported 52 cases of herpes zoster in vaccinated individuals, 10 of which were confirmed to be due to vaccine strain VZV and 7 of which were due to wild-type VZV (15). In the remaining cases, the VZV was not further specified. Two of these cases had herpes zoster and meningitis and were confirmed to have vaccine strain VZV in their CSF. A recent review article comparing VZV reactivation meningitis after natural infection and after immunization showed that the reactivation meningitis occurred at a younger age and at a shorter interval after immunization (9). Most of the children in the review received only one dose of the vaccine. A two dose schedule is currently recommended.

In our patient, lumbar puncture showed an elevated opening pressure of > 50 cmH2O, but fundoscopy showed no signs of papilledema. Nitrous oxide was used during the procedure, which may cause an increase in intracranial pressure, especially in patients with altered intracranial compliance (16). There were no other factors that could increase the intracranial pressure during the procedure. The pronounced increase in intracranial pressure is unlikely to be entirely due to the use of nitrous oxide. An increase in intracranial pressure has been reported in the literature in patients with viral meningitis, particularly varicella and enterovirus meningitis (17, 18). In an observational retrospective study of patients with aseptic meningitis, 16 of the 116 patients had increased intracranial pressure, but only 40% had papilledema (18).

Cerebrospinal fluid (CSF- analysis showed lymphocytic pleocytosis with high protein and low glucose levels. This may also be associated with tuberculous meningitis. Therefore, the differential diagnosis may be more difficult, especially in regions where tuberculosis is endemic,. Although we expect lower CSF glucose levels in tuberculosis meningitis than presented in our case. However, low CSF glucose are also seen in other viral central nervous system infections such as West Nile virus, herpes simplex virus, cytomegalovirus and HIV infection (19).

The Infectious Disease Society of America recommends the use of acyclovir IV (10–15 mg/kg every 8 hours for 10-14 days) for VZV encephalitis (20). This recommendation is based on case reports and small case series, but no clinical trial has been conducted. There are no recommendations for VZV meningitis. However, the same therapy is initiated because of the potential morbidity and sequelae after a central nervous system infection with VZV. Data on the sequelae of VZV meningitis in the pediatric population are limited and further research is needed.

Conclusion

We have presented a case of an atypical presentation of meningitis with persistent headache, photophobia, nausea and vomiting, but without nuchal rigidity or vesicular rash. Our case highlights the need for further investigation in the setting of atypical, debilitating and persistent acute-onset headache. If no common cause is found in the initial investigations, PCR analysis must be performed. Our case shows that a sudden onset of persistent headache, even in absence of a typical rash is rarely caused by reactivation of VZV.

Conflict of interest

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

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Van Wyk-Grumbach Syndrome: case report and review of the literature

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Keywords

Hypothyroidism ; precocious puberty ; Van Wyk-Grumbach syndrome ; case report.

Abstract

Van Wyk-Grumbach syndrome (VWGS) is a rare cause of precocious puberty due to long-standing hypothyroidism. We report an 8-year-old girl presenting with vaginal bleeding. She had short stature and normal bone age. Pelvic ultrasound showed enlarged multicystic ovaries and cranial imaging revealed pituitary hyperplasia. Laboratory results showed elevated follicle-stimulating hormone with suppressed luteinizing hormone, hyperestrogenism, and hyperprolactinemia. Subsequent evaluation revealed severe autoimmune hypothyroidism. Based on the clinical findings and imaging VWGS was diagnosed and showed excellent response to thyroid replacement therapy. Hypothyroidism should be considered in prepubertal females with incomplete precocious puberty even in patients with a normal bone age.

Introduction

First described in 1960, Van Wyk-Grumbach syndrome (VWGS) is characterized by long-standing primary hypothyroidism, isosexual precocious puberty, delayed bone age, multicystic ovaries and pituitary enlargement, in varying combinations (1,2). In isosexual precocity, children develop early phenotypically appropriate secondary sexual characteristics. This rare syndrome is a clinical diagnostic challenge as untreated juvenile hypothyroidism classically leads to delayed puberty. The reversion of the pubertal development after thyroid hormone replacement was an essential finding in this syndrome (1).

Here, we report an 8-year-old patient presenting with vaginal bleeding who was subsequently diagnosed as VWGS, highlighting the importance of careful clinical evaluation of patients with precocious puberty for concurrent signs of hypothyroidism. We provide a brief review of the literature.

Case presentation

An 8-year-old girl presented to the emergency department of our institution with vaginal bleeding. There was no history of local trauma or other bleeding manifestations. Her past medical history was unremarkable. On physical examination, her height was 122,5 cm (-1.5 standard deviation score (SDS)), her weight was at the mean at 27,9 kg and her body mass index was 18,6 kg/m² (+2 SDS). Her breast and pubic hair development were staged as Tanner 2 and she had no axillary hair. The external genitalia showed signs of estrogenization including increased size and color of the labia majora. There were no traumatic lesions.

On investigation, bone age was in accordance with the chronological age using the Greulich and Pyle atlas. Pelvic ultrasound revealed a pubertal size uterus with a body to cervix ratio > 1.2, a thickened endometrium and enlarged cystic ovaries (Figure 1). Hematologic investigations revealed mild normocytic anemia and a normal coagulation profile. Hormonal laboratory results showed low prepubertal luteinizing hormone (LH) levels but elevated follicle-stimulating hormone (FSH) levels,

Figure 1: Pelvic ultrasonographic findings. (a) Sagittal image showing a pubertal size uterus measuring 50 x 21 mm with a thickened endometrium (1.6 cm). (b, c) Multicystic enlarged right and left ovaries measuring 42 x 18 x 14 mm and 60 x 27 x 24 mm respectively.

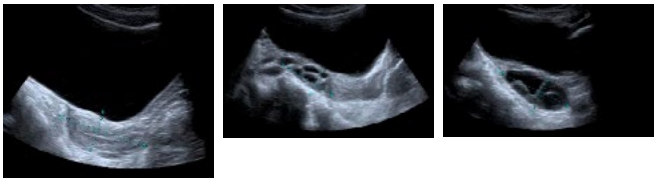
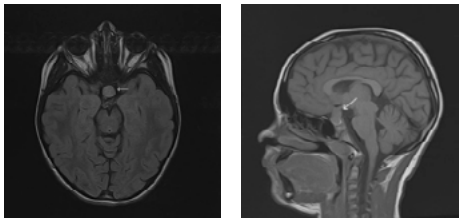


Figure 2: Cranial magnetic resonance imaging. (a, b) Sagittal and transverse scan showing enlargement of the pituitary gland (arrow) measuring 18.5 x 17.5 x 11.5 mm with homogeneous enhancement, suprasellar extension and compression of the optic chiasm.



hyperestrogenism, and hyperprolactinemia (Table 1). The luteinizing hormone-releasing hormone stimulation test showed a predominant FSH response with suppressed LH. Cranial magnetic resonance imaging revealed pituitary gland hyperplasia with suprasellar extension and invasion of the cavernous sinus (Figure 2).

At follow-up, physical examination revealed features suggestive of hypothyroidism: increasing weight gain, dry scaly skin, constipation, and dull behavior. There was no goiter. Workup revealed severe primary hypothyroidism, with highly elevated levels of thyroid-stimulating

Table 1: Laboratory results at diagnosis and at follow-up.

Laboratory test (SI unit)	At diagnosis	After 2 months of treatment	After 12 months of treatment	Normal range
FSH (IU/l)	8.4		4.7	Prepubertal : 0,3-3
LH (IU/l)	< 0,1		0.8	Prepubertal : 0.3-2
Estradiol (pg/ml)	32			< 10
Prolactin (ng/ml)	61		5.5	< 20
TSH (mUI/l)	920	0.9	0.53	0.66-4.14
FT4 (ng/l)	0.3	18.6	13.4	9-16.5
FT3 (pg/ml)	< 0.26			2.7-5.2
Anti-TG (UI/ml)	5370		340	<40
Anti-TPO (UI/ml)	> 3000		59	< 25
Anti-TPO (UI/ml)	1 (3%)	1 (6%)	0 (0%)	
Anti-TPO (UI/ml)	1 (3%)	1 (6%)	0 (0%)	

(FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; Anti-TG: Anti-thyroglobulin antibody; Anti-TPO: Anti-thyroid peroxidase antibody).

hormone (TSH), extremely low levels of free thyroxine (FT4) and free triiodothyronine (FT3). Autoimmune hypothyroidism was diagnosed with significant elevations of antithyroid antibodies (Table 1). Thyroid doppler ultrasonography showed a normal volume for age, heterogeneous echogenicity and normal parenchymal vascularity.

Thyroid hormone replacement was initiated at 100 mcg/day and resulted in significant clinical improvement after 2 months: prompt cessation of vaginal bleeding, weight loss, resolution of constipation and improvement in mood and school performance. Her height had increased by 1 cm, and her weight decreased by 2.9 kg. There was no regression, nor progression of pubertal development. Her TSH level normalized and her free thyroxine level increased. There was a normalization of the FSH, LH, estradiol and prolactin (Table 1). She developed normal puberty with menarche at 12.5 years of age. At her last examination at the age of 16 years, her weight was 55 kg (mean) and her height was 162 cm (-0.5 SDS). Her adult height fell within her mid parental height range.

Discussion

Precocious puberty may be a rare complication of untreated juvenile hypothyroidism which is usually associated with delayed puberty. A 10-year retrospective study reported a 24% incidence of precocious puberty among 33 children with severe hypothyroidism (3). The classic features of this isosexual precocity include breast development with or without galactorrhea, menstrual bleeding and large multicystic ovaries (2,4). Although less commonly described in boys, affected males present with premature testicular enlargement without virilization (5). Other unique pubertal features include delayed pubic and axillary hair growth and paradoxically short stature with delayed bone maturation. Biochemical evaluation reveals high FSH concentrations with low non-stimulable LH (2,4,5). These discordant features should draw the clinicians' attention and help to point towards the diagnosis of VWGS.

We present a case of VWGS in an 8-year-old patient with severe long-term untreated autoimmune hypothyroidism, peripheral precocious puberty including early menarche and thelarche, along with enlarged multicystic ovaries and pituitary hyperplasia. She had a short stature without delayed bone maturation which is usually a distinguishing feature to differentiate VWGS from the classic causes of precocious puberty (1). A review of the literature revealed 3 cases of VWGS with normal bone age (6–8). Durbin et al reported an 11-year-old girl whose precocious pubertal changes were not obvious and whose bone age was normal. They explained that their patient already experienced pubertal changes prior to the development of hypothyroidism. They concluded that VWGS can occur at different stages of pubertal development and lead to different clinical presentations (6). The delay in bone age presumably also depends on the duration and severity of hypothyroidism. Moreover, high serum estradiol levels, which promote growth, could decrease the degree of bone age delay.

Although all patients present with a clinical phenotype of hypothyroidism, this is often not the primary reason for referral (5). the insidious onset of vague symptoms such as short stature, weight gain, dry skin, constipation, fatigue and poor school performance may delay diagnosis (9). In addition, the other associated symptoms of VWGS may distract clinicians from the underlying causal hypothyroidism. This is illustrated in our case report as several suggestive features of hypothyroidism were discovered only at follow-up. Careful clinical examination and thyroid function should therefore be performed in patients with precocious puberty and short stature, especially when bone maturation is not advanced. VWGS is predominantly associated with long-standing acquired hypothyroidism such as autoimmune thyroiditis, but cases have been reported secondary to unrecognized congenital hypothyroidism (5).

Although discussed by many authors, the pathophysiologic mechanisms of VWGS remain unclear. In primary hypothyroidism, the reduction of thyroid hormones leads to a lack of negative feedback on the hypothalamus resulting in elevated thyrotropin-releasing hormone (TRH) (2,9). Elevated TRH induces thyrotrophic hyperplasia, which is responsible for pituitary enlargement and increased TSH production. It can also lead to lactotrophic hyperplasia resulting in hyperprolactinemia as seen in our case (2,5,9). Although early studies hypothesized that high levels of TRH also induced excessive production of gonadotropins through the pituitary-hypothalamic axis, later studies demonstrated molecular similarities between TSH and FSH receptors, which share a common alpha subunit leading to cross-reactivity (1,10). The most accepted theory is that high levels of TSH stimulate the FSH receptor, resulting in increased estrogen secretion, cystic ovarian enlargement and precocious puberty with breast development and vaginal bleeding (10). Axillary and pubic hair are absent as there is no adrenarche. Another theory explaining the discordance of FSH and LH postulates that hyperprolactinemia increases ovarian sensitivity to gonadotrophins and in turn inhibits LH secretion while producing FSH (2–4). However, prolactin levels are not always elevated (2).

VWGS has good prognosis after thyroid hormone replacement therapy. In the present case, stabilization of pubertal development and normalization of biochemical parameters were achieved after substitution therapy with L-thyroxine. Although no imaging follow-up was performed in our patient, regression of ovarian cyst size and pituitary gland hyperplasia have been described in the literature (2,5,6). Moreover, our patient entered physiologic puberty at an appropriate age, resumed a normal growth velocity and eventually reached her target height. Although most case reports describe remarkably rapid catch-up growth after thyroid hormone replacement, some report a reduced final height compared to mid-parental height (5). Niedziela et al. report that even in the setting of long-term acquired hypothyroidism, the predicted

final height may be within the normal range (8). In contrast, Cabrera et al. report that more than half of their prepubertal patients with severe hypothyroidism were smaller than 2 SDS beneath their target height (3). Indeed, growth recovery may be incomplete, depending on the severity of hypothyroidism prior to treatment and the catch-up period before true puberty occurs (2,5). Longer-term studies are needed to better characterize growth outcomes in these pediatric patients with severe, long-standing hypothyroidism.

Conclusion

This rare syndrome represents a diagnostic challenge. Although delayed bone age is a distinctive feature, VWGS can occur in individuals with normal bone maturation. Thyroid function tests should therefore be performed in patients with precocious puberty without advanced growth and bone maturation. Thyroid hormone replacement provides rapid clinical improvement although adult height should be documented in long-term and multicenter studies.

Conflicts of interest

There are no conflicts of interest.

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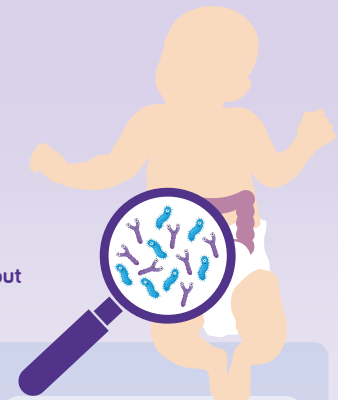
DIETARY MANAGEMENT OF COW'S MILK ALLERGY (CMA) CLINICAL BENEFITS OF SYNBIOTICS



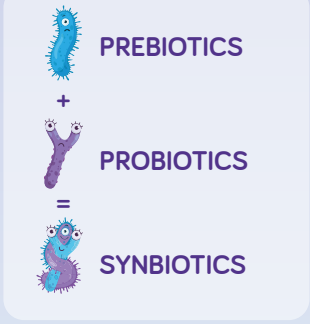
CMA is common in infants and children, presenting with a range of symptoms affecting the gastrointestinal (GI) tract, skin and respiratory tract[1-3]. The gut microbiota plays a pivotal role in the development of the immune system. However, research has shown that infants with CMA have an altered gut microbiome compared with healthy breastfed infants[4-9]. In addition, infants with CMA also face an increased susceptibility to infections compared with infants and children without CMA[10]. The impact of CMA goes beyond the clinical symptoms, impacting families and the wider healthcare system[11].

Breastmilk composition contains a wide range of important bioactive compounds which promote a healthy gut microbiota and immune system development[12].

Synbiotics are a combination of prebiotics (substrates that are selectively utilised by host microorganisms conferring a health benefit[13]) and probiotics (live microorganisms which when administrated in adequate amounts confer a health benefit on the host[14])[15].

New innovations have allowed formula advancements with the inclusion of synbiotics in extensively hydrolysed formulas (eHF) and amino acid based formulas (AAF).

Studies have shown that hypoallergenic formulas with synbiotics support the gut microbiota in infants with CMA, prompting favourable shifts in gut microbial composition that are more reflective of the gut microbiota of healthy breastfed infants[9,16-19]. Evidence consistently shows positive effects of synbiotics on immune-related outcomes[9,17-20].



CLINICAL STUDIES

To date, several studies have been conducted with hypoallergenic formulas with a unique blends of synbiotics (eHF: B. breve M-16V and scGOS/lcFOS[17,21,22] and AAF: B. breve M-16V and scFOS/lcFOS[9,21,23]). Results have consistently demonstrated that these formulas are well tolerated, have a good safety profile, and support normal growth. Exploratory outcome data* from these studies have reported additional interesting and clinically relevant findings.

- = eHF related research
- = AAF related research

Dermatological symptoms

- Demonstrated greater improvement of atopic dermatitis**[17]

Infections

- Fewer infections[18] and GI infections[20]
- Fewer ear infections[19]

Medication use

- Reduced need for medication for functional GI disorders[18]
- Lower percentage of infants required antibiotics[9,18]
- Lower use of dermatological medication[19]
- Reduction of asthma medication at one year follow up[21]

Respiratory

- Lower prevalence of asthma-like symptoms at one year follow-up[21]

Hospitalizations

- Fewer hospitalizations due to infections[20]

GI

- Improved stool consistency and colour, closer to those of healthy breastfed infants[23]
- Reduction in constipation and dry stools[17]

* based on evaluation of adverse events and safety parameters in studies in infants with CMA receiving an hypoallergenic formula with synbiotics in comparison with hypoallergenic formula without synbiotics.
** in the subgroup of infants with IgE-associated atopic dermatitis.

REAL WORLD EVIDENCE (RWE) STUDIES

Randomised controlled trials (RCTs) and RWE studies are often considered complementary[24,25]. RWE reflects how treatments are utilized and their effectiveness in routine clinical practice, providing insights into real-world treatment patterns, adherence, and outcomes. To date, RWE studies in CMA infants given eHF or AAF with a synbiotic blend have shown consistent results with published RCTs.

Hubbard et al. (2022)[26]

Single-arm, prospective study of CMA infants receiving eHF with synbiotics

- Improvements in severity of abdominal pain, burping, flatulence, constipation
- Improvements in atopic symptoms including rhinitis and itchy eyes
- Reduction in hospital visits and medications in the six months follow-up
- Improvements in caregiver reported quality of life

Sorensen et al. (2021)[27]

Retrospective matched cohort comparing case records of CMA infants managed with AAF with synbiotics or AAF without synbiotics, found AAF with synbiotics to be associated with

- Lower rate of healthcare contacts
- Lower rates of infections and medication prescriptions
- Fewer gastro-intestinal, skin and/or respiratory symptoms
- Potential healthcare cost-savings

SYSTEMATIC REVIEW

Sorensen et al. (2021)[28]

Meta-analysis of four RCTs of CMA infants receiving AAF with synbiotics compared to AAF without synbiotics

- Significantly fewer infections
- Lower overall medication use
- Fewer hospital admissions

PEPTI SYNEO® (EHF) AND NEOCATE® SYNEO® (AAF)

Pepti Syneo (eHF) and Neocate Syneo (AAF) contain both the probiotic *(Bifidobacterium breve M-16V)*, and prebiotics (eHF: short chain GOS/long chain FOS; AAF: short chain FOS/long chain FOS, ratio 9:1). The synergy between the probiotic and prebiotics helps mimic the diversity, quantity and functionality of oligosaccharides in human milk and have a bifidogenic effect[29,30].

These key components modulate the gut microbiota of CMA infants to improve the compositional profile closer to that of a healthy breastfed infant. This is important to support immune system development and therefore long term health[9,17-19,27].

Pepti Syneo (eHF)

Pepti Syneo is an extensively hydrolysed formula for the dietary management of mild to moderate CMA.

Beyond clinical improvements and symptom relief in CMA infants[17,21,26].
Pepti Syneo has been shown to:

- Be safe and well tolerated[31]
- Promote normal growth and development[22]
- Rebalance the gut microbiota by increasing levels of bifidobacteria[17]
- Reduce asthma-like symptoms at one year follow-up[21]
- Be the most palatable eHF by HCPs and parents in the UK[32,33]

Neocate Syneo (AAF)

Neocate Syneo is an amino acid based formula for the dietary management of severe or complex CMA. Studies have consistently shown clinical improvements and symptom relief in CMA infants with Neocate Syneo[19,27,28]. Neocate Syneo has also been shown to:

- Be safe and well tolerated[23]
- Promote normal growth and development[18]
- Rebalance the gut microbiota of CMA infants closer to that of healthy breastfed infants[9,18-20]
- Result in fewer infections[18-20,27,28]
- Result in lower medication use[9,18,19,27,28]
- Result in lower hospital admissions[20,27,28]

Important: Nutrilon Pepti Syneo is a food for special medical purposes. For the dietary management of cow's milk protein allergy. Neocate Syneo is a food for special medical purposes. For the dietary management of cow's milk protein allergy, multiple food allergies and other indications where an amino acid-based diet is recommended. Must be used under medical supervision after full consideration of all feeding options including breastfeeding. Information intended for Healthcare Professionals only.

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Diagnosis of Fanconi Anaemia in child with massive pulmonary embolism: case report and literature review

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Keywords

Fanconi anaemia ; pulmonary embolism ; persistent cytopenia ; children ; case report.

Abstract

Fanconi anaemia is a rare inherited syndrome characterised by bone marrow failure, congenital anomalies and predisposition to malignancy. We report the case of a teenager who presented with massive pulmonary embolism and persistent moderate cytopenia. His biological work-up revealed an abnormal chromosomal break leading to the diagnosis of Fanconi anaemia and antithrombin III deficiency. Despite the presence of other promoting factors, we discuss whether the risk of thromboembolic events might be increased in patients with congenital or acquired aplastic anaemia.

Introduction

Fanconi anaemia (FA) is a rare inherited (mainly autosomal recessive) disorder characterised by congenital abnormalities, progressive bone marrow failure, and a predisposition to malignancy. FA is caused by mutations in the *FANC* family of genes, which encode for proteins involved in desoxyribonucleic acid (DNA) repair, leading to genomic instability. The most frequently mutated genes are *FANCA*, *FANCC* and *FANCG* (1).

Congenital malformations are the most common presenting features. They typically include skin findings like café-au-lait spots, short stature, thumb or other radial ray abnormalities, axial skeletal malformations, congenital heart disease and genitourinary, renal, gastrointestinal, central nervous system, ear, and eye abnormalities. Haematological manifestations include thrombocytopenia, macrocytic anaemia or pancytopenia due to progressive bone marrow failure. Myelodysplastic syndromes (MDS), acute myeloid leukaemia and squamous cell carcinoma of skin, head, neck and tongue are among the malignancies that are increased in patients with FA (1).

FA is usually diagnosed in the first decade of life. However, recent studies on large registries supported by genetic analysis have shown a wide spectrum of clinical presentation with diagnosis sometimes delayed into adulthood (1).

We report the clinical history of a teenager who presented with massive pulmonary embolism (PE). Careful examination revealed discrete phenotypic abnormalities and persistent moderate cytopenia suggesting the diagnosis of FA. This observation was consistent with other reports describing an increase of venous thromboembolism (VTE) in patients with acquired or congenital aplastic anaemia (AA) (2-5).

Case reports

A 15-year-old boy was initially treated for right pneumonia. Biology showed an inflammatory syndrome (C-reactive protein 149 mg/L [N <5]), aregenerative macrocytic anaemia (haemoglobin: 10.5g/dl [N 11-14.3], MCV: 104 fL [N 81-87], reticulocytes: 44*10^{e}3/mm^3 [N 39-100]) with normal folic acid and vitamin B12, normoleukocytosis (WBC: 5.21*10^{e}3/mm^3 [N 5.2-9.7], neutrophils: 2.77*10^{e}3/mm^3 [N 2.7-6.7]) and thrombocytopenia (platelets: 71*10^{e}3/mm^3 [N 180-299]). He clinically improved after antibiotherapy and biological evolution showed a decrease of the inflammatory syndrome but persistence of macrocytic anaemia (haemoglobin: 9.7 g/dl, MCV: 104 Fl), thrombocytopenia (platelets: 66*10^{e}3/mm^3) and appearance of a mild neutropenia at 1.26*10^{e}3/mm^3 (Table 1).

Two months later, after a four-hour bus journey, the child presented with acute dyspnoea and chest oppression. Blood tests showed macrocytosis without anaemia (haemoglobin: 14.4g/dl, MCV: 105fl), normal leukocytosis (WBC: 6.62*10^{e}3/mm^3), thrombocytopenia (platelets: 40*10^{e}3/mm^3), and no inflammatory syndrome (Table 1). He rapidly progressed to hypoxemic respiratory failure and obstructive shock. Computed tomography pulmonary angiography showed a massive bilateral pulmonary embolism (PE). The patient was treated urgently with surgical thrombectomy with sternotomy (thrombocytopenia contraindicated thrombolysis) followed by anticoagulation with enoxaparin. Doppler examination of the lower limbs revealed no deep vein thrombosis (DVT). The respiratory condition improved rapidly but biological abnormalities such as thrombocytopenia (platelets: between 49 and 53*10e3/mm^3) and macrocytosis (MCV: between 103 and 128 fL) persisted with the progressive onset of moderate leukopenia (WBC: 3.01*10^{e}3/mm^3) and anaemia (haemoglobin: 7.1 g/dl) (Table 1).

The initial coagulation work-up was normal (before anticoagulant treatment): INR 1.15, ACT (activated cephalin time) 34 seconds (N 25-42), C and S protein levels at 105% and 93% respectively (N 70-130%). Lupus anticoagulant and antiphospholipid tests were negative. Thorough thrombophilia evaluation revealed antithrombin III (ATIII) deficiency with repeated levels between 50 and 60 % and serum homocysteine levels at the upper limit of normal (11 µmol/L for a standard between 4 and 10). Low ATIII levels were also found in the patient's mother and two sisters, suggesting a familial deficiency. Genetic workup revealed no factor V LEIDEN mutation or factor II mutation.

Several clinical features were noted in the context of moderate cytopenia: small size (height: 156cm, (< 5th percentile), triangular face, hypotelorism, subtle hypotrophy of the thenar eminence and an increase in foetal haemoglobin to 8.5% (N < 2%). Medullary puncture showed moderate hypoplasia without myelodysplasia or clonal abnormalities. The mitomycin C test showed an increase in chromosomal breakages, suggesting the diagnosis of FA. Molecular analysis confirmed that the patient was a heterozygous carrier of 2 deletions of the *FANCA* gene. Morphological examination revealed no other cardiac, renal or bone abnormalities.

The patient was anticoagulated with dabigatran. He required 2 red blood cell transfusions and is currently being considered for unrelated hematopoietic cell transplantation. Anticoagulation will need to be maintained throughout the transplantation.

Discussion

FA is a genetically and phenotypically heterogeneous disorder. A large study analysing data from the International Fanconi Anaemia Registry (IFAR) has shown that approximately one third of patients have no major congenital malformations. In these patients, diagnosis is usually delayed and made after the occurrence of haematological dysfunction (1). Similarly, investigations in children and young adults have suggested that genetic screening should be considered in all patients presenting AA or MDS even in the absence of familial history or physical abnormality (6). Our patient displayed discrete dysmorphic signs and short stature but the FA diagnosis was finally evoked in the context of PE, revealing persistent macrocytic aregenerative anaemia and moderate thrombocytopenia.

PE is rare in children. It has a bimodal distribution with higher incidence in infants and adolescents. The Canadian and Dutch registries report incidence rates of VTE - which includes both DVT and PE - of 0.07 to 0.14 per 10,000 children (7). In paediatrics, the main risk factors for VTE are central venous catheters, hereditary thrombophilia, immobility, inflammatory conditions such as systemic infections or inflammatory diseases, haematological malignancies, solid cancers, trauma, surgery, use of hormonal contraceptives and nephrotic syndromes. More than 95% of children with VTE have at least one underlying clinical condition (7).

Several factors may have favoured PE in our patient. First, the repeated low ATIII levels observed were consistent with an inherited deficiency. Inherited ATIII deficiency is an autosomal dominant disorder caused by a mutation in the *SERPINC1* gene that results in a reduction in AT levels of between 40 and 60% (type I) or functionally defective AT (type II). Although we do not have genetic confirmation, the reduced levels measured in the patient and several family members suggest a hereditary AT III type I deficiency.

Second, venous stasis resulting from 4 hours of immobilisation during the bus journey may also have promoted thromboembolism. In a systematic review, Rajpurkar and colleagues reported a prevalence of immobilisation of 38% in paediatric patients with PE (62 out of 163 patients) (8). In our patient, echo doppler of the lower limb showed no DVT. In large series, only 30 to 60% of patients with PE associated with immobilisation have DVT (7).

A previous pulmonary infection may also have contributed to the PE in our patient. By increasing blood coagulability and venous stasis, infection and subsequent inflammation are known to promote thromboembolism. This risk of VTE increases 2-4-fold following respiratory infection, and the association is strongest in the first 2 weeks after the onset of infection, with a gradual decline thereafter (9).

Finally, we wondered whether the diagnosis of FA in our patient was merely coincidental or whether it might have played a role in the development of PE in addition of other risk factors. A prospective comparative study has shown a 2.5-fold higher incidence of VTE in patients with AA compared with non-AA patients. This study involved mainly adult patients (with only 24% of subjects under 49 years of age) treated exclusively for secondary and idiopathic AA (5). VTE has also been reported in children and young adults with inherited AA such as Blackfan-Diamond syndrome. Several risk factors have been identified in these cases: central venous catheters, treatment with interleukin-3 for Blackfan-Diamond anaemia, and snakebite in a patient with iron overload induced by repeated transfusions (2-4). These observations do not exclude a role of immune dysregulation and altered haematopoiesis in promoting VTE in AA. Pro-inflammatory cytokines namely tumour necrosis factor alpha (TNFα), interleukin 6, and interleukin 2 contribute to the pathogenesis of bone marrow failure in AA. TNFα also induces the production of reactive oxygen species and the activation of several transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B). In addition, NF-kappa B plays a role in vascular smooth muscle cell growth, vascular remodelling, atherogenesis, and VTE (5). A potential link between FA and thromboembolism has also been supported by a recent animal model of FA. Raman and colleagues reported that *FANCA*-/- and *FANCO*-/- zebrafish had a shortened venous time to occlusion. They hypothesised that erythrocyte lysis due to complement, as observed in aplastic anaemia, may promote this thrombotic feature (10).

Conclusion

To our knowledge, this is the first report of PE in a patient with FA. There is insufficient evidence to confirm a link between the two diseases. However, a review of the scientific literature revealed some interesting observations. In addition to ATIII deficiency and immobilisation, the prothrombogenic immune changes associated with bone marrow failure and the recent pulmonary infection may have favoured the occurrence of VTE in our patient.

This report also highlights the importance of considering the diagnosis of congenital aplastic anaemia when faced with unexplained persistent cytopenia in children, adolescents and young adults, even in the absence of an obvious congenital abnormality.

Acknowledgements

The authors would like to thank the patient and his parents for allowing us to publish this interesting case.

Table 1: Laboratory examination at the first admission with pneumonia, two months later at the second admission with pulmonary embolism and during the follow-up.

Parameters, Normal Values	Day 0 Pneumonia	*Day 10*	*Day 60 Pulmonary embolism*	*Day 66 Post- thrombectomy*	Day 150 Follow-up
Haemoglobin, 11.0-14.3 g/dL	10.5	9.7	14.4	10.1	7.1
MCV, 81-87 fL	104	104	105	103	128
Reticulocyte, 39-100 $10^e3/mm^3$	44		11	97	200
Total leukocyte count, 5.2-9.7 $10^e3/mm^3$	5.21	4.66	6.62	4.42	3.01
Neutrophil count, 2.7-6.7 $10^e3/mm^3$	2.77	1.26	5.73	1.7	1.37
Platelet count, 180-299 $10^e3/mm^3$	71	66	40	49	53
CRP, <5 mg/L	150	16	7		

MCV = mean cell volume; CRP = C-reactive protein.

Disclosure statement

All authors declare that they have no conflicts of interest.

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Multifocal Invasive Group A Streptococcus Infection in a Previously Healthy 17-Month-Old Child: A Rare Case Report

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Keywords

Group A β-hemolytic *Streptococcus*; urinary tract infection; multifocal infection; case report.

Abstract

Group A β-hemolytic *Streptococcus* is a highly pathogenic organism with multiple virulence factors enabling it to invade a wide range of sterile sites. Multifocal dissemination of infection is not uncommon. However, urinary tract infection is very rarely reported.

We describe an atypical case of a 17-month-old boy in whom a streptococcal urinary tract infection delayed the diagnosis of a multifocal invasive infection with more classic joint involvement.

Case Report

Group A β-hemolytic *Streptococcus* (GAS), also known as *Streptococcus pyogenes*, is a human-restricted gram-positive bacterium that colonizes epithelial surfaces. It can lead to asymptomatic carriage or cause a wide spectrum of clinical presentations ranging from local infections such as pharyngitis to invasive disease including streptococcal toxic shock syndrome (STSS) (1). Indeed, this pathogenic organism possesses multiple virulence factors that allow it to invade many sterile sites (2). Invasive group A streptococcal infection (iGAS) is defined by the isolation of GAS from a normally sterile body site (3). iGAS can manifest as bacteremia without focus, severe pneumonia, osteoarticular infection, endocarditis, meningitis, necrotizing fasciitis, STSS, etc. However, urinary tract infections (UTI) due to GAS are exceptionally reported. Necrotizing fasciitis and STSS are both associated with the production of exotoxins that act superantigens inducing an exaggerated immune response resulting in a severe clinical picture (1,4,5). Over the past forty years, the incidence and severity of iGAS has steadily increased worldwide (1,2). Although it can affect individuals of all ages, the highest rates are found in children under the age of 5 and adults over the age of 60 (1,5,6). The clinical manifestations of iGAS in children differ from those in adults. Pediatric patients have a lower rate of STSS and necrotizing fasciitis. Osteoarticular infections are uncommon but, in contrast, more frequent than in adults, accounting for 4.5% to 24% of pediatric patients with iGAS (1,4,5). Most cases of iGAS occur in otherwise healthy children without chronic conditions. The main points of entry are the respiratory tract and the skin (6). Surgical wounds, skin lesions and chickenpox are therefore some of the known predisposing risk factors, although nearly half of affected children have none (5,6). The overall case fatality rate for iGAS is 8-19%, corresponding to an estimated 160,000 deaths per year worldwide and it rises to nearly 50% when the infection is complicated by a STSS (4,6,7,8). In all studies, the mortality rate in children is at least half that of adults (1,5,7,8). However, iGAS is often severe in children, accounting for approximately 40% of intensive care unit admissions (5).

We present the case of a previously healthy 17-month-old boy who developed an iGAS with an unusual multifocal presentation: upper urinary tract infection, hip arthritis and bacteremia.

Case presentation

A 17-month-old boy presented to the emergency department with a 2 day history of fever up to 39.6°C and intermittent episodes of vomiting. Since the previous day, his general condition had deteriorated with a decreased feeding and avoidance of standing and walking. He had no contributing medical history other than recurrent acute otitis media. His vaccinations were up to date. Vital signs were within normal limits (heart rate = 137 bpm, oxygen saturation = 96%, blood pressure = 101/70 mmHg). On physical examination, the toddler was pale, with pharyngeal erythema and showed signs of discomfort. He refused to stand up, remaining in a sitting position. Mobilization of both hips appeared to be painful, but without range of motion limitation, joint swelling, warmth or erythema. Laboratory tests revealed a severe inflammatory syndrome (white blood cell (WBC) count = 32.12 x10e9/L with an absolute neutrophil count = 25.6 x10e9/L and C-reactive protein = 359 mg/L). A urine sample obtained by transurethral bladder catheterization showed leukocyturia with >800 WBC/μL. The patient was admitted and started on intravenous antibiotics with temocillin 50 mg/kg/day in 2 doses, given the diagnosis of urinary tract infection. The day after admission, a limp in the left lower limb was noted. In contrast to the previous day, the patient had now markedly restricted range of motion of the left hip, but still no associated local signs of inflammation. Ultrasound imaging confirmed a left hip joint effusion, and an evacuating joint aspiration was promptly performed. The macroscopic purulent appearance and the microscopic analysis of the synovial fluid were consistent with bacterial arthritis. Therefore, on the first day of hospitalization, the antibiotic therapy was changed to a broad-spectrum antibiotic, ceftriaxone 100mg/kg/day in a single dose. The patient became apyretic on the same day. Blood, urine and joint fluid cultures all showed the presence of *Streptococcus pyogenes*, leading to the final diagnosis of multifocal iGAS with bacteremia, upper urinary tract infection, and left hip arthritis. Antibiotic susceptibility testing revealed that the bacterium was susceptible to penicillin-G, erythromycin, clindamycin, levofloxacin and vancomycin. On the third day of hospitalization, the patient was switched from broad-spectrum antibiotic coverage with ceftriaxone to dual therapy with intravenous amoxicillin (200mg/kg/day in 4 doses) and clindamycin (30mg/kg/day in 3 doses). Despite the absence of hemodynamic instability, a potentially toxic erythematous rash developed, justifying the addition of clindamycin without requiring intravenous immunoglobulin. The patient's gait gradually improved, albeit with a residual limp. Magnetic resonance imaging of the left lower extremity performed on the ninth day of hospitalization showed no osteomyelitis associated with septic arthritis. Abdominal ultrasound showed no deep focus of infection between the bladder and the left hip

and no urinary tract abnormalities were found on abdominal ultrasound. Laboratory tests gradually returned to normal, and a baseline immune blood workup was unremarkable. On the 10th day of hospitalization, after 7 days of intravenous antibiotic therapy with amoxicillin and clindamycin, considering the criteria of clinical improvement and resolution of the inflammatory syndrome, oral amoxicillin (100mg/kg/day) was continued for 14 days, while clindamycin was discontinued. At the two-month follow-up visit, the limp was completely resolved.

Discussion

Since the mid-1980s, iGAS has increased in incidence and severity worldwide. It may be partly attributed to the emergence of new virulent strains (1,9). In high-income countries, the reported annual incidence ranges from 1.6 to 3.8/100,000 (6,8). This is at least two to three times higher than the incidence of invasive meningococcal disease in Europe. Indeed, due to the development of vaccines against childhood pathogens such as *Neisseria meningitidis* and their introduction into immunization programs, iGAS has become an emerging cause of severe infection in children (7). After a period of reduced incidence related to the lockdown during the COVID-19 pandemic in 2020-2021, several European countries have reported a new increase in the number of iGAS cases since September 2022, especially in children younger than 10 years (10).

In our case of multifocal iGAS, although bacteremia and arthritis are classic manifestations, UTI is exceptionally reported. In children, we found only one observational study conducted in Kenya from 1998 to 2011 that revealed that UTI could be one of the manifestations of iGAS, identifying 6 patients with UTI among 369 cases of pediatric iGAS (4). In addition, the propensity of GAS to disseminate to multiple sites can complicate management. In our patient, because of the early diagnosis of upper UTI on admission, the clinical signs of limping, highly suspicious for osteoarticular infection, were ignored and delayed the diagnosis and appropriate treatment of hip arthritis (i.e., joint cavity drainage and appropriate antibiotic therapy).

The adjunction of an antitoxin antibiotic such as clindamycin to conventional beta-lactam therapy is widely recommended in the literature for the treatment of iGAS, particularly in case of necrotizing fasciitis, STSS or clinical signs suggestive of toxin production (rash, gastrointestinal signs, hemodynamic disturbances) (9,11). In our patient, the addition of clindamycin was justified by the appearance of an erythematous-macular rash, which raised concern of a toxic rash. Clindamycin is a lincosamide that inhibits protein synthesis and thus exotoxin production. Compared to penicillin, in addition to its antitoxin activity, clindamycin has a superior post-antibiotic effect, better tissue penetration and activity against bacteria in stationary phase, so it is not affected by inoculum size or growth stage (9). However, clindamycin should not be used alone as a small proportion of GAS are resistant to it (5-10% in Belgium but almost 30% in the USA), whereas there is no resistance to penicillin to date (1,2). Nevertheless, GAS strains with unusually high minimum inhibitory concentrations for ampicillin and amoxicillin have recently been reported in the United States, although they are still clinically susceptible to β-lactams (12). The optimal total duration of antibiotic therapy for iGAS is unclear because data are limited. Without specifying the minimum intravenous duration, most authors recommend a minimum of 10 to 14 days of treatment, to be tailored to each patient's situation. The occurrence of septic arthritis in our patient's clinical picture explains the total duration of amoxicillin treatment of 21 days. Intravenous immunoglobulins are generally recommended for all hemodynamically unstable patients and/or patients admitted to intensive care and/or those with STSS or necrotizing fasciitis (9,11). Since our case did not meet any of its severity criteria, immunoglobulins were not required. There is no international consensus regarding secondary chemoprophylaxis for contacts. In a systematic review published by Laho et al. in 2021, the authors recommend prophylaxis with first-generation cephalosporins for all household members of the patients and for contacts at high risk of complications related to iGAS (11).

Conclusion

Given its increasing incidence and severity, early recognition of iGAS is imperative to ensure prompt and appropriate treatment. However, the initial clinical presentation is often non-specific, may even be unusual and plurifocal as in our patient, and therefore challenging to diagnose. Despite decades of research, the development of an effective vaccine for the prophylaxis of GAS infections remains a major issue and has been declared a priority by the World Health Organization (WHO) in 2018 (13).

Conflict of interest

The authors have no conflicts of interest to declare.

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Juvenile trabecular ossifying fibroma in an 12 year old patient, a case report

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Keywords

Juvenile ossifying fibroma ; Trabecular ossifying fibroma ; Benign fibro-osseous tumors.

Abstract

Juvenile ossifying fibroma (JOF) is one of the rarest entities within the very heterogeneous and large group of benign fibro-osseous tumors. It is often diagnosed in the first two decades of life, is usually asymptomatic, and affects males and females equally. JOF commonly arises in the mandibular or maxillary region and has a particularly aggressive behavior, characterized by rapid growth and a high risk of recurrence (estimated at 20-50%). Surgical enucleation, followed by curettage and/or osteotomy remains the mainstay of treatment.

Case Report

A 12-year-old boy presented for investigation of a painful mandibular mass noted after minor trauma to the mandible. The patient was apyretic and there was no evidence of infection. His past medical history was uneventful. Physical examination confirmed an inferior-lateral right mandibular mass that was firm and nonmobile, without skin lesions. Full mouth opening was prevented by the lesion, thus solid food intake was compromised.

Blood tests showed no evidence of inflammation. Serological screening was negative. A CT scan of the mandible showed an encapsulated formation of approximately 5 cm in width, located within the right ascending branch of the lower mandible, facing the dental root 48. MRI showed no evidence of bone destruction. An FDG PET-CT showed hyperavidity of the lesion with a suspicious adenopathy in level IIa (upper jugular nodes), homolaterally (Figure 1 and 2).

A biopsy was performed and revealed a tumoral structure with osteogenic differentiation and lamellar osteoid matrix, amidst a disrupted osteoblastic and connective structure. Histology was consistent with a juvenile trabecular ossifying fibroma.

Conservative surgical endobuccal resection was performed, followed by 6 weeks of maxillomandibular block to optimize bone consolidation (Figure 3).

Full mandibular mobility and masticatory forces were regained after removal of the consolidation block.

However, the 12 month follow-up MRI showed clear signs of relapse in the lower right mandible. The CT scan confirmed the presence of multiple tumoral lesions located within the right posterior mandible and possibly the coronoid process.

Considering the extent of the lesion and the short remission period, curettage was not considered an appropriate option. A radical resection of the posterior mandible, including the condylar process, is planned. Reconstruction will be performed with a fibular graft.

Discussion

Juvenile ossifying fibroma (JOF) is a rare benign entity belonging to the group of fibro-osseous tumors. JOF has a clinically more aggressive nature and a high recurrence rate compared to a conventional ossifying fibroma generally seen in adults (1,2). The underlying molecular mechanisms remain largely unknown (1,3).

There are two histological subtypes of JOF: the trabecular and the psammomatoid JOF (1-4).

The trabecular subtype is characterized by a cellular fibrous stroma composed of spindled fibroblast cells with a lamellar osteoid matrix without osteoblastic rimming and immature bony trabeculae surrounded by plump osteoblasts (1,4,5). Trabecular JOF affects the craniofacial bones, predominantly the jaw (1,5).

In contrast, the psammomatoid subtype contains cellular fibroblastic stroma with curved and spherical ossicles (1,2,4,5). Psammomatoid JOF more commonly involves the paranasal sinuses and the periorbital region (2,5).

Figure 1: Head and neck MRI T1 with fat suppression and contrast (Gadolinium).

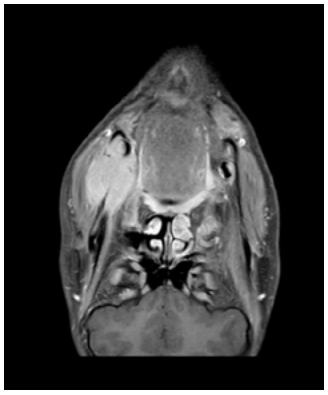
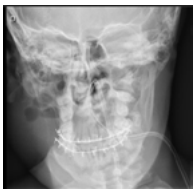


Figure 2: FDG PET-CT.

Figure 3: Post Surgery X Ray.



Trabecular JOF is generally found in younger patients (< 15 years) compared to psammomatoid JOF (mean age 16-33 years) (2,3,5,6). There doesn't seem to be a gender predilection, although some studies describe a male:female ratio of 3:2 (1-4).

Clinical presentation is silent in most cases. Dental displacement and indolent swelling are often described (1,2,3,5). Nasal obstruction, ptosis or exophthalmos may be found in paranasal or periorbital locations.

In some cases, previous trauma is associated with JOF (1).

Although JOF is often locally aggressive and prone to recurrence (estimated 20-50% recurrence rate), malignant transformation to sarcoma has not been reported so far (2,3). Even though the lesions are usually well demarcated, their rapid growth and its osteolytic nature with cortical thinning may mimic malignant entities such as sarcoma, hematopoietic neoplasms, secondary metastasis or odontogenic tumors (3,6,7).

The lesions often present as unilocular mixed lesions, with radiolucent and radiopaque entities (1,2). The cortical outline remains intact, although cortical thinning may be seen (3,5).

Clinical, histological and radiological features assist the clinician in differentiating a malignant lesion from a benign lesion. An overview of the differential diagnosis can be found in the Appendix.

There is no consensus regarding optimal treatment. Enucleation and curettage with peripheral ostectomy remains the main first-line treatment strategy (1,6). Second line treatment consists of hemimaxillectomy and peripheral resection (8). In some cases bone grafting is required for reconstruction. This procedure is particularly challenging in the pediatric population, as bone growth is still ongoing.

In most studies, there doesn't seem to be a difference in outcome between limited or extensive surgery (1). However, some studies have reported lower recurrence rates after complete resection (5,8). Because osteotomy has a much higher morbidity rate, it remains the second treatment choice (5,8).

Patients often face a long rehabilitation process with prolonged maxillomandibular block, esthetic challenges and articular mandibular dysfunction leading to feeding difficulties.

Conclusion

JOF is a benign fibro-osseous tumor without potential of malignant transformation. Still, its rarity and its silent presentation can make diagnosis challenging. Differential diagnosis with odontogenic tumors, sarcoma, hematopoietic neoplasms, Langerhans cell histiocytosis or secondary metastasis is important. Surgical resection is the mainstay of treatment, although harboring its own challenges, such as aggressive surgery, sometimes requiring bone grafting, an high local recurrence rates. These features contribute to increase JOF's potential morbidity. Long-term follow-up is strongly recommended (1).

Conflict of interest

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

APPENDIX: Recapitulative chart of the differential diagnosis.

	Sex Ratio	Age	Radiological features	Histological features	Treatment	Prognosis
Juvenile ossifying fibroma	No gender predilection	< 15 years	Osteolytic nature with cortical thinning	Trabecular or psammomatoïd type	Enucleation/curettage or peripheral ostectomy	High recurrence rate: 20-50%
Ossifying Fibroma	9:5 female:male ratio	Mostly adults, 20-40 years	Mixed radiolucent / radiopaque lesion	Trabeculae of woven bone lined by active osteoblasts	Enucleation/curettage or peripheral ostectomy	Very rare recurrence
Langerhans cell histiocytosis	2:3 male:female ratio	Children < 15 years, often 1-4 years	Osteolytic lesion with irregular margin	Clonal proliferation of Langerhans Cells	Surgical curettage / systemic chemotherapy / corticosteroids	- Depending on initial site - Unisystemic or multisystemic lesion
Osteoblastoma	Male predilection	Adults, often 20-30 years	Mixed radiopaque and radiolucent lesion	Bony trabeculae lined by osteoblasts	Surgical Excision (+ Radiotherapy)	Recurrence rate: up to 20%
Osteosarcoma	Male predilection	Adults, often 30-40 years	Osteolytic and osteogenic nature witch cortical destruction	Immature osteoid formation: proliferation of neoplastic mesenchymal cells with spindle-shaped, epithelioid, or plasmacytoid appearance	- Ablative surgery - Adjuvant chemotherapy - Adjuvant radiotherapy	5 year survival rate of 65%
Odontogenic tumors	9:7 male:female ratio	Mean age 11.6 years	Radiolucent lesion	Fibromyxoid tissue with variable cellularity surrounded by a cuboidal to columnar odontogenic epithelium	Excision / enucleation	No reports of recurrence
Hodgkin Lymphoma	Male preponderance 3:1	Peak in 4th decade, but affects also children	FDG/PET-CT MRI with increased T2 signal	Presence of Hodgkin/ Reed Sternberg cells	Radiotherapy/chemotherapy	Ten year survival 80-99%
Non Hodgkin Lymphoma	Male predilection	Average age of 65 years (Several types mostly in children like Burkitt's Lymphoma)	FDG/PET-CT MRI with increased T2 signal	Absence of Hodgkin/ Reed Sternberg cells	Radiotherapy/ chemoimmunotherapy	5 year survival rate of 72,7%
Fibrous Dysplasia	Slight female predilection	Mean age 20 years	CT Scan: - Radiodense lesion with ground glass appearance - Radiolucent/cystic lesion	Cellular fibrous connective tissue with irregular bony trabeculae	- Surgical resection - Bisphosphonates - « Wait and see »	Recurrence rate: up to 84%

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Pseudomonas aeruginosa skin infections in two immunocompetent children under one year of age

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Keywords

Pseudomonas aeruginosa, ecthyma gangrenosum, panniculitis, neutropenia.

Abstract

We describe two cases of Pseudomonas aeruginosa skin infections in immunocompetent children, both following viral infections. The first one presented with fever and erythematous cutaneous nodules that enlarged and developed into abscesses. Biopsy of a nodule revealed panniculitis with P. aeruginosa. The second case presented with deep necrotic inguinal ulcers consistent with ecthyma gangrenosum. These two presentations are rare conditions in healthy infants without bacteremia. This report aims to answer questions such as the source of the contamination, the usefulness of the antibiotics or surgical drainage in the treatment, and the association of leukopenia with infection or immunodeficiency.

Introduction

Pseudomonas aeruginosa is a ubiquitous, aerobic, gram-negative bacillus that preferentially thrives in moist environments (1). The primary condition for a *P. aeruginosa* infection is to be colonized. After that, several conditions must be present such as a huge bacterial load, virulence factors (adhesion, antibiotic resistance, biofilm formation, secretion of toxins and enzymes), or an immune deficiency (transient or permanent). *P. aeruginosa* is frequently reported in cutaneous infections, more often in primary infections, by contact with a damaged skin or skin maceration, as seen in conditions such as pyoderma, folliculitis, bathtub contact, intertrigo, but also in secondary infections by blood dissemination in immunocompromised patients, such as in ecthyma gangrenosum (EG), a necrotic ulcerating skin lesion (1). Recently, however more cases have been reported in immunocompetent children (2). Although ecthyma gangrenosum is a well-described entity, a case of nodular *P. aeruginosa* panniculitis in an immunocompetent child without bacteremia has never been described in the literature so far.

Cases Reports

We report a 6-month-old girl with a 3-day history of fever and bronchitis. She presented with three erythematous cutaneous nodules on the right arm and left leg (Figure 1A). A blood analysis revealed a C-reactive protein (CRP) level of 177.1 mg/L [N < 5.0 mg/L] with hyperleukocytosis. The next day, the number of nodules increased to eight. Systemic antibiotherapy was started for suspected cutaneous bacterial infection, first with intramuscular ceftriaxone for two days due to lack of easy venous access, then with intravenous amoxicillin plus clavulanic acid for nine days. The neutrophil count dropped to 1590/mm3 [N 6000-17500/mm3], while the CRP level decreased. In the following days, the nodules evolved into clinical, ultrasound-documented abscesses with a dark erythematous central aspect and painful fluctuation. On the seventh day, the skin began to peel (Figure 1B). Biopsy of a nodule showed panniculitis with pus, leukocyte infiltrate, and culture showed massive growth of *P. aeruginosa*. Surgical punctures of the other abscesses also drained pus with positive *P. aeruginosa* cultures. The child recovered rapidly. On day 10, systemic antibiotics were discontinued and oral ciprofloxacin was started for two weeks. Repeated blood cultures were negative. An extensive workup did not reveal any deep infectious damage (cardiac and abdominal ultrasound, bone scintigraphy). Humoral immunity (dosage of all types and subtypes of immunoglobulins) and cellular immunity (dosage and types, subtypes of lymphocytes) were normal. The child experienced a progressive decrease of abscesses with and after antibiotics. An uneventful second decrease in the neutrophil count was noted after one month (minimal at 260/mm^3), but later it remained steadily normal, and complete cutaneous healing was noted after three months.

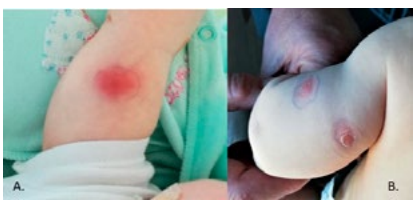

Figure 1: A. The nodule on the right arm at admission. / B. New nodules appeared the next day on the left arm and began to peel 7 days after admission.

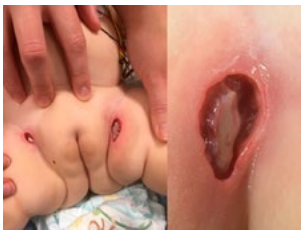

Figure 2: inguinal ulcerative necrotic lesions. Left ulcer close-up view.

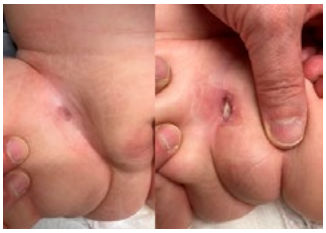

Figure 3: healing status at the time of discharge.

The second case is a 10-month-old girl who presented to the pediatric emergency department with a 4-day history of fever and two inflammatory necrotic lesions on both inguinal folds. She had a recent history of bronchiolitis and right otitis media. The cutaneous lesions rapidly progressed to deep ulcers with inflammatory margins and fibrin deposition (Figure 2). Blood samples initially showed an elevated CRP level (167 mg/L) and a decreased neutrophil count (940/mm3). Cellular immunity (dosage and types, subtypes of lymphocytes) and humoral immunity (dosage of all types and subtypes of immunoglobulins) were normal. Nitroblue tetrazolium blood test was unremarkable. Blood cultures remained negative. Ulcer swab cultures grew *P. aeruginosa* and confirmed the diagnosis of ecthyma gangrenosum. Piperacillin and tazobactam were administered intravenously for 10 days, and ciprofloxacin was continued per os until ulcer swab cultures were negative. Wound management consisted of physiologic solution cleansing, alginate foam, and silver dressing. Both ulcers healed completely within one month (Figure 3). Neutrophil counts remained consistently normal after discharge.

Discussion

Our two cases are similar in that they were immunocompetent children who had a viral infection prior to the *P. aeruginosa* skin infection and both developed mild neutropenia. They hadn't received antibiotics before and they didn't have sepsis or bacteremia proven by a positive blood culture.

In the first case, the eruption could be mistaken for erythema nodosum, but this hypersensitivity reaction is usually located on the lower limbs. It belongs to a broader group of cutaneous manifestations called panniculitis. Panniculitis is characterized by inflammation of the subcutaneous adipose tissue. It can be associated with infections, enzymatic disorders, post-steroid, malignant, lipoatrophic, physiological agents (cold panniculitis, injections, blunt trauma), subcutaneous fat necrosis of the newborn, sclerema neonatorum, selected syndromes (H syndrome, CANDLE syndrome) (3). When panniculitis is due to bacterial infection, a neutrophilic infiltrate is found throughout the fat lobules, sometimes extending into the dermis, and very often developing into an abscess. In erythema nodosum, the inflammation is localized in the septa of the hypodermis. Differential diagnosis with erythema nodosum or other causes of panniculitis can be challenging before evolution to abscess (4). Bacterial panniculitis may be caused directly by contamination in close proximity (an infected skin wound or a device containing a contaminated fluid) or by hematogenous spread (bacteremia) (4). Most cases of nodular panniculitis due to *P. aeruginosa* presented with bacteremia and in immunocompromised patients (5,6,7). Three cases of nodular panniculitis in the adult population have been reported in the absence of bacteremia but with the presence of an infected skin defect in close proximity (6). In our case, the child did not have a skin-breaking lesion before the appearance of the nodules. Given the presence of disseminated lesions, we postulate a blood, intestinal, or respiratory route rather than a cutaneous source. We therefore searched for an external source of *P. aeruginosa* contamination, but found none at home in the plastic bathtub, the tap used for filling, the aerosol mask and connector used for bronchitis treatment, and the "Babycook" device. However, the aerosol mask and connector were tested after being properly washed by the mother. Her twin brother and the family did not have any skin lesions. Azapagası et al. described a case of sepsis associated with subcutaneous nodules rapidly progressing to ecthyma gangrenosum in a 6-month-old infant with bilateral otitis media (5). In our case, the immune defense of the child, a transient, undetectable bacterial entry with less virulent associated factors could explain the less aggressive local evolution and the absence of ecthyma gangrenosum.

In the second case, ecthyma gangrenosum (EG) is a rare skin lesion caused by *P. aeruginosa* in 73.65% of cases, but other bacteria have been described such as *Escherichia coli, Citrobacter freundii, Klebsiella pneumoniae*, as well as some fungi (*Candida albicans, Fusarium*, and others) (8). The clinical presentation is hemorrhagic bullae or red nodules that develop into necrotic ulcers surrounded by an inflammatory halo within 12-24 hours, with a central black crust masking the deep ulcer. The mechanism is an uncommon vasculitis involving the media and adventitia of blood vessels in the dermis. It can be due to a hematogenous infection or primary cutaneous infection. This skin manifestation often heralds a *P. aeruginosa* sepsis, but may also reveal a predisposing condition such as malignancy or immunodeficiency (9). It has also been described in preterm infants, skin burns, and malnutrition. In our case, we cannot confirm the route of inoculation, but given preserved clinical condition of the child, we assume a cutaneous contamination due to local maceration of the napkin area. This maceration site may explain the absence of black crust.

The neutropenia present in both cases may be due either to the viral bronchitis, causing a transient neutropenia, or to a direct neutropenic effect of *P. aeruginosa*. *P. aeruginosa* is known to secrete toxins that reduce the number of neutrophils in the blood vessels and inhibit their migration to infected areas (10). We know that neutrophils are the predominant host defense against *P. aeruginosa*. Immune deficiency should be evaluated in all patients, especially chronic or cyclic neutropenia, hypogammaglobulinemia or immunodeficiency (acquired and primary), and malignancy (2). Cohen et al. discussed five cases of previously healthy children who presented with ecthyma gangrenosum (2). Two of them had a viral infection and neutropenia. The presence of a viral infection or recent antibiotic therapy are risk factors in immunocompetent children (2,9). Chusid and Hillmann postulated that viral infection affects the gastrointestinal mucosal barrier and subsequently reduces host defense (11).

The need for antibiotic therapy targeting *P. aeruginosa* and careful wound care is well known in EG. However, in the healing of abscess lesions, it is discussed in addition to surgical drainage (12). In the first case, the identification of *P. aeruginosa* was delayed due to the initial absence of abscesses and negative blood cultures. We were not able to assess the efficacy of the intravenous non-targeted antibiotics, but we noted an actual improvement with the surgical punctures and decided not to change the antibiotics until the results of the skin biopsy were available. Ciprofloxacin, although theoretically more appropriate, did not seem to improve the presumed spontaneous healing process after surgery and was not timely correlated with the previous decrease in blood inflammatory tests. In comparison, we know that the surgical treatment is more effective than antibiotic therapy alone in cutaneous abscesses caused by *Staphylococcus aureus* (12). It is important to perform this initial step of surgical drainage and bacteriologic sampling when faced with multiple abscesses.

Conclusion

Skin infections due to *P. aeruginosa* in healthy children have been described in recent years. Transient neutropenia induced by viral infection is a risk factor that allows *P. aeruginosa* to infect the child, but may also be a consequence of the direct action of *P. aeruginosa*. Immunodeficiency must always be excluded. Ecthyma gangrenosum requires prompt diagnosis and treatment with the appropriate antibiotic because of the serious skin injury and the potential association with sepsis. The diagnosis and the treatment of a panniculitis due to *P. aeruginosa* is more challenging as this entity is not well described. In our case, the surgical approach seemed more valuable than the antibiotics.

Conflict of interest

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

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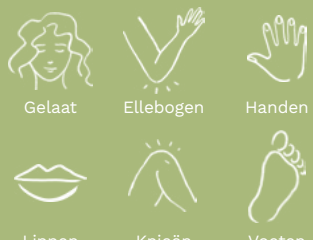

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Vomiting, constipation, and weight loss as presenting symptoms of primary hyperparathyroidism in a paediatric patient: a case report

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Keywords

Primary hyperparathyroidism ; Hypercalcemia ; Paediatrics ; Case report.

Abstract

A 15-year-old boy presented with vomiting, constipation and weight loss. Venous blood gas showed high ionised calcium. Serum calcium and parathormone were elevated. ECG showed signs consistent with hypercalcaemia. CT-scan of the parathyroid glands showed two nodules suspicious for adenoma. Symptomatic hypercalcaemia was treated with intravenous hyperhydration and bisphosphonates. Electrolyte imbalances were supplemented. Definitive treatment consisted of parathyroidectomy. There were no postoperative complications and calcium homeostasis was restored.

PHPT is uncommon in paediatric patients and can present with a diverse range of symptoms. Knowledge of its primary diagnosis and treatment is important for general paediatricians, especially in cases of hypercalcaemia.

Introduction

Primary hyperparathyroidism (PHPT) is a medical condition characterised by excessive production of parathormone (PTH), resulting in hypercalcemia (1, 2). It is an uncommon condition in children, with an incidence of 1 in 300,000. The aetiology includes a single parathyroid adenoma (60-92%), four-gland hyperplasia (0-40%), or rarely parathyroid carcinoma. PHPT can manifest with a broad spectrum of symptoms, including gastrointestinal, renal, psychiatric/neurological and bone manifestations. However, it can also present as an asymptomatic incidental biochemical finding or lead to end-organ damage. Given its rarity and diverse symptomatology, there is often a delay in the diagnosis of PHPT in children, who typically exhibit symptoms at the time of presentation (3). Although PHPT is infrequent in the paediatric population, the initial approach to diagnosis and the management of hypercalcemia in children remains crucial for general paediatricians. As cases of PHPT in children are scarce, the principles of care are mainly extrapolated from broader experience in adults.

Case presentation

Clinical presentation

A 15-year-old male patient with no relevant prior medical history presented at the emergency department with symptoms of persistent vomiting for two weeks and a total weight loss of eight kilograms (12% of his total body weight). He had a fever at the onset of the symptoms, which resolved spontaneously. He complained of vasovagal tendencies and constipation. There were no other complaints. He had recently travelled to Morocco but there were no other environmental risk factors. Metoclopramide, domperidone, paracetamol and ibuprofen were started by the family doctor without any effect. On referral, he showed signs of dehydration with a capillary refill of four seconds and abdominal pain in the right and left fossa.

Diagnostic assessment

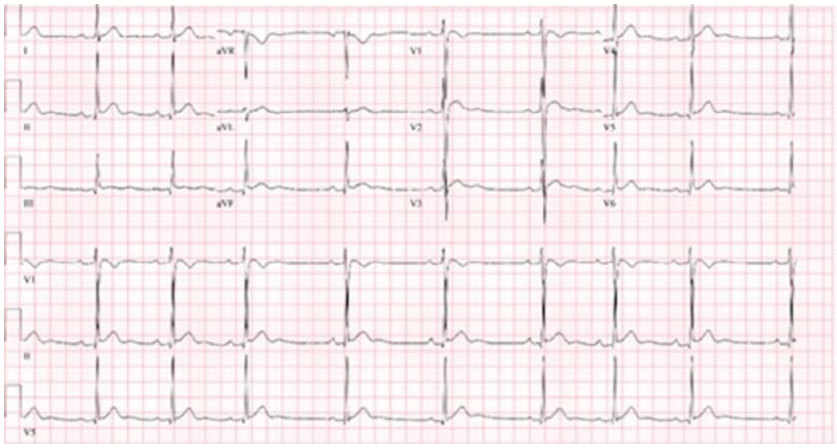
The venous blood gas was normal except for an ionised calcium of 2.34 mmol/L (1.20-1.32). Pending further laboratory results, a CT scan of the brain was performed, which showed no evidence of space-occupying lesions. Abdominal ultrasound visualised some enlarged lymph nodes in the right fossa and hyperechoic kidneys. Initial laboratory findings included a sedimentation rate of 20 mm/h (0-10), thrombocytosis of 457,000/µL (166,000-396,000), C-reactive protein 4.4 mg/L (<10); creatinine 1.26 mg/dL (0.60-1.10), urea 84 mg/dL (13-43), uric acid 9.8 mg/dL (2.4-7.9), with an estimated glomerular filtration rate of 48.2 mL/min/1.73m2 (>90) due to acute kidney injury caused by dehydration and hypovolemia. Calcium was 3.97 mmol/L (2.25-2.67), phosphorus 0.79 mmol/L (1.00-1.78), parathormone 374 ng/L (18.5-88.0), di-OH vitamin D 98.3 pg/mL (19.0-95.0). Lipase was 76 IU/L (12-53) with no other liver function tests abnormalities. Neuron specific enolase (NSE) was 33.1 µg/L (<16.3). Electrocardiogram at presentation showed ST elevation in V2 and V3 and a short QTc interval due to hypercalcaemia. CT scan of the parathyroids showed two nodules, one inferior to the left thyroid lobe and a smaller one posterior to the right thyroid lobe, suspicious for parathyroid adenoma.

Therapeutic intervention

In the emergency department, our patient received a bolus of normal saline after which a maintenance fluid infusion was started. Constipation was treated with a single enema and the initiation of macrogol. Because of the PHPT caused by multiple parathyroid adenomas and an increase in serum calcium, fluid administration was increased to hyperhydration at 3000 mL/m²/24h and pamidronate 1 mg/kg was given intravenously over a period of 4 hours. The evening after the second dose of pamidronate the patient developed a fever without clinical focus and with low inflammatory parameters. There was no need for antibiotic therapy. There was no

Figure 1: Electrocardiograms of our patient: A) ECG at presentation , B) ECG day two of hospitalisation.

A



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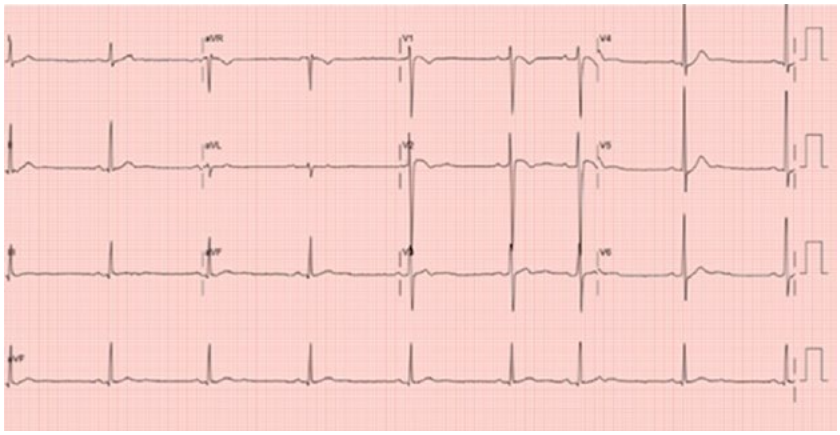


recurrence of fever. It was most likely caused by the administration of bisphosphonate. Two days later serum calcium normalised, phosphate decreased, for which supplementation with sodium phosphate was started. However, he developed paraesthesia of the left arm and the face, for which supplementation was increased. Because of further decrease in calcium after pamidronate there was need for intravenous calcium supplementation. He also developed hypokalaemia and hypomagnesemia, which required supplementation. After two days of intravenous calcium supplementation, switch to oral therapy was possible. With this regimen, the electrolyte imbalances were restored. Al supplements were weaned over a period of fourteen days, after which they could all be stopped. A surgical resection, parathyroidectomy, was planned three weeks after initial presentation. By the time of re-admission for surgery, he had developed hypercalcaemia again for which hyperhydration was restarted, resulting in stable calcium levels. After parathyroidectomy there was no need for intravenous calcium supplementation because of the hypercalcaemia on admission. One day after surgery calcium carbonate was started, (1000 mg, three times a day). After surgery he developed hypophosphatemia which resolved without supplementation. Parathormone normalised rapidly after parathyroidectomy. After two days he was discharged from the hospital with only calcium carbonate and paracetamol.

Follow-up and outcomes

Calcium was checked weekly after discharge. Supplementation could be weaned and was stopped ten days after surgery. Due to low vitamin D, vitamin D and calcium supplementation was restarted and continued to date. Genetic testing for MEN1 and MEN2A/2B were negative, a spinal radiograph showed a sclerotic aspect of the endplates of the thoracic and lumbar vertebrae with early signs of Rugger jersey spine morphology as seen in parathyroidism. Abdominal MRI scan was normal and showed no evidence of an insulinoma.

Discussion

Although PHPT is rare in the paediatric population, it is important for general paediatricians to have a clear understanding of its diagnosis and management. Early recognition and appropriate management of hypercalcaemia are crucial for optimal patient outcomes.

Asymptomatic PHPT is common in adult patients (1). In paediatric patients, symptomatic presentation is more frequent. It is therefore important to be aware of the symptoms caused by hypercalcaemia. Our patient presented with predominantly gastrointestinal complaints. Non-specific symptoms such as vomiting, weight loss and constipation. Acknowledging the combination of hypercalcaemia and elevated PTH was essential in our case. This led to the diagnosis of PHPT. We also screened for malignancy, even though hypercalcaemia caused by malignancy usually shows suppressed PTH (1).

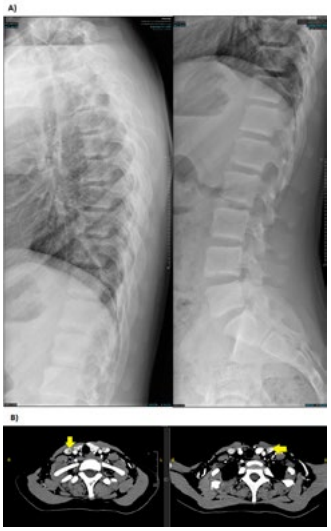
The initial assessment of hypercalcaemia should include a complete blood count, total and ionised calcium, PTH, phosphorus, renal function tests, 1,25-hydroxyvitamin D, 25-hydroxyvitamin D levels, bone density scan, and renal ultrasound (3). To distinguish PHPT from familial hypocalciuric hypercalcaemia (FHH) a urine calcium/creatinine ratio should be obtained. The UK guidelines also recommend genetic testing of all children with PHPT, including screening for CaSR and menin mutations (CASR and MEN1 genes). Additional tests should be performed if the former tests are normal, if there is a positive family history, or if anatomopathology shows an atypical adenoma, or carcinoma (3, 4).

The goal of medical management in paediatric patients with PHPT is to control the hypercalcaemia. The first step is hydration to restore euvolemia, this may include a bolus infusion followed by an infusion of three to four litres of normal saline over a period of 24-48 hours. Denosumab or bisphosphonates may be added to the treatment plan to inhibit bone resorption. Pamidronate 60-90 mg in 500 mL NaCl 0.9% over 2-4 hours can be given intravenously. Bisphosphonates can cause transient fever, flu-like symptoms, myalgias and transient hypocalcaemia and hypophosphatemia as seen in our patient. The result can be seen after four days and the effect can last from a few days to eight weeks. In addition, calcitonin can be used to achieve a more rapid fall in serum calcium. Loop diuretics can be associated tp induce calciuresis. Glucocorticoids should be considered for refractory hypercalcaemia. Ketoconazole should be considered in certain conditions. Calcimimetics can be given as adjuvant therapy when treating patients with bisphosphonates or denosumab. In case of severe refractory hypercalcaemia, dialysis should be started. Finally, mobilisation should be initiated as soon as possible (3-5).

The definitive treatment for PHPT is surgery: parathyroidectomy. Based on recommendations from the National Institutes of Health (NIH), all paediatric patients with PHPT should undergo surgery. The goal of this surgery is to remove the abnormal parathyroid glands and preserve the normal ones.

Figure 2:

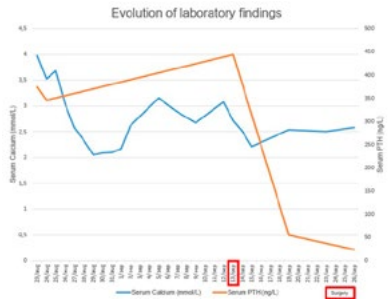
Medical imaging in the work-up of our patient with PHPT: A) Spinal radiography ; Rugger jersey spine describes the prominent endplate densities at multiple contiguous vertebral levels to produce an alternating sclerotic-lucent-sclerotic appearance, this mimics the horizontal stripes of a rugby jersey (6). B) CT-scan parathyroids ; nodule 1 (posterior to the right thyroid lobe, inferior part, 0.5x0.4x0.7 cm) and nodule 2 (inferior to the left thyroid lobe, 13x10x21 mm), shown with arrows.



Preoperative imaging is critical because of the aforementioned potential for abnormal localisation of the adenoma. Cervical ultrasound can be a first-choice investigation as it is easily accessible and non-invasive. A better investigation, especially for the detection of ectopic adenomas is a dual-phase technetium-99m-sestamibi scan with single-photon emission computed tomography/computed tomography (SPECT/CT) (2). In our case, this study was requested, but could not be performed because our patient had undergone a CT scan with contrast administration the day before. Therefore, ectopic adenomas could not be definitively excluded, although the CT scan did not show any mediastinal masses. CT has a sensitivity of 40-86% for detecting an adenoma. Another option would have been an MRI-scan with contrast, which has a sensitivity of 69-88%. This preoperative imaging will determine the surgical approach. If possible a minimally invasive procedure is the first choice because of its advantages: shorter operative time, lower hospital costs, shorter length of stay, and fewer episodes of postoperative hypocalcaemia (2).

Figure 3:

Evolution of laboratory findings in our patient. Serum calcium (in mmol/L), with normal values between 2.25 mmol/L and 2.67 mmol/L; and serum parathormone (in ng/L), with normal values between 18.5 ng/L and 88.0 ng/L. Both in function of time. Marked date (September 13th) is the date on which surgery, parathyroidectomy, was performed as definitive treatment for PHPT.



Our patient underwent a minimally invasive procedure, which resulted in a short hospital stay and no hypocalcaemia. The most common post-operative complication is hypocalcaemia (hungry bone syndrome), which requires supplementation. Follow-up of serum calcium is necessary to assess surgical outcome, as PTH levels may remain elevated despite normal calcium levels (2).

Conclusion

Primary hyperparathyroidism is a rare condition in the paediatric population and can present with a large variety of symptoms, from asymptomatic to end-organ damage. This case demonstrated that the presenting symptoms can be very non-specific and therefore a patient with these symptoms may present to any emergency department. Therefore, a general knowledge of the initial diagnosis and management of PHPT and hypercalcaemia is essential for all healthcare professionals.

Conflict of interest

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

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Capillary malformation – arteriovenous malformation syndrome (CM-AVM): a diagnosis not to be missed

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Keywords

CM-AVM, capillary malformation – arteriovenous malformation syndrome, case report, child.

Abstract

We present 2 patients with multifocal, small, round to oval, red and pink spots, some with a white halo. The diagnosis of capillary malformation - arteriovenous malformation syndrome (CM-AVM) was made based on their (common) characteristic clinical features and confirmed genetically by documenting a (different) germline heterozygous mutation in the *RASA1* gene. In patients with a genetically confirmed diagnosis of CM-AVM, we recommend that at least one brain MRI angiography be performed at baseline and on a low-threshold basis in individuals with symptoms to rule out intracranial arteriovenous malformations and arteriovenous fistulas.

Introduction

Capillary malformation – arteriovenous malformation syndrome (CM-AVM) is a subtype of capillary malformations, clinically characterized by the presence of multifocal, small, round to oval, pink or red spots, often with a white halo (1).

We present 2 recent cases from our department, in which the presumptive diagnosis was clinically made and genetically confirmed.

Case reports

Case 1

An otherwise healthy 4.5-year-old boy presented with multiple round to oval pink lesions 1-2 cm diameter, some with a white halo, on his face, neck and extremities (Figure 1). Some of these lesions had been present since birth, while others had appeared more recently. Based on the characteristic appearance of these lesions a presumptive diagnosis of CM-AVM syndrome was made.

When this diagnosis was explained to the parents, the 33-week pregnant mother reported having similar lesions on her trunk and extremities (Figure 2).

We performed peripheral blood genetic testing on the boy and his mother and found the same heterozygous nonsense mutation (NM_002890.2): c.2125C>T, p. (Arg709Ter) in the *RASA1* gene in both.

Case 2

A few months later, a 16-month-old boy presented with similar lesions. The pink oval macules on his back and buttocks had been present since birth, whereas the lesions on his arm and knee appeared more recently (Figure 3). Genetic testing documented a heterozygous deletion of 2 nucleotides (NM_002890.2): c.261_262del, p. (Gly89Argfs*22) in the *RASA1* gene.

Discussion

CM-AVM is an autosomal dominant disorder with a prevalence of approximately 1 in 100,000. In the current International Society for the Study of Vascular Anomalies (ISSVA) classification (last updated in 2018), CM-AVM is a subtype of simple vascular malformations (2) (Table 1).

Based on the underlying germline mutation CM-AVM is further subdivided into CM-AVM1 with a mutation in the *RASA1* gene (50% of cases) and CM-AVM2, caused by a mutation in the *EPHB4* gene (25% of cases) (3). On top of the germline mutation, a somatic "second hit" is required for the disease to develop. This explains the high inter- and intrafamilial clinical variability and the variable penetrance (1,4,5).

Both CM-AVM1 and CM-AVM2 are characterized by the presence of multifocal, small, round to oval, pink or red macules, often with a white halo. Some of these capillary malformations are already visible at birth, while others appear during the next few years of childhood.

However, CM-AVM1 and CM-AVM2 differ in some aspects. Annular lesions, lip telangiectasia, and Bier spots are found only in CM-AVM2, while associated fast-flow vascular malformations are more common in CM-AVM1 (10% of cases) than in CM-AVM2 (3% of cases). These fast-flow vascular malformations include intracranial and extracranial AVM, AVF and Parkes-Weber syndrome. Symptoms of intracranial AVM/AVF can occur already early in life, with life-threatening complications including hemorrhage, congestive heart failure, and neurological consequences.

In both cases presented here (and in the mother of case 1), MRI angiography of the brain and spine excluded the presence of intra- and extracranial AVM and AVF.

Recently ultrasound examination showed that CM in CM-AVM syndrome are also fast-flow lesions, suggesting that the capillary malformations in CM-AVM should be considered as pre-AVM. This implies that CM-AVM syndrome will have to be classified differently in the next ISSVA classification.

In the differential diagnosis, the skin lesions may be confused with other macular skin lesions such as café-au-lait macules and cutaneous mastocytosis. Other syndromes with cutaneous vascular malformations include Klippel-Trénaunay-Weber syndrome, Parkes-Weber syndrome, hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome), and Sturge Weber syndrome (6).

The presumptive clinical diagnosis should be confirmed by genetic testing of the patient and any at-risk family members. Routine performance

Table 1: ISSVA Classification 2018| International Society for the Study of Vascular Anomalies (2).

Simple vascular malformations	Causal gene
Capillary malformations (CM)	
Naevus simplex (aka "salmon patch", "angel's kiss" and "stork bite")	
Cutaneous and / or mucosal CM (aka "port-wine" birthmark)	
Nonsyndromic CM	*GNAQ*
CM with CNS and /or ocular anomalies (Sturge-Weber syndrome)	*GNAQ / GNA11*
CM with bone and / or soft tissue overgrowth	*GNA11 / PIKCA / HRAS / PIK3R1 / AKT*
Diffuse CM with overgrowth (DCMO)	*GNA11 / PIK3CA*
Reticulate CM	
CM of MIC-CAP (microcephaly-CM)	*STAMBP*
CM of MCAP (megalencephaly - CM - polymicrogyria)	*PIK3CA*
CM of CM-AVM	*RASA1 / EPHB4*
Cutis marmorata telangiectatica congenita (CMTC)	*GNA11*
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT)	*ENG / ACVRL1 / SMAD4*
Others	

of MRI angiography of the brain and spine is still a matter of debate. However, based on recent research documenting the potential life-threatening complications of associated AVM and AVF early in life, we recommend that brain MRI be performed at baseline and repeated in symptomatic individuals (7).

Treatment depends on the clinical manifestation of CM-AVM. For CM and telangiectasias that are only of cosmetic concern the patient may be referred to a dermatologist for pulsed dye laser treatment. For associated AVM or AVF, the risks and benefits of intervention must be considered, with embolization and surgery being the 2 interventional options. If the patient experiences cardiac overload, referral to cardiology required. For hemihyperplasia and/or leg-length discrepancies an orthopedist may be consulted, and an otolaryngologist for epistaxis.

Conclusion

In both cases presented here the diagnosis of CM-AVM was made on the basis of their (common) characteristic clinical features, and confirmed genetically, documenting a (different) germline heterozygous mutation in the *RASA1* gene. In patients with a genetically confirmed diagnosis of CM-AVM we recommend that at least a brain MRI be performed at baseline and on a low-threshold basis in individuals with symptoms to exclude intracranial AVM and AVF.

Conflict of interest

The authors have no conflict of interest to declare.

Financial support

There was no external funding.

Informed consent

Informed consent was obtained from both patients.

Figure 1: 4.5 year old boy with small, round to oval, pink macules on the face, neck, trunk and extremities.

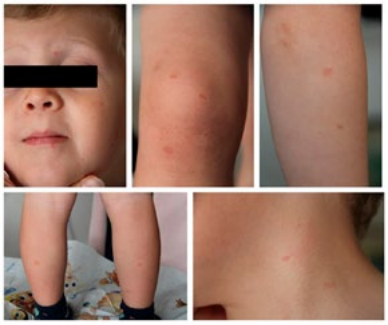


Figure 2: Mother of the 4.5 year old boy with round to oval, pink macules on trunk and extremities.

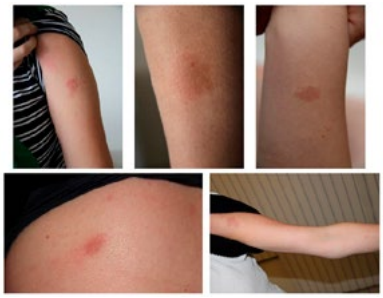
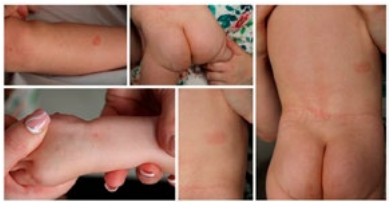


Figure 3: 16-month-old boy with pink macules on back, buttocks and extremities.



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Burden of Helicobacter pylori infection in children undergoing upper gastrointestinal endoscopy in Vietnam

PhD thesis presented on November 28th, 2023 at the Université Libre de Bruxelles, Belgium

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Keywords

Helicobacter pylori ; Antibiotic resistance ; Heteroresistance ; Eradication rate ; VacA genotypes ; CagA gene ; Biopsy-based tests ; Monoclonal stool antigen test ; Peptic ulcer disease ; Point mutations of 23S rRNA gene.

Helicobacter pylori, first described in 1983, is one of the most common chronic bacterial infections worldwide (1, 2). It is mainly acquired in childhood, persists for life if left untreated, and can cause chronic gastritis, peptic ulcers and, in some cases, contribute to the development of gastric cancer later in adulthood (3–5). Vietnam has a high prevalence of *H. pylori* infection in adults and children (70%) (2). The incidence of peptic ulcer disease in children is on the rise, while the eradication effectiveness is decreasing mainly due to high antibiotic resistance (6-10). The important questions in *H. pylori* research remain what is the true burden of *H. pylori* infection in terms of its prevalence, the incidence of H. pylori-associated gastroduodenal complications, its antibiotic resistance patterns, and the effectiveness of treatment in Vietnamese symptomatic children?

In this context, a prospective multicenter clinical series study was conducted at the two tertiary Children's Hospitals in Ho Chi Minh City, Vietnam's largest city to investigate the burden of *H. pylori* infection among Vietnamese children. Between October 2019 and May 2021, a total of 394 children were included with a mean age of 9.4 ± 2.5 years and 217 were girls (55%). Five gastric biopsies were obtained during endoscopy to perform *H. pylori* culture, histological examination, polymerase chain reaction (PCR) to detect urease gene (*ureA*), virulence genes (cytotoxin-associated gene A (*cagA*), vacuolating cytotoxin A (*vacA* genotypes)), and point mutations on 23S rRNA gene conferring clarithromycin resistance. Diagnosis of *H. pylori* infection was based on a positive culture or histological evidence in combination with a positive rapid urease test or a positive PCR assay of *ureA* according to internationally recognized criteria. An eradication treatment was prescribed for patients with confirmed *H. pylori* infection. After completion of therapy, a monoclonal stool antigen test was performed to evaluate the eradication status.

The first result showed a very high prevalence of *H. pylori* infection (80%). In particular, children living in Ho Chi Minh City had a higher prevalence than other neighboring provinces in Southern Vietnam. Level comparable to school-aged children in the community, peptic ulcer disease was more common than anticipated with a prevalence of 19% while nodularity was the most common endoscopic finding (60.7%) (11). Erosion and erythema accounted for 7.7% and 12.2%, respectively. Of children diagnosed with peptic ulcers, 93.8% were infected with H. pylori. Interestingly, among these patients, the vacA genotypes *s1/m1* (31.4%) and *s1/m1m2* (indicating mixed infections, 40.4%) were found to be the prevalent strains. Furthermore, cagA+ strains were significantly higher in children with ulcers while the vacA *s1/m2* genotype was more common in children without ulcers.

The second result addressed the question of antibiotic resistance. *H. pylori* culture with two separate antimicrobial susceptibility testing was positive in 123 patients. The minimum inhibitory concentrations were determined by the Etest method. A remarkably high primary antibiotic resistance was demonstrated, especially for clarithromycin (68.5%), levofloxacin (55.1%), and metronidazole (31.5%). Notably, amoxicillin resistance reached 25.8%, far exceeding the typical worldwide resistance rate of less than 5% (12). The multidrug resistance accounted for 67.7%. The rate of heteroresistance, the coexistence of susceptible and resistant strains in the same patient, was 6.5%. This is posing significant challenges for treatment since, if only one biopsy is taken in routine, the resistant strains can be missed when only the susceptible strains grow on a plate. Additionally, the prevalence of the A2143G point mutation on the 23S rRNA gene, associated with macrolide resistance, was frequent. However, no other point mutations were detected in Vietnamese children. Interestingly, this is the first report of heteroresistant strains emerging in Vietnamese children.

The third result focused on the accuracy of a monoclonal stool antigen test used to confirm *H. pylori* eradication after treatment in Vietnamese children and for epidemiological purposes. The stool test's sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 87.4%, 95.2%, 99.2%, 51.3%, and 88.4%, respectively. This indicates its useful role in detecting *H. pylori* in epidemiological studies and confirming the eradication post-treatment.

The last result investigated the effectiveness and tolerability of first-line regimens. Among 280 patients prescribed for eradication treatment, the

most commonly used regimen was standard triple therapy containing esomeprazole, amoxicillin, and metronidazole (EAM) (65.4%), followed by quadruple therapy containing esomeprazole, amoxicillin, metronidazole, and bismuth subcitrate (EAMB) (25.7%), and clarithromycin-based triple therapy (EAC) (4.6%). Eradication status was assessed at six weeks after completing the treatment regimens, using a monoclonal stool antigen test. Overall, the success rate was disappointingly low, with only 56.1% (78/139) in the per-protocol analysis and 27.9% (78/280) in the intention-to-treat analysis. The per-protocol eradication rate with EAMB was higher compared to EAM or EAC, but the differences did not reach statistical significance. Surprisingly, the study revealed a higher treatment success rate in boys, but lower rates in underweight children and those infected with cagA-positive *H. pylori* strains.

In summary, the findings of this work highlight the problematic prevalence of *H. pylori* infection and peptic ulcer disease in symptomatic children. A complex and high-level antibiotic resistance pattern, including multi-resistance and heteroresistance, necessitates an appropriate management strategy for *H. pylori* infection in Vietnamese children. This includes raising clinician awareness of accurate diagnosis, implementing strict antibiotic stewardship, and optimizing tailored treatment to improve eradication rates and reduce ulcer complications., reinfection, and antibiotic resistance.

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Exploring the Immune Horizon: Systemic Inflammatory Diseases in the Era of SARS-CoV-2 and Beyond

TPhD thesis presented on November 16th, 2023 at Ghent University, Ghent, Belgium

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Keywords

Mis-C ; Inflammation ; SARS-CoV-2.

Introduction

Fever is one of the oldest and most common symptoms in humans (1). Research on fever as a aetiology, outcome, or by-stander effect of disease has advanced our understanding of hundreds of clinical entities that are characterized by systemic inflammation.

The immune system plays a pivotal role in the induction and mediation of fever and in its recovery (2, 3). Soluble molecules, such as signalling messengers (cytokines) and cellular players, such as leukocytes, participate in complex, intertwined, and evolutionarily conserved relationships to promote health, avoid sickness, and repair damage to the body. The variability of immune responses largely determines inter-individual differences in the susceptibility to and severity of infection, autoimmunity, and other inflammatory diseases. Likewise, when the delicate balance between pro-inflammatory and counter-regulatory immune signals is disturbed, (hyper)acute, chronic, or recurrent systemic inflammation may develop (4). Patients presenting with such symptoms may carry specific genetic variants, or their diseases may be part of a growing number of heritable or non-genetic autoinflammatory (AID), systemic autoimmune (AI), or hyperinflammatory (HI) disorders.

Challenges, aims and objectives

The underlying cause of systemic inflammation remains undefined in a significant proportion of patients, for which *four important challenges* can be identified. First, the diagnosis of patients with systemic inflammation is challenging owing to the *non-specificity of symptoms* (including fever but also arthralgia, skin rash, lymphadenopathy, etc.). Second, routine laboratory tests, such as increases in white blood cells, C-reactive protein, and erythrocyte sedimentation rate are frequently abnormal both during and between symptomatic episodes. In line with clinical features, these routine tests frequently do not distinguish between types of inflammation. Owing to next-generation sequencing techniques, the diagnostic value of genetic research has skyrocketed, while its costs and turn-over time are rapidly tumbling. Nevertheless, as a third challenge, *genetic mutational screening* has limited sensitivity in most diseases characterized by systemic inflammation. Fourth, the therapeutic landscape in inflammatory disorders has broadened with the increasing availability of *biologicals*. These novel treatments allow for an unprecedented possibility to provide tailored therapy and improve morbidity and mortality of patients. However, access to these therapeutics has been impeded for multiple reasons, such as high procurement costs and restrictive reimbursement criteria. Because of diagnostic challenges, these therapies can be prescribed to the wrong populations, curtailing the usefulness of these compounds.

Because of these four challenges, large numbers of patients with suspected and even genetically proven inflammatory disorders are refrained from relevant risk stratification and appropriate treatment, which potentially causes irreversible organ damage and increased morbidity and mortality. This burdens not only patients but also the healthcare system. Hence, accurate, specific, and timely diagnosis is important for further patient management, including diagnostic investigations and subsequent personalized treatment to improve patient outcomes (5).

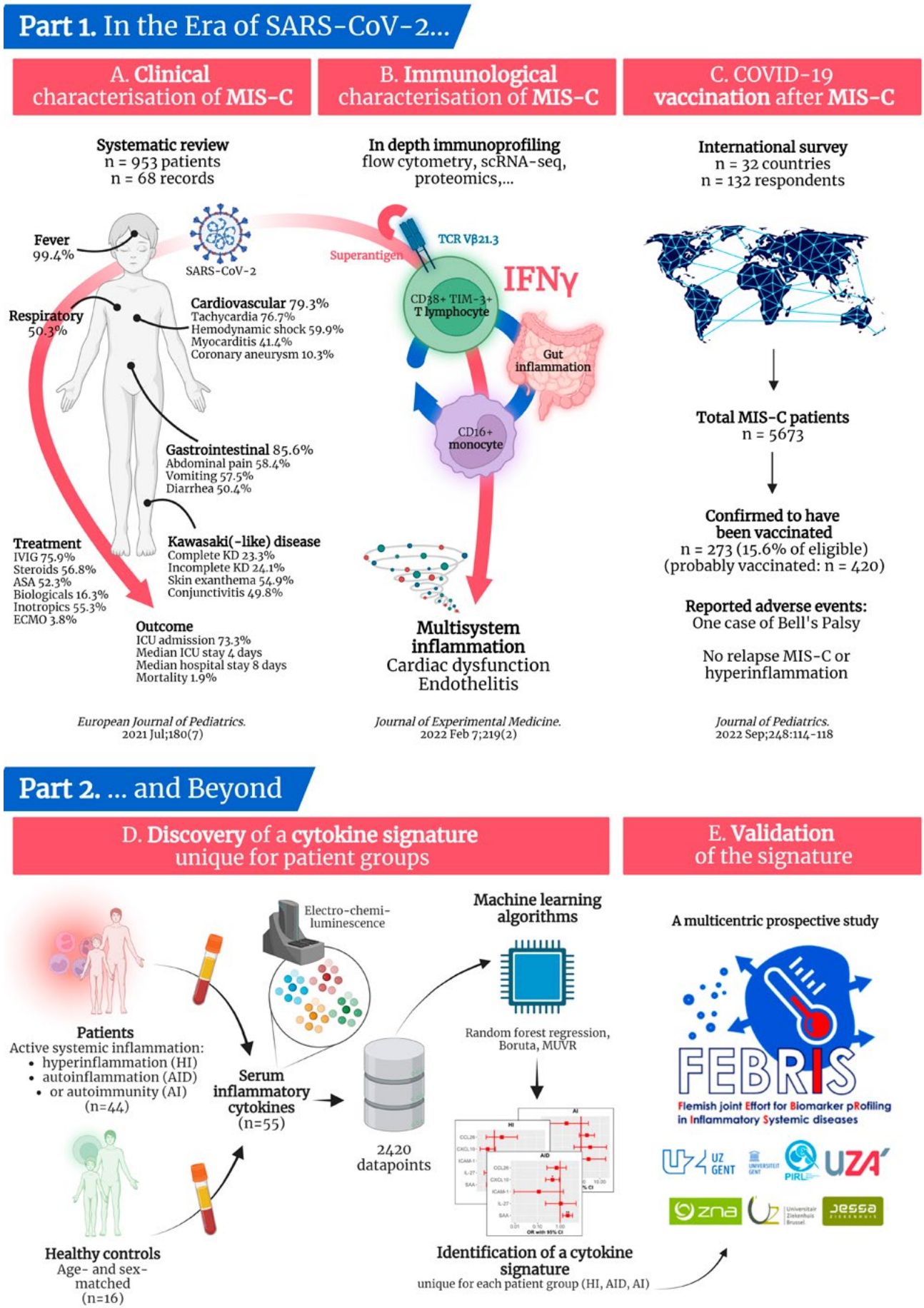
Faced with these problems, specific aims were identified. It was envisioned that *immunological characterization of patients presenting with systemic inflammatory conditions would advance our pathophysiological understanding* of these diseases, which would subsequently contribute to solutions that efficiently and effectively *tackle the aforementioned challenges*.

Part 1: A novel virus out for blood

The coronavirus 2019 (COVID-19) pandemic imposed unseen challenges for clinical research and care for patients. The series of events that took place from March 2020 onwards were unanticipated at the start of this thesis but would develop as a notable opportunity to study paediatric and adult immunopathology associated with febrile disease in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The occurrence of multisystem inflammatory syndrome in children (MIS-C), a novel and rare hyperinflammatory condition that affects children weeks after SARS-CoV-2 infection, was exemplary of this, making that – as it turned out - the lion's share of research during this doctoral research was dedicated to MIS-C.

First, a systematic literature review encompassing the first 953 published patients was performed (Figure 1A) (6). MIS-C was characterized as a heterogeneous febrile disease (99.4% have fever at presentation), mostly affecting school-aged children (median age of 8 years). Patients with MIS-C were found to frequently present gastrointestinal (85.6%) and cardiocirculatory (79.3%) manifestations, including that more than half of patients (56.3%) present with hemodynamic shock. Although

Figure 1: Overview of research performed during this PhD. Activities related to MIS-C research are shown in panels A, B, and C (in the Era of SARS-CoV-2). Research on blood cytokine signatures in patients with HI, AID or AI is outlined in panels D to E. Abbreviations used: acetylsalicylic acid (ASA), autoimmune disease (AI), autoinflammatory disease (AID), extracorporeal membrane oxygenation (ECMO), hyperinflammation (HI), intensive care unit (ICU), interferon gamma (IFNγ), intraveneous immunoglobulins (IVIG), Kawasaki disease (KD), multisystem inflammatory syndrome in children (MIS-C).



intensive care interventions (73.3%) were needed in the majority of cases, the associated mortality rate was less than 2%, and short-term outcomes were favourable. Comparing with historical Kawasaki disease cohorts or COVID-19 children, MIS-C patients were older, and represent more systemic inflammation, lymphocytopenia and thrombocytopenia, and higher markers of myocardial injury and coagulopathy. Finally, the sensitivity of MIS-C case definitions was studied. From our dataset, we established that the WHO definition was preferred, as it was more precise (its criteria encompass a proven association with SARS-CoV-2 and multisystem involvement), while comprising 97% of cases.

Second, an extensive immunological evaluation was performed in a cohort of 14 patients, all of whom clinically mirrored the description from the systematic review and whose blood was stored during maximal inflammation and early clinical resolution (7). In-depth immune profiling was carried out using flow cytometry, single cell RNA sequencing (scRNA-seq), T cell receptor repertoire analysis and serum proteomics, and findings were compared with healthy controls and adult patients with severe COVID-19 (Figure 1B). We established that MIS-C is associated with vascular endothelitis and gastrointestinal epithelial injury, as witnessed by increased blood levels of FABP2. Persistence of patrolling monocytes was found to differentiate MIS-C from severe COVID-19. MIS-C was characterized by an excess of IFNγ whereas serum concentrations of type I interferon were enhanced in severe COVID-19. T cells implicated in MIS-C pathogenesis were activated, functional, proliferative and cytotoxic. Cells harbouring the T cell receptor (TCR) Vβ21.3 were selectively expanded. This skewed TCR repertoire was characterized by promiscuous usage of Va and unbiased V(D)J recombination, indicating interactions outside the classical complementarity determining regions, akin to immunopathology driven by superantigens (SAg) such as toxic shock syndrome. Using a computational tool modelling intercellular communication, we confirmed IFNγ as a central cytokine. Finally, normalization of IFNγ, loss of TIM-3, and contraction of patrolling monocytes upon clinical resolution highlight their potential role in immunopathogenesis. Based on this study, we propose that MIS-C is characterized by gut epithelium damage and IFNγ-mediated inflammation driven by superantigen stimulated T cells. Putting a break on type 2 interferon might abrogate the systemic hyperinflammation. Emapalumab, a monoclonal antibody blocking IFNγ, or interfering with JAK/STAT signalling might represent attractive alternatives for rare cases of refractory MIS-C.

Because our immunological work-up suggested that a superantigen is involved in MIS-C pathogenesis, a relevant question to ask was whether re-exposure to viral proteins, for example, as with SARS-CoV-2 messenger RNA vaccines, could trigger relapses of hyperinflammation (8). By an international survey performed in 32 countries by the end of 2021, substantial variation in vaccine policy after MIS-C was established. Reassuringly, at that time, at least 273 patients had received a SARS-CoV-2 vaccine after MIS-C without reports of MIS-C relapses or other severe inflammatory side effects (Figure 1C).

Part 2: Moving Beyond SARS-CoV-2

With the near-vanishing of MIS-C in the final year of this doctoral thesis and in keeping with the original objectives of this thesis, the focus of research again shifted to patient populations suffering from a diverse repertoire of immune-mediated inflammatory diseases. We recruited 44 patients (median age 6.5y; 18/26 M/F) with active inflammatory disease of known clinical and/or genetic origin, including nine patients with HI, 27 with AID, 8 with systemic AI, and 16 healthy controls (Figure 1D). Fifty-five serum proteins were quantified and a multidimensional biomarker dataset was created. Its 2420 datapoints were mined by a combination of unsupervised machine learning algorithms (random forest classification, MUVR, and Boruta). From this discovery cohort, a five-plex signature (CCL26, CXCL10, ICAM-1, IL-27, and SAA) was purified that maximally separated patients by disease group. In our cohort, high ICAM-1 levels were associated with HI. In AID, a higher SAA was found, but relatively less CXCL10. A trend for higher CXCL10 levels and statistically low SAA levels was observed in patients with systemic AI. Using the five cytokines in logistic regression modelling revealed a high statistical significance for HI ($P=0.001$), AID, and systemic AI ($P<0.0001$). Predictive accuracy was excellent for systemic AI (AUC 0.94) and AID (AUC 0.91) and good for HI (AUC 0.81). Principal component analysis and unsupervised hierarchical clustering confirmed the separation of disease groups. In current experimental work, this cytokine signature is being prospectively validated in a multicentre cohort study that received FWO-TBM funding (FEBRIS) (Figure 1E).

Conclusions

The results from this thesis illustrate the potential benefits of clinical data synthesis and biomarker and immune cell profiling to characterize inflammatory diseases. It was shown that such an approach is feasible, appealing from a scientific point of view, and has clinical relevance, whether or not occurring in the context of novel diseases elicited by emerging viruses, or in a host of febrile diseases with extensive heterogeneity of immunopathology. Future work adopting similar and alternative tools for extensive immunological characterization should be facilitated in order to identify, interpret, and operate on the source, mediators, or downstream pathways in multiple febrile diseases and to offer additional clues regarding the diagnosis, staging, and prognosis, which will have a relevant impact on patients affected by these and other diseases.

Conflict of interest

None to be declared.

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The Belgian Journal of Paediatrics aims to connect all Belgian paediatricians with stimulating, scientifically sound, peer-reviewed articles.

The Journal is published quarterly. The journal is available in a printed version and electronic version. The electronic version is accessible through the website of the Belgian Society of Paediatrics at https://bvk-sbp.be/bjp.php.

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Editorship: All papers submitted to the *Belgian Journal of Paediatrics* are previewed by a member of the editorial team. Papers that are of sufficient novelty and impact for publication are forwarded for peer review. Other papers are returned without review after editorial decision. If one of the editors has a conflict of interest with a submitted manuscript or with the authors, he or she will abstain from the editorial board decision process.

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Complaints: Complaints regarding Editorial decisions have to be addressed to the Editorial Office bjp@belgjpaediatrics.com. All complaints will be analysed by the Editorial Team and a detailed answer will be provided.

Instructions for authors

Journal Sections

The *Belgian Journal of Paediatrics* publishes the following types of manuscripts:

Research Articles: Research articles are papers reporting the results of original research (clinical study, clinical trial, meta-analysis). Articles are limited to 250 words for the Abstract, 500 words for the Introduction, 1500 words for the Discussion and overall 4500 words (excluding abstract and references), 30 references and eight figures or tables. Note that BJP does not permit supplementary material, hence all of the methods and results must be described in the body of the manuscript. We ask authors to aim for accuracy, clarity and brevity and not to repeat results in detail that are clearly shown in a table or figure. We encourage the use of the EQUATOR reporting guidelines (https://www.equator-network.org). For clinical trials and clinical studies, the number and place of approval by an ethical committee has to be mentioned in the 'methods' section, as well as the registration number and the site of registry for clinical trials.

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- Systematic Review: A systematic review aims to answer a research question by a systematic literature search based on specific in and exclusion criteria and an evaluation of the methodological quality of the included articles. A systematic review may possibly be accompanied by a meta-analysis of the results. Authors are encouraged to use the PRISMA checklist (available from https://www.prisma-statement.org). A PRISMA style flow diagram has to be included (https://www.prisma-statement.org//PRISMAStatement/FlowDiagram).
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- Narrative Review: A narrative review gives an update on the current understanding of the pathophysiology, diagnosis and treatment of a disease, in a descriptive format. A narrative review may be illustrated by one or more case descriptions.

Case Reports: Case reports are limited to an abstract of 100 words, main text of 1500 words (excluding abstract and references), three tables and/or figures, and 10 references. Authors are encouraged to follow the CARE Case Report Guidelines (https://www.care-statement.org).

Photo quiz: The aim of this section is to stimulate visual recognition of clinical images that paediatricians may encounter in their practice. Clinical images include photographs of visible clinical signs, medical imaging, procedures, histological or cytological preparations. Submissions to this section should consist of 2 separate parts. The title of the manuscript should not mention the diagnosis. Manuscripts should be submitted without abstract. Keywords may be descriptive but must not contain the diagnosis. Make sure to remove any information that could identify a patient.

A first part with maximum 2 high quality figures without legends and a brief clinical history of maximum 500 words, but no mention of diagnosis. The last sentence should be 'What is the diagnosis?'

Second part: maximum 800 words for diagnosis, description of figures and short discussion and maximum 5 references.

Written informed consent for publication of the images should be obtained from the patient (if possible) and both parents or guardians. This should be added to the manuscript as a separate page(s).

Short Communications: Short Communications are limited to an abstract of 100 words, main text of 1500 words (excluding abstract and references), 1 table and/or 1 figure, and 10 references. They should be approved for publication by the editors.

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References: Arrange references in order of first appearance in the text. The references must be formatted according to Vancouver style (Quick reference guide available from: https://guides.lib.monash.edu/ld.php?content_id=48260115) .

Reference numbers in the text must be put at the end of the sentence, between brackets and inside the punctuation. Separate by a comma if more than one reference is cited, for example (1,5,8). For sequences of consecutive numbers, the first and last number of the sequence should be separated by a hyphen, for example (1-4). Only published papers or papers in press should be included in the reference list. Personal communications or unpublished data must be cited in parentheses in the text with the author's names, the source and year.

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For an article published online ahead of the print version: Bilal J, Riaz IB, Naqvi SAA, Bhattacharjee S, Obert MR, Sadiq M, at al. Janus Kinase Inhibitors and Risk of Venous Thromboembolism: A Systematic Review and Meta-analysis. Mayo Clin Proc. 2021 Apr 8:S0025-6196(21)00054-9. doi: 10.1016/j.mayocp.2020.12.035. Online ahead of print.

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Manuscripts must comply with the guidelines described in the instructions for authors. After submission, the manuscripts are first reviewed editorially. Manuscripts not prepared according to the instructions for authors will be returned to the author(s) before starting the review process.

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When resubmitting a manuscript after review the authors should indicate clearly their responses to the reviewers' comments. A document in which the reviewers' comments are answered point by point should be provided with the revised manuscript and include a copy of the original manuscript with track changes displaying the changes made. All co-authors should approve the revised manuscript version. The corresponding author should confirm approval in the point-by-point answer document. All components of the manuscript (point-by-point response letter, clean revised manuscript, manuscript with track changes, figures, tables, etc.) must be resubmitted even if no changes have been made at revision. To submit a revision, go to https://belgjpaediatrics.com/index.php/bjp/login and log in as an Author. Your submission record can be found by clicking on "View" → "Revisions" → "Upload file".

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Review of a submitted manuscript by at least two external and independent reviewers who are solicited by the editors. The reviewers' names will be blinded to the authors. Authors' identities are not blinded to the reviewers.

Reviewers should only agree if they feel qualified to review a manuscript and are able to return the review within a reasonable time-frame of maximum three weeks. If they cannot review, it is helpful to make suggestions for alternative reviewers.

Reviewers must refuse to review a manuscript in case of any potentially conflicting or competing interest.

Reviewers are requested to maintain confidentiality about the manuscripts and the information they contain.

Reviewers must provide a fair, honest, and unbiased assessment of the strengths and weaknesses of the manuscript. Comments to the authors will be passed in full to authors. The reviewers can also provide additional confidential comments to the editors, which will not be passed to the authors.

If the reviewer has concerns about misconduct during the elaboration or submission of the manuscript, he must notify the editor. This also applies to the case where the reviewer notices important similarities between the manuscript and a published article.

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Each year, a number of issues address a special chapter dedicated to a particular topic. Two guest editors, a Dutch-speaking and a French-speaking, are responsible for the content of these chapters.

A number of six manuscripts per chapter is expected. If more than six articles are needed to elaborate the topic of the chapter correctly, the editors can decide to spread the chapter over two issues.

The tasks of the invited editors are:

- To make choices of topics
- To invite authors
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