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Articles

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

Acquired primary hypothyroidism with profound anemia in an adolescent girl: a case report and a brief narrative review

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A qualitative study on the knowledge and attitude of primary school students towards pediculosis capitis

Case Reports

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A complicated course of meningitis caused by Haemophilus influenzae serotype a

Insights

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Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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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. **Indications thérapeutiques :** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration :** Posologie : **Tableau 1. Résumé de la posologie : Age lors de la première dose :** Nourrissons de 2 à 5 mois[a] : **Primovaccination :** Trois doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b,c]. - **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel[b,c]. • **Age lors de la première dose :** Nourrissons de 6 à 11 mois : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 12 à 23 mois : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 2 mois minimum. **Rappel :** Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel[c]. • **Age lors de la première dose :** Enfants de 2 à 10 ans : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • **Age lors de la première dose :** Adolescents (à partir de 11 ans) et adultes* : **Primovaccination :** Deux doses de 0,5 ml chacune. **Intervalles entre les doses de primovaccination :** 1 mois minimum. **Rappel :** Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]. • [a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne devrait pas être administrée audelà de l'âge de 24 *mois*. [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'autres doses de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration : Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications :** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Mises en garde spéciales et précautions d'emploi :** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vasovagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique «Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contreindication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation (voir rubrique 5.1 du RCP complet). Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles postvaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique (voir rubrique 5.1 du RCP complet). Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à *Neisseria meningitidis* du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Ce médicament contient moins de 1 mmol (23 mg) de sodium par dose, c'est-à-dire qu'il est essentiellement « sans sodium ». Traçabilité : Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **4.8 Effets indésirables :** Résumé du profil de sécurité : La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10 565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6 837 étaient des nourrissons et des enfants (de moins de 2 ans), 1 051 étaient des enfants (entre 2 et 10 ans) et 2 677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3 285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69 % à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44 % à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables : Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) - Fréquent : (≥ 1/100 à < 1/10) - Peu fréquent : (≥ 1/1 000 à < 1/100) - Rare : (≥ 1/10 000 à < 1/1 000) - Très rare : (< 1/10 000) - Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles). Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans) :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Troubles du métabolisme et de la nutrition : Très fréquent : troubles alimentaires. Affections du système nerveux : Très fréquent : somnolence, pleurs inhabituels, céphalée - Peu fréquent : convulsions (y compris convulsions fébriles). - Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections vasculaires : Peu fréquent : pâleur (rare après le rappel). - Rare : syndrome de Kawasaki. Affections gastrointestinales : Très fréquent : diarrhée, vomissements (peu fréquents après le rappel). Affections de la peau et du tissu souscutané : Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel). - Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans). - Peu fréquent : eczéma. - Rare : urticaire. Affections musculosquelettiques et systémiques : Très fréquent : arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité. - Peu fréquent : fièvre (≥ 40 °C). Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois). **Adolescents (à partir de 11 ans) et adultes :** Affections hématologiques et du système lymphatique : Fréquence indéterminée : lymphadénopathie. Affections du système immunitaire : Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques). Affections du système nerveux : Très fréquent : céphalée. - Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire). Affections gastrointestinales : Très fréquent : nausées. Affections de la peau et du tissu sous-cutané : Fréquence indéterminée : rash. Affections musculosquelettiques et systémiques : Très fréquent : myalgies, arthralgies. Troubles généraux et anomalies au site d'administration : Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise. Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois). Déclaration des effets indésirables suspectés : La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique :** Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance - Boîte Postale 97 - 1000 Bruxelles - Madou - Site internet : **www.notifieruneffetindesirable.be** - e-mail : **adr@afmps.be**. **Luxembourg :** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé - Site internet : **www.guichet.lu/pharmacovigilance**. **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ :** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie. **DATE D'APPROBATION DU TEXTE :** 09/2022 (v14). **MODE DE DELIVRANCE :** Sur prescription médicale.

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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Contents

- **Editorial** 5
- **Save The Date** 6
- **Articles**

Late onset neonatal Candida albicans osteomyelitis and arthritis: a case report and literature review
N. Kirat, K. Van Mechelen, J. De Beaumont, K. Vanden Driessche, K. Fabry, E. De Smet, L. Mahieu 11

Acquired primary hypothyroidism with profound anemia in an adolescent girl: a case report and a brief narrative review
A. Leeuwerck, J. Hellinckx, S. van der Straaten 19

Neurodevelopmental outcome of preterm infants with isolated grade I intraventricular hemorrhage: a matched case-control study
J. Dewulf, L. Breysem, K. Jansen, E. Ortibus, L. Thewissen, G. Naulaers 25

A qualitative study on the knowledge and attitude of primary school students towards pediculosis capitis
M. Daenen, J. Toelen 33

- **Case Reports**

Autoimmune pancreatitis in Children: Case Report and Review of the Literature
S. Deruyter, R. De Bruyne, L. Janssen 41

Familial chronic metallic mercury intoxication due to a broken sphygmomanometer, a case report
L. Callewaert, L. Steurbaut, L. Régal, A. Casteels, K. Anseeuw 45

A complicated course of meningitis caused by Haemophilus influenzae serotype a
H. Van Roeyen, I. Corthouts, S. Lampmann, B. Rutteman 50

- **Insights**

You have a (paediatric) research idea: How to fund it in Belgium? The 6 Be's of grants-woman-man-ship.
Pierre R. Smeesters 54

- **Made In Belgium**

Optimizing diagnosis in drug hypersensitivity
Marie-Line M. van der Poorten 59

- **Paediatric Cochrane Corner**

Prognosis following a first unprovoked seizure
A.-C. Vanhove, T. Bekkering, F. Cools 61

- **Editorial Policy** 63

Mustela®

Voor de **hele familie**

RESPECT OCEAAN

BIO GEÜPCYCLEDE AVOCADO'S

De juiste zonnebescherming

Hoge tolerantie voor baby's en kinderen, geschikt vanaf de geboorte*
en voor zwangere vrouwen in geval van onvermijdelijke blootstelling

*Baby's die de neonatologie hebben verlaten - Respect oceaan: filters overeenkomstig de Hawaïaanse regelgeving, zonder oxybenzone en octinoxaat. Bio geüpcyclede avocado's afkomstig van duurzame landbouw en verantwoorde bevoorradingsketen

Editorial

Artificial intelligence and natural imagination

April 2, the day we are writing this editorial and finalizing this issue of the Belgian Journal of Paediatrics, is the International Children's Book Day. This event exists since 1967 and is celebrated on the birthday of Hans Christian Andersen, the famous Danish storyteller. The goal of this initiative was to fight against illiteracy by transmitting the taste for reading. Through this editorial and the cover by Serge Ernst, we want to join this celebration. We want to highlight the pleasure and the benefits that books can bring to the child's development and to promote place we give to imagination and creativity.

In 2023, artificial intelligence (AI) and the famous ChatGPT are making the headlines of many newspapers. This system exploits vast amounts of text data, such as news articles, books, and online conversations to develop a predictive analysis of language that makes it capable of generating text and answer based on the context and the intention of the interlocutor. While the efficiency and the possibilities offered by this system are praised, more than 1100 experts in the field ask for a moratorium on the AI based developments. They denounce an uncontrolled race to develop and deploy ever more powerful AI systems that no one, not even their creators, can reliably understand, predict or control. In an open letter, they raise questions about the relationship between humans and machines: *"Should we automate all tasks, including fulfilling ones? Should we develop non-human brains that could eventually be more numerous, more intelligent, [...] and replace us? Should we risk losing control of our civilization?"*

We certainly need to consider the place we give to machines and how they can be instrumental in our future lives, but we must also make sure to keep and to nurture our ability and our freedom to create, to imagine, to innovate. Human beings organize themselves and evolve based on analytical thinking, on a logic built on observation and previous personal and historical learning and experiences. This ability has allowed us to make great advances and to give the human species a privileged place on earth. We must also recognize the contribution of another form of consciousness in our collective development and personal balance. Our perception of the outside world and of ourselves depends also on imagination, a way of thinking that is less linked to the space-time dimensions and is more related to emotions and intuitions. Imagination is natural and innate. It is present in children, and they switch very easily from one mode of thinking to the other. All of us, as pediatricians or parents, have seen for instance, children playing with plastic plates as if they had suddenly become great cooks. In care, we also appreciate how this imagination can be a resource that help to overcome the challenges of illness, hospitalization, or treatment. At a personal level, we also have experienced how an evening at the movies or simply reading a good book can help us to take a step back, gain perspective, and inspire us in our daily lives. On a broader scale, the ability to step outside of pre-established logic, to approach a situation or a problem differently, is recognized as a source of innovation and progress. To take an example from psychiatrist and explorer Bertrand Picard: *"In the field of lighting, it was not the candle makers who invented the light bulb"*.

Creativity is the first point that Pierre Smeesters develops in his Insights article on research in Belgium. Through 6 "Be" tips, he gives interesting perspectives to increase the chances of founding and success in the research process. Two original studies are also published in this issue: a matched case controle study about neurodevelopmental outcome of preterm infants with isolated intraventricular hemorrhage by Jantien Dewulf and colleagues and an analysis of knowledge and attitude of primary school students towards pediculosis capitis by Myrten Daenen and Jaan Toelen. We are also proud to report several clinical cases decribed by colleagues from all over the Belgian pediatric community: a late onset neonatal candida albicans osteomyelitis and arthritis, an acquired primary hypothyroidism with profound anemia in an adolescent girl, an autoimmune pancreatitis, a familial chronic metallic mercury intoxication due to a broken sphygmomanometer and a complicated meningitis caused by Haemophilus Influenzae serotype A. Our "Made in Belgium" section summarized the Ph.D thesis of Marie-Line M. van der Poorten (University of Antwerp) about the optimization of drug hypersensitivity diagnosis. In front of this increasing health problem, she further investigated the cut-off of specific Ig E quantification and the optimal modalities for skin tests and drug provocation test. The Paediatric Cochrane Corner discusses the prognosis of first unprovoked seizures.

We also take the opportunity of this editorial to congratulate and thank the organizing scientific committee of the 51st edition of the annual SBP/BVK congress. The team chaired by prof Inge Gies, UZ Brussels, set up a very attractive and varied program with the challenging central theme: "Climate Changes in Pediatrics: from Society to Environment". We thank the participants, speakers, and all contributors to this great annual event.

In our next edition, we will highlight some of the scientific achievements of the BVK/SBP, officially founded one hundred years ago, on Sunday January 14th 1923. History is indeed the memory of our civilization and helps us to reflect nuanced about the present and the future, not only of our profession but of our life in general.

We wish you an enjoyable reading of this issue of the Belgian Journal of Paediatrics. We hope that it will contribute to stimulate your pediatric knowledge and creativity!

Christophe Chantrain and Marc Raes

Uw vragen of commentaar
Vos questions ou commentaires

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Save The Date

Saturday **May 6th 2023**

CHILDHOOD IMMUNOLOGY

SYMPOSIUM

"Can we influence external triggers in order to prevent airway diseases?"

Organised by **the Clinical Division of Pediatrics, UZ Leuven** and **Allergy and Clinical Immunology Research Group, KU Leuven**

Program

Moderator: Prof. dr. Dominique Bullens

9u-9u30: Registration and coffee

9u30-9u40: Welcome and introduction

9u40- 10u55: **Part I**

- What's new in GINA 2022?
  Prof. dr. Mieke Boon (UZ Leuven)
- Immunologic screening in children with recurrent upper respiratory tract infections: when to consider pneumococcal antibody deficiency?
  Dr. Heidi Schaballie (UZ Gent)
- Anaphylaxis anno 2023.
  Prof. dr. Françoise Smets (UC Louvain)

10u55-11u20: Coffee break

11u20-13u00: **Part II**

- External triggers inducing epithelial cell damage in exercise induced bronchoconstriction.
  Drs. Janne Goossens (KU Leuven)
- Green space and airway diseases.
  Prof. dr. Raf Aerts (Sciensano)
- Rise in allergic diseases.
  Dr. Sven Seys (KU Leuven)
- Early life exposure to plasticizers and childhood allergies and asthma.
  Prof. dr. Greet Schoeters (U Antwerpen)

13u00: Lunch + discussion

Registration required
marleen.jannis@uzleuven.be
€15: Lunch included (<35 years: free)
BE43 4320 0172 2101
Communication: Childhood Immunology + (sur)name + RT0389

Location
Thermotechnisch Instituut
Aula van de Tweede Hoofdwet
KU Leuven
Kasteelpark Arenberg 41
3000 Leuven

Accreditation ethics & economics is requested

KU LEUVEN

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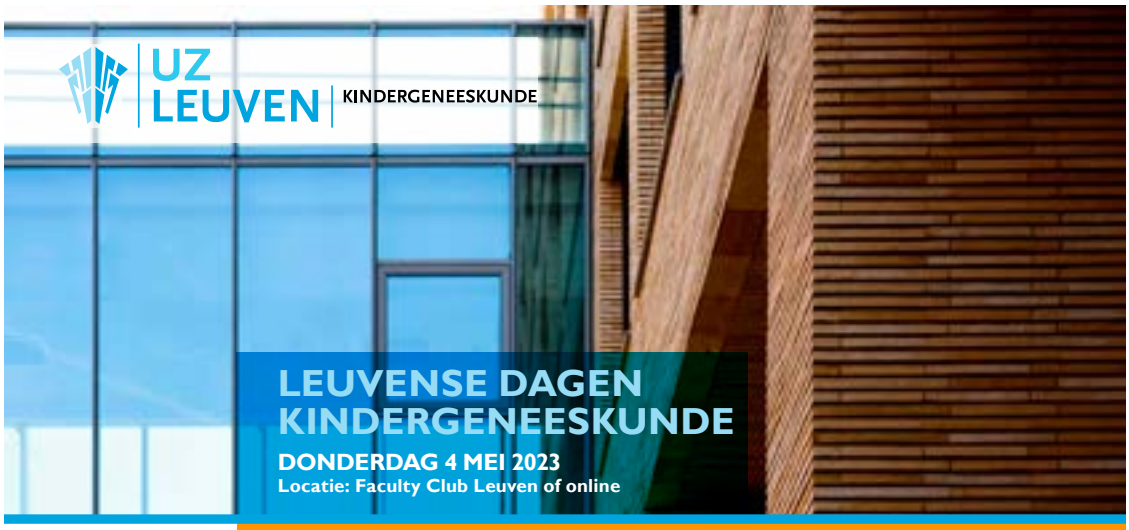
Save The Date



UZ LEUVEN | KINDERGENEESKUNDE

LEUVENSE DAGEN KINDERGENEESKUNDE

DONDERDAG 4 MEI 2023
Locatie: Faculty Club Leuven of online

DONDERDAG 4 MEI 2023: VOORMIDDAG

9.30 - 9.55 uur	Onthaal (met koffie)	
9.55 - 10.00 uur	Welkom	
10.00 - 11.15 uur	**State of the art I** - *voorzitter: prof. dr. Gunnar Buyse*	
	10.00 - 10.25 uur	**Neonatale hypoglycaemie** *dr. Anneleen Dereymaeker en prof. dr. Daisy Rymen*
	10.25 - 10.50 uur	**Sondevoeding in de mix** *prof. dr. Ilse Hoffman*
	10.50 - 11.15 uur	**'Wekelijkse kost': kooktips voor tolerantie-inductie bij kippenei-allergie** *prof. dr. Dominique Bullens*
11.15 - 11.45 uur	Koffiepauze	
11.45 - 12.35 uur	**State of the art II** - *voorzitter: prof. dr. Heidi Segers*	
	11.45 - 12.10 uur	**Wanneer een pneumonie gecompliceerd wordt** *prof. dr. Marijke Proesmans*
	12.10 - 12.35 uur	**De ductus arteriosus: van foetus tot zuigeling** *prof. dr. Marc Gewillig*
12.35 - 13.45 uur	Lunchpauze	

Accreditering (rubriek 3) werd aangevraagd.

DONDERDAG 4 MEI 2023: NAMIDDAG

13.45 - 15.15 uur	**Clinical cases of the year** - *voorzitter: prof. dr. Jaan Toelen*	
15.15 - 15.45 uur	Koffiepauze	
15.45 - 17.45 uur	**Effecten van pandemie op gezondheid en welzijn van kinderen en jongeren** *voorzitters: prof. dr. Marijke Proesmans en Trudy Havermans*	
	15.45 - 16.15 uur	**Levenstevredenheid van lagere schoolkinderen in Vlaanderen voor en tijdens de coronapandemie** *Jasper Dhoore, JeugdOnderzoeksPlatform (JOP); Vakgroep Sociologie – Onderzoeksgroep TOR*
	16.15 - 16.45 uur	**Effecten van de pandemie op de schoolse prestaties en mentale gezondheid van jongeren** *prof. Kristof De Witte, Economie en Bedrijfswetenschappen KU Leuven*
	16.45 - 17.15 uur	**Effecten van de pandemie/maatregelen op eetstoornissen bij onze jeugd** *An Vandeputte, coördinator Eetexpert vzw*
	17.15 - 17.45 uur	**Paneldiscussie**
18.00 uur	Prijsuitreiking clinical cases en aperitief (Infirmerie) Diner (Infirmerie)	

Accreditering voor Economie en Ethiek (rubriek 6) werd aangevraagd.

INSCHRIJVEN

Voor 1 mei via https://forms.gle/6u87MPWAyHvSJQac8

Inschrijving voor deelname is verplicht.

Het congres vindt plaats in de Faculty Club, Groot Begijnhof 14, 3000 Leuven, maar kan ook online gevolgd worden.

Meer info: secretariaat kindergeneeskunde, tel. 016 34 38 34 of mail an.devroey@uzleuven.be.

Ontwerp & realisatie: dienst communicatie UZ Leuven | 23EV0025

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

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Keywords

osteomyelitis; arthritis; invasive candidiasis; Candida albicans; neonate; beta-D-glucan

Abstract

Objectives: Invasive candidiasis in neonates is an important cause of morbidity and mortality in the neonatal intensive care unit. Well known complications from invasive Candida albicans infections include kidney infections, endophthalmitis, endocarditis, meningitis and dermatitis. Candida arthritis and osteomyelitis have been reported less frequently, but have been observed months to even years after systemic antifungal therapy for candidiasis was completed.

Case report: We present a preterm neonate with a fungal proven central line associated infection, treated with antifungal therapy, who developed secondary a delayed presentation of osteomyelitis and arthritis as a complication of the Candida albicans fungemia. The infection was suspected by a positive serum beta-D-glucan (BDG) test and the diagnosis of invasive Candida infection was proven by tissue culture. Prolonged treatment during six months with oral fluconazole cured the infection in this case. A literature review revealed limited guidance on how to manage this complication in neonatal and pediatric patients. Previously described cases received amphotericin B more often than fluconazole, but both options appear to be curative. However, compared to amphotericin B, fluconazole has less adverse effects, such as nephrotoxicity, has better tissue penetration and can be administered orally.

Conclusions: Skeletal infections secondary to Candida albicans infections in the neonatal population are serious, but prolonged oral treatment is curative in most cases. It is important to raise awareness for the long lag time between initial infection and secondary complication, so these newborns receive a close follow-up. The beta-D-glucan serum antigen tests can be contributive to a timely diagnosis.

Introduction

Invasive *Candida* infections are regularly being encountered in premature infants admitted to the neonatal intensive care unit (NICU). The overall incidence is approximately 5 to 10 cases per 100.000 live births (1,2). The incidence of invasive fungal infection ranges from 2 to 4% in very low birth weight (<1500g) and from 4 to 16% in extreme low birth weight (<1000g) infants [3]. This has been attributed to many underlying factors including the improved survival of very low birth weight infants, the use of central venous catheters, prolonged administration of parenteral alimentation, the increased use of corticosteroids and broad-spectrum antibiotics, surgery and damaged or abnormal skin barrier (4-7). Disseminated disease mostly prompts simultaneous renal, cerebral, cardiac, dermatological or ophthalmic complications, whereas osteoarticular involvement is rare (6,8). Over the past few decades a small number of case reports presented delayed arthritis and osteomyelitis as a rare complication of neonatal *Candida* infection. Most cases presented after treatment completion for the initial infection (4-6,9,10). In this case report we present a premature infant with *Candida* septicemia, who developed arthritis and osteomyelitis several weeks after completion of antifungal therapy with fluconazole. We will also discuss pathogenesis, predisposing factors, diagnostic tools and treatment options based on our experience with this case and current knowledge provided by published literature. With this case report we want to summarize what is already known about this subject and propose a treatment regimen for *Candida* arthritis based on our findings.

Case report

A female infant, the first member of a dichorionic diamniotic twin with a birth weight of 840 gram (10th percentile), was born at 27 weeks of gestation to a multiparous mother by spontaneous vaginal delivery. The mother was pre-treated with one dose of penicillin for prolonged premature rupture of membranes. Only one dose of antenatal corticosteroids was administered after onset of preterm labor. The Apgar scores were 5 and 6 at 1 and 5 minutes respectively. At birth insufflation breaths and continuous positive airway pressure (CPAP) was given. There was no need to administer surfactant. An umbilical venous catheter was placed at a peripheral position to administer parenteral nutrition. The infant was empirically treated for 48 hours with penicillin and amikacin intravenously (IV) for possible early onset sepsis. Meconium culture was negative for *C. albicans,* suggesting no risk for invasive candidiasis. Fluconazole prophylaxis was therefore not started in this infant. Initial blood cultures were negative and C-reactive protein (CRP) remained low. A peripheral intravenous central catheter (PICC) was placed on the second day of life (DOL) to ensure parenteral nutrition. On DOL 9 the infant presented with progressive respiratory insufficiency requiring endotracheal intubation. A sepsis work-up was initiated and the PICC was removed. Flucloxacillin and amikacin IV were started to treat a suspected late onset sepsis. Blood tests revealed a slightly elevated white blood cell count (WBC 11,4 x10E9/L; normal 9 – 24x10E9/L) and a normal CRP level of 5,4 mg/L (normal < 20 mg/L). Cultures of blood and tip of the central catheter turned positive within 24 hours for *C. albicans.* Maternal cervical cultures turned also positive for *C. albicans.* Antibiotics were discontinued and treatment with fluconazole IV was initiated. A starting dose of 25 mg/kg was administered followed by a maintenance dose of 12 mg/kg every 72 hours. On DOL 14 treatment was changed to a dose of 12 mg/kg every 48 hours. Urine and cerebrospinal fluid cultures remained negative. Ultrasound (US) exams of

the brain, abdomen and kidneys were normal, nor were there signs of endocarditis nor thrombi on echocardiography. Ophthalmologic examination was also normal. Clinically the patient improved with this antifungal treatment and was extubated at DOL 29. Fluconazole was given intravenously for seven consecutive days and the same dose was continued orally for 14 days after the first negative blood culture was obtained on DOL 17. Altogether the infant was treated for 21 days with fluconazole. On DOL 55 she developed a painful and swollen right knee with an impaired ability to extend the limb. Imaging studies of the affected knee (ultrasound, radiographs and magnetic resonance imaging (MRI) (Figure 1) showed signs of osteomyelitis and synovitis of the right knee and right distal femur. The patient was started empirically on IV flucloxacillin, amikacin and fluconazole for presumed septic osteoarthritis. Synovial fluid cultured stayed negative. Blood culture turned positive for a multi-sensitive *Escherichia coli*, so the antibiotic regimen was switched to amoxicillin-clavulanic acid. Because of the previously proven *C. albicans* fungemia a beta-D-glucan (BDG) blood test was requested which suggested the presence of fungi (244 pg/ml; normal <60 pg/ml). Ten days after initiation of treatment the swelling had not subsided. A second aspiration and joint lavage was performed. Cultures from this synovial fluid were positive for *C. albicans*, which was sensitive for fluconazole. A second screening for disseminated disease with cerebral MRI, echocardiography and abdominal US, was normal. New urine and cerebral fluid cultures also remained negative. Follow-up radiographs at DOL 57 showed a bilateral distal diametaphysical femur fracture and reactive periost (Figure 2). The right proximal tibia showed a fracture along with osteolysis located in the medial metaphysis. Radiographs of the wrists were taken and showed osteopenia and delayed ossification. These findings could be explained by underlying metabolic bone disease and rickets due to vitamin D deficiency (8 ng/L; normal >30 ng/L) and hyperparathyroidism (PTH 87 ng/L; normal 14 – 65 ng/L). Adequate suppletion of vitamin D, calcium and phosphorus was started. Because of the reoccurrence of the fungal infection a screening for immunodeficiency was performed; blood levels of IgG, IgA, IgM and complement C3 and C4 were all normal. Antibiotic and antifungal treatment were administered intravenously for 7 days and continued orally. Clinically and biochemically our patient improved and antibiotic treatment was discontinued after three weeks. Fluconazole (6 mg/kg once per day) was continued orally for 6 months. Radiographic follow-up after 3 months showed improved ossification and healing of the previously seen fractures (Figure 3). After discharge from the NICU laboratory monitoring showed normalization of PTH, calcium and phosphorus. Suppletion was therefore discontinued. The patient was lost to follow-up due to international relocation of the family. Therefore, no data for growth or long-term outcome were available.

Literature review

Methodology

A comprehensive literature search was undertaken using the PubMed database from their inception to December 2022. English language restriction was applied. Search terms included various combinations of the following keywords: “neonatal candidiasis”, “neonatal osteomyelitis”, “neonatal arthritis”, “neonatal candida arthritis”, “neonatal *Candida* treatment” and “neonatal Candidiasis treatment”. Furthermore, a manual review of reference lists from key articles was performed and studies who fulfilled our inclusion criteria were selected. Articles in which neonates and infants developed osteomyelitis after a *Candida* sepsis were included. Most of these articles were case reports or small case series. The most recent case report was published in 2013 (4).

Our search revealed 12 relevant articles describing a total of 87 pediatric cases of osteomyelitis due to *C. albicans* since 1976, of which 48 concerned infants admitted to the NICU.

Pathophysiology

C. albicans remains a common cause of nosocomial bloodstream infections in children and neonates due to numerous risk factors associated with prematurity (4,7,9,11) (Table 1). Published case reports similar to our case, confirm that *C. albicans* osteomyelitis commonly runs with an indolent course, resulting in delayed diagnosis and treatment (4). The pathogenesis of *Candida* arthritis/osteomyelitis remains unclear. Harris M.C. described three cases, similar to our case, in which three infants suffered from *Candida* arthritis after a completed treatment course for systemic candidiasis (6). Preterm neonates often have a prolonged need of central lines due to the inability to feed orally. These central lines easily become colonized. *Candida* species have a special ability to adhere on endothelial and prosthetic surfaces. Formed biofilms can become the source of not only systemic spread but also end-organ complications, such as osteomyelitis (11). The indolent course of skeletal involvement may be related to a new infection or a relapse due to incomplete treatment of the initial infection. It is hypothesized that during initial *Candida* infection or mucosal reinfection, seeding of joints occur. According to Swanson et al. the infection occurs primarily in joints where the metaphysis is constraint within the joint capsule. Infection originates hematogenous and seeds either in the synovium or metaphyseal vessels, causing arthritis (9). Clinical symptoms were suppressed but the infection not eliminated due to antifungal therapy (6,11). In most cases osteomyelitis or arthritis occurred within months of initial infection. Only two articles describe a case of in immunocompetent patient who developed *Candida* arthritis one year after initial fungemia. Both patients were infants at the time of initial *Candida* infection (4,9). Swanson et al. compared DNA analysis of the initial bloodstream isolate and of the isolate from the infected joint of this patient. The strains were identical by all typing methods used in this article. Control specimens from other patients collected during the same period showed different electrophoretic karyotyping whereas both samples from this case patient were identical. This could support the theory of organ inoculation during the initial infection followed by an extended dormant period. How reinfection was triggered remains unclear (9).

Table 1: Risk factors for Candida infections in NICU patients.

Risk factors for Candida infections in NICU patients
Candida colonization (11, 15)
Indwelling catheters (4, 11, 15)
Extreme prematurity and/or very low birthweight (4, 9, 11, 15)
History of sepsis or usage of broad spectrum antibiotics (e.g. cephalosporines/carbapenem or >2 different antibiotics) (4, 11, 15).
Prolonged parenteral feeding (> 5 days) or intralipid use (>7 days) (4, 9, 11, 15)
Underlying immunodeficiency or malignancy (4, 9)
Skin immaturity or damage (9,11)
Use of antacids (15)
Use of corticosteroids (11)
Mechanical ventilation (11,15)
NEC or other gastrointestinal disease, abdominal surgery (9, 11, 15)
Male gender (11)
Thrombocytopenia (< 150x10E9/L) (11)
Cross transmission by health care professionals (11)

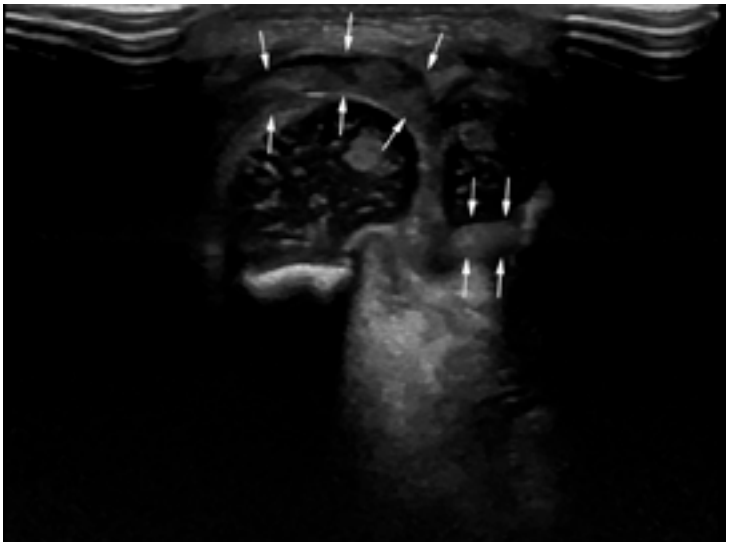
Management

Diagnostic work up

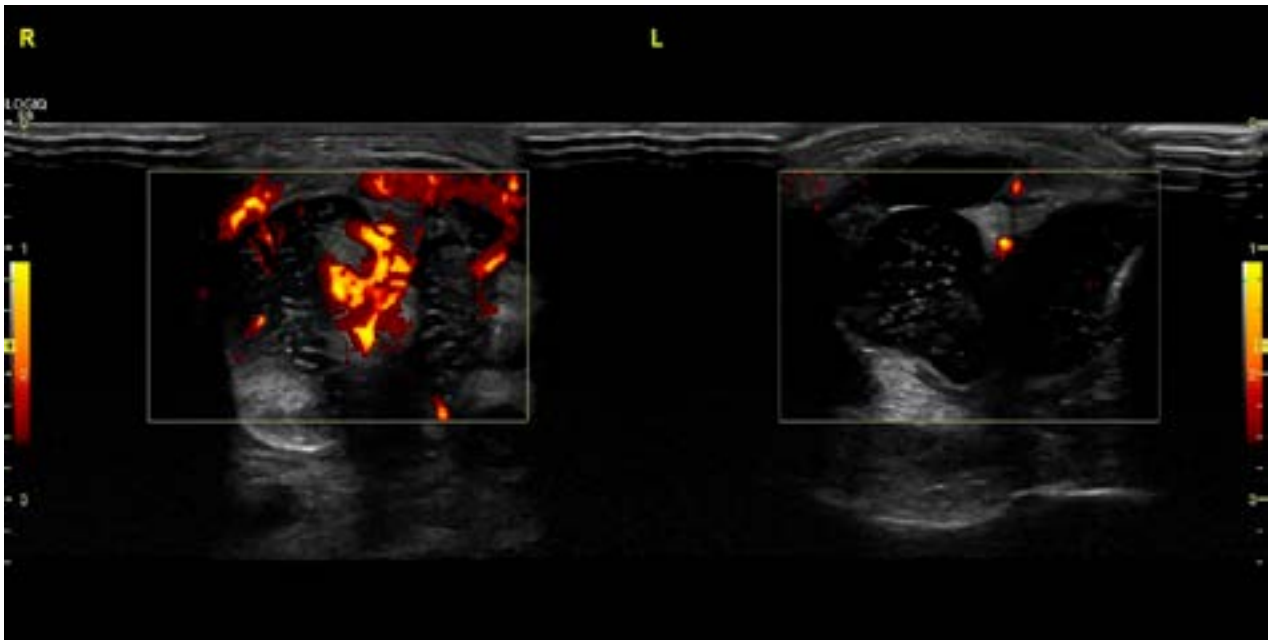
It could be suggested that removal of central lines once nosocomial infection is suspected, in combination with a thorough work-up, will facilitate early detection and therefore timely treatment of disseminated *Candida* infection (4,11). However, prompt diagnosis is chal-

Figure 1: (a) High frequency ultrasound (15MHz) of the right knee shows an irregular iso- to hypoechogenic structure between the femoral condyles and tibia (arrows), consistent with extensive synovial thickening. (b) Doppler ultrasound reveals increased vascularity of the synovium of the right knee (R) compared to the left knee (L). There is only minimal joint fluid present.

(a)



(b)



lenging due to false negative results when sampling too small volumes of blood for cultures, therefore delaying intervention and increasing risks for complications (11).

Diagnostic tools such as β-D-glucan blood test can be a used to detect invasive candidiasis. This test has a high negative predictive value, meaning it can exclude invasive candidiasis (11). A disadvantage is that the test does not differentiate between fungal species and can be false positive when other fungal and/or bacterial infections are present. False positive results have also been reported with many therapeutic interventions including antibiotics. Bassetti et al. recommend repeated measurements of BDG to increase the diagnosis accuracy. BDG concentrations decline in successfully treated patients, however usage to monitor clinical response is debated (13).

Antifungal treatments

Three published guidelines were found in our literature search. These guidelines all list recommendations for neonates with *Candida* infections. There is no specific differentiation in treatment regiments of *Candida* arthritis or osteomyelitis. Guidelines of the Infectious disease Society of America (IDSA) and Manzoni P. et al. suggest treatment with antifungals of at least 14 to 21 days for proven septicemia in neonates (Table 2).

Table 2: Overview of current treatment recommendations for Candida osteomyelitis in neonates

Current treatment recommendations for Candida osteomyelitis in neonates	
Manzoni P et al. (11)	Micafungin 7 – 10 mg/kg daily IV Amphotericin B IV Liposomal: 2.5 – 7 mg/kg every 24 hours Deoxycholate: 1 mg/kg every 24 hours Duration for all treatments: 12 months
Pappas G et al. (15) IDSA Guideline	Fluconazole 6 mg/kg daily IV or orally Echinocandin for 14 days IV, followed by Fluconazole 6 mg/kg daily orally Lipid formulation of Amphotericin B 3-5 mg/kg IV for 14 days followed by Fluconazole 6 mg/kg orally is a less attractive alternative Surgery is recommended in selected cases Duration for all treatment: 6 to 12 months

For osteomyelitis the IDSA recommends 6 to 12 months of continued therapy with fluconazole 6 mg/kg orally, whereas Manzoni recommends at least 12 months. The European Society of Clinical Microbiology and

Table 3: Overview of data from included articles. None of the included articles explicitly mentioned which type of amphotericin B was used. Often times details of treatment regiments were not reported on.
/= not disclosed in article, GA=gestational age, w= week, d= day, m=month, M=male, F=female, UAC = umbilical artery catheter, UVC = umbilical venous catheter

Reference	GA	Age of onset	Sex	Reported risk factors	Neonatal candidemia	C. albicans cultures	Joint involvement	Therapy	Outcome
Pan N et al. (4)	/	6 m	M	/	No	Joint fluid	Right knee	Fluconazole 12 mg/kg/d IV later switched to PO Duration: 12 months Surgical debridement	Mild leg length discrepancy
Hsieh WB et al. (5)	29 w	6 m	M	CVC, parenteral antibiotics	Yes	Joint fluid	Left knee	Fluconazole 8 mg/kg/d PO Duration: 6 weeks	Cured
Harris MC et al. (6)	28 w	98 d	M	UVC, UAC, parenteral antibiotics	Yes	Joint fluid	Right hip	Amphotericin B 1 mg/kg/d IV Duration: 3 weeks Open hip lavage	Cured
	28 w	104 d	M	Parenteral antibiotics	Yes	Joint fluid	Right hip, knee	Amphotericin B 1 mg/kg/d IV Duration: 6 weeks AND 5-fluorocytosine 15 mg/kg Duration 12 weeks	Cured
	30 w	166 d	M	CVC, UAC	Yes	Joint fluid	Right hip	Amphotericin B 1 mg/kg/d IV Duration: 6 weeks	Cured
Yousefzadeh DK et al. (8)	/	67 d	M	Parental antibiotics, hyperalimentation GI problems	No	Catheter tip, bone marrow	Humerus, elbow, both knees, right ankle	5-fluorocytosine Duration: 33 days	Cured
	/	34 d	M		Yes	Blood, catheter tip, joint fluid	All extremities and joints	5-fluorocytosine Duration: 33 days	Deformed
	34 w	4 d	M		Yes	Blood, catheter tip, joint fluid	Hip	Amphotericin B Duration: / Surgical debridement	Improved
Swanson H et al. (9)	28 w	1 yr	F	CVC, parenteral antibiotics	Yes	Joint fluid	Left knee	Fluconazole 5 mg/kg/d PO Duration: 8 days Amphotericin B 15 mg/kg Duration: 3,5 weeks	Cured
Pittard WB et al. (10)	30 w	34 d	M	UVC, UAC	/	Blood, Skin, periumbilical area, CSF, joint fluid	Knee	5-Fluorocytosine 50 mg/kg/d PO Duration: /	Deceased
	36 w	54 d	M	UVC, UAC, GI surgery	/	Skin, periumbilical area, CSF, joint fluid	Knee	Amphotericin B 1 mg/d IV Duration: / Multiple needle aspirations	Cured
	28 w	28 d	F	UVC, UAC	/	Skin, periumbilical area, joint fluid	Knee	Amphotericin B 1 mg/d IV Amphotericin B 0,1 mg/d IA Duration: /	Deceased
Brill PW et al. (10)	40 w	6w	M	UVC	No	Blood, umbilical vein catheter tip, CSF, joint fluid, stool	Both humeri, femora, tibiae, left radius and ulna	Amphotericin B AND 5-fluorocytosine Duration: /	Cured
		6 w		UVC	yes	Blood, umbilical vein catheter tip, tracheal aspirate, urine, stool	Left humerus, ulna, right radius, tibia	Amphotericin B AND 5-fluorocytosine Duration: /	improved
Adler S et al. (18)	36 w	21 d	F	UVC Parenteral antibiotics	Yes	CSF, joint fluid	Both Knees	Amphotericin B 2,4 mg/d IV Duration: 4 weeks	Cured
Bayer AS et al. (19)	/	30 d	M	UAC, corticosteroids, parenteral antibiotics GI surgery	/	Sputum, CSF, stool, gastric aspirate, umbilical catheter, joint fluid	knees	Amphotericin B 2,8 mg/d IV Duration: 10 weeks Amphotericin B 5 mg IA Duration: once Multiple needle aspirations	Cured
Pruitt AW et al (20)	/	56 d	F	Parenteral antibiotics	/	Saphenous vein, joint fluid	Knee	Amphotericin B 9,5 mg/d IV Duration: 3 weeks Amphotericin 12,5 mg – 5 mg IA Duration: twice	Cured
Merchant RH. et al. (21)	31,6 ± 1,2 w	29 d	/	Parenteral antibiotics, environmental contamination	/	Blood joint	Both knees	6 out of 8 infants received Fluconazole 7,5 mg/kg IV Fluconazole 7,5 mg/kg PO Duration 6 weeks	Cured
		19 d	/			Blood, urine, joint fluid	Both knees		Cured
		50 d	/			Blood, urine, joint fluid , CSF	Both knees		Deceased
		21 d	/			/	Both knees		Cured
		18 d	/			/	Left knee		Cured
		21 d	/			Blood, urine	Both knees		Cured
		16 d	/			Blood	Both knees		Improved
		34 d	/			Urine	Both knees		Cured
Freeman JB et al. (23)	Term	18 d	M	Hyperalimentation Parenteral antibiotics	No	Blood, urine, venous catheter, joint fluid	Right knee, elbows	5-fluorocytosine 150 mg/kg/d Duration: 4 weeks	Cured

Infectious Diseases (ESCMID) guidelines however recommend the use of echinocandins as empirical treatment, but makes no recommendation towards cases with osteomyelitis (14)]. Based on recent studies, 2016 IDSA guidelines favor treatment with fluconazole or echinocandins over liposomal amphotericin B for *Candida* osteoarthritis in neonates. When choosing echinocandins, they recommend intravenous administration for 2 weeks followed by 6 to 12 months fluconazole orally.[15] Compared to liposomal amphotericin B, fluconazole has less adverse effects, such as nephrotoxicity and has better tissue penetration. Amphotericin B deoxycholate is not as recommended to use in neonates because of a less favorable toxicity profile compared to lipid preparations (1). A meta-analysis by Chen Yu-Hung et al. assessed the efficacy and safety of echinocandins in comparison with amphotericin B in treating invasive candidiasis. They revealed no significant differences in clinical response, however the risk of discontinuing treatment due to adverse effects was significantly lower in the echinocandins group than in the amphotericin B group. No differentiation was made between liposomal and deoxycholate amphotericin B (16). Despite growing evidence of superiority of echinocandins, there is no oral formula and usage is more expensive in comparison to fluconazole (1). The IDSA guidelines therefore state that fluconazole remains an acceptable drug of choice.[15] All three guidelines underline the importance of adequate prophylaxis in very low birthweight infants (2, 3, 4).

When consulting published case reports and case series different treatment regiments are being proposed{Table 3}. Amphotericin B is the most commonly used drug to treat *Candida* osteomyelitis and arthritis in infants and children. Combination therapy of amphotericin B and fluconazole has less commonly been described (4,9,17). The use of amphotericin B for *Candida* arthritis is mostly described in older studies (6,10,18,19). Bayer et al. suggested intraarticular amphotericin B as a potential adjunctive therapeutic measure in cases without disseminated disease (19). Only two other publications to date have reported successful results using high doses of intraarticular amphotericin B (10,20). Fluconazole monotherapy has been reported to yield successful recovery in patients of multiple studies (4,5,7,21-23). Yousefzadeh et al. report treatment with 5-flucytosine for osteomyelitis in two infants for 33 days. The article did not specify whether treatment was started intravenously or orally. One was reported to make a full recovery. The other patient had a severe case of *Candida* arthritis with involvement of all long bones, follow-up visits revealed disparity of the limb lengths (7). Merchant et al. and Hsieh et al. reported successful treatment with fluconazole treatment regimens of 6 weeks. They were treated intravenously or orally with a dose of 7.5 mg/kg in three divided doses. Merchant et al. reported eight neonates with neonatal candida arthritis, treated with IV or oral fluconazole, of which six made a full recovery (5,21). Pan et al. continued treatment for 12 months whereas Weigl et al. opted to treat for 6 months. Both patients were reported to make a full recovery (4,22).

Gamaletsou et al. reported on 207 pediatric (n=37) and adult (n=170) cases of *Candida* osteomyelitis, revealing a median treatment duration of 3 months. Relapse was reported in 32% of patients who eventually achieved complete response to therapy. Premature discontinuation of therapy was established to be the most common cause of these relapses regardless of which antimicrobial agent was used. However only 11 included patients were neonates (17). Previous reviews have underlined the importance of prolonged treatment to prevent relapse (4,17).

Surgical debridement

Literature review of Pan et al. revealed surgical incision and drainage in only 3 patients. The youngest patient was seven months at the time of receiving surgical intervention (24). Gamaletsou et al. reports on 201 cases of *Candida* osteomyelitis. Only 37 were pediatric patients, 10 of which received surgical intervention. Surgery was indicated in more complicated cases with persistent symptoms or clinical deterio-

Figure 2: Conventional radiographs reveal cortical buckling in both distal femurs (arrows), consistent with fractures. Lamellar periostal reaction (arrowheads) is already present. There is localized ostelysis in the proximal tibial metaphysis right (asterisk), also with associated lamellar periostal reaction (arrowheads).

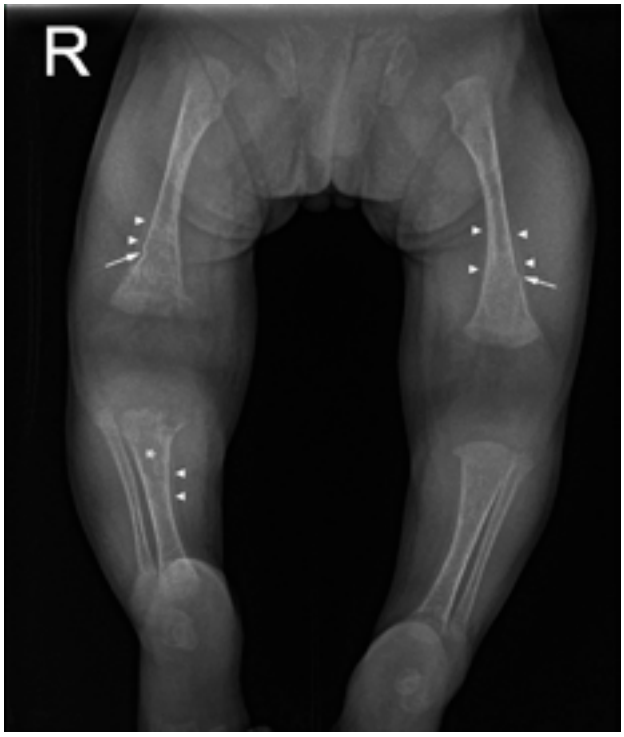
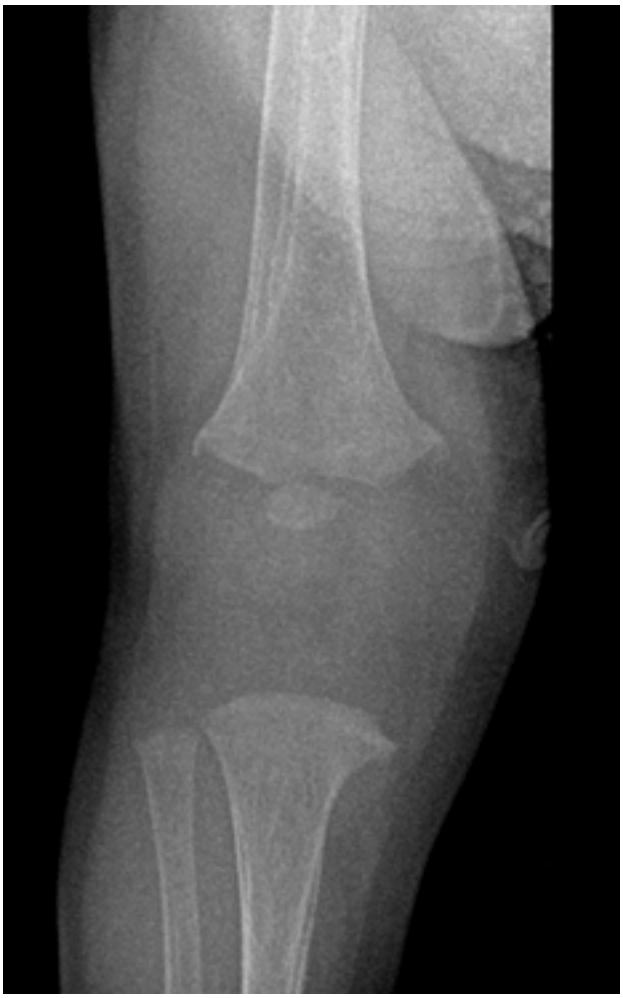


Figure 3: Follow-up radiography 10 weeks later shows complete consolidation of the fractures in the right femur and tibia.



ration, to warrant successful eradication and structural stability (17). The 2016 IDSA guidelines recommend surgical debridement in all cases of septic arthritis or in patients with persistent or worsening symptoms during therapy (15).

Outcome

Our literature search shows different treatment regiments, however clinical outcome seems to be favorable in almost all surviving patients. Yousefzadeh et al. reports 4 cases out of 13 neonates with orthopedic sequalae due to *Candida* osteomyelitis. Two of those had severe complications; one patient had femoral head dislocation three years after onset of the osteomyelitis and another patient had a severe disparity between limb lengths due to extensive and persistent arthritic involvement (7). Pan et al. also describes one case of *Candida albicans* osteomyelitis in a 13-month-old boy who developed a mid-length discrepancy (4). Other case reports reveal a full recovery six to twelve months after initial diagnosis of *Candida* osteomyelitis or arthritis. There are no long-term follow-up or growth chart data available.

Discussion

We hypothesize that our patient developed a *Candida* osteomyelitis due to hematological spreading of the yeast and eventually seeding in the joint. Since clinical symptoms were seen less than a month after completing treatment for the initial *C. albicans* infection, this supports the previously mentioned theory of inoculation followed by a dormant period (4). Since multiple cases have described dormant periods ranging from weeks to one year, close follow-up of children with a history of candidiasis is important. Awareness of a patient's history of neonatal *Candida* infection can help diagnose *Candida* arthritis faster if symptoms occur. No other case has used the BDG test as a marker for fungal infection. False positive results are definitely possible in neonates, however this test can be used if invasive candidiasis is suspected but not cultured, to make fungal etiology more or less likely. Meconium and skin cultures can be useful to determine the risk for invasive candidiasis in preterm infants. According to research provided by Mahieu L. et al. the number of sites colonized with *C. albicans* at birth contributes to invasive candidemia (25).

As shown in the literature review there is no consensus about the correct treatment regimen for neonates with *Candida* osteomyelitis/arthritis. Multiple treatment regimens have yielded various results. Our choice of treatment both for the initial candidemia as the osteomyelitis was in line with the IDSA guideline (15). However caution is warranted as the recommendations in this guideline are mostly derived from adult and pediatric studies and expert opinion. This can be explained by limited described data in current publications. Most case reports haven't included the used dosage of antimicrobial treatment neither mention exact duration. Since the condition is rare, no study has sufficient cases to draw meaningful conclusions. As to indication for surgical debridement there is very limited data. In our patient we did perform a surgical debridement which confirmed the presence of *C. albicans*, since blood cultures remained negative. The need for surgical intervention remains to be decided on a case-to-case basis. Unfortunately, similar to our case, many patients are lost to follow-up. Important findings after recovery such as growth, radiological findings and motoric development are often not included in many case reports.

Conclusion

Neonatal *Candida* osteomyelitis is a rare complication of *Candida* septicemia in neonates. Well justified use of fluconazole prophylaxis could prevent *Candida* infections in infants. Guidelines regarding optimal treatment of neonates with *Candida* osteomyelitis are limited. Prolonged and timely initiated treatment with fluconazole with oral courses of six to twelve months and surgical intervention, when indicated, can be curative. Echinocandins can be a new therapeutic option for the treatment of *Candida* osteomyelitis but are expensive and can only be given intravenously. Osteomyelitis as a complication of candidiasis is rare but early recognition and therapy may prevent residual and permanent deformity. Uniformity in reporting on similar cases is necessary to draw meaningful conclusions

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Declarations of interests

The authors report that there are no competing interests to declare.

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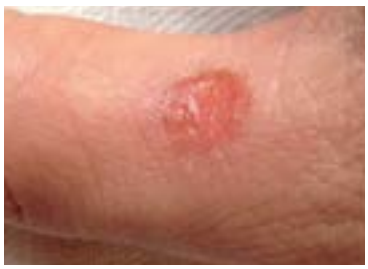
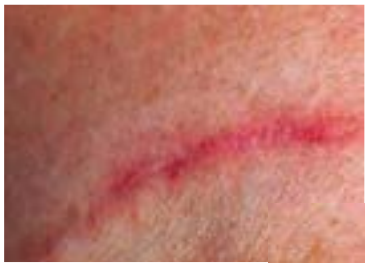

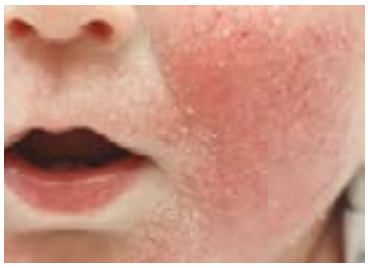
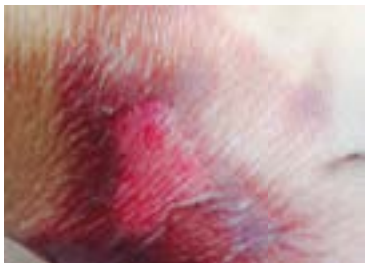


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Acquired primary hypothyroidism with profound anemia in an adolescent girl: a case report and a brief narrative review

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Keywords

autoimmune thyroiditis, adolescent, anemia, hypothyroidism

Abstract

Autoimmune thyroiditis is the most common cause of acquired thyroid disease in children and adolescents. Because the initial presentation can be very heterogeneous, diagnosis can be a challenge. Untreated, hypothyroidism has a significant impact on overall health and quality of life. Best outcome requires early detection as well as appropriate treatment. We present a case report of primary acquired hypothyroidism with a special presentation and a brief narrative review about hypothyroid autoimmune thyroiditis. Besides, we want to warn for delayed diagnosis in children with developmental disabilities.

Introduction

Hypothyroidism is characterized by an inadequate action of thyroid hormone at tissue level, with a decrease in metabolism as a consequence. A normal thyroid action through childhood is necessary for normal growth and neurodevelopment and is essential to the function of most organ systems.

Hypothyroidism may present at birth (congenital hypothyroidism) or appear later in life (acquired hypothyroidism). The cause of hypothyroidism can be at any level of the hypothalamic-pituitary-thyroid axis. Central hypothyroidism refers to disorders with decreased production of thyroid stimulating hormone (TSH) in the pituitary gland (secondary hypothyroidism) or decreased production of thyrotropin releasing hormone (TRH) in the hypothalamus (tertiary hypothyroidism). In central hypothyroidism, serum free thyroxine (FT4) is low and serum TSH is usually low or normal. By contrast, primary hypothyroidism is due to a defect in the thyroid gland itself, characterized by a low or normal FT4 and free triiodothyronine (FT3) and an increase of TSH (1).

In developed countries, autoimmune thyroiditis (AIT), also known as Hashimoto thyroiditis, is the most common cause of primary hypothyroidism in children and adults, with an estimated prevalence of 1-2%. In developing countries, hypothyroidism due to iodine-deficiency is the most common cause (1).

The clinical presentation of hypothyroidism reflects mainly the decrease of metabolic rate, which leads to fatigue, decreased heart rate, constipation, mild to moderate weight gain and decreased growth velocity. In severe forms, accumulation of matrix glycosaminoglycans in the interstitial spaces occurs, leading to myxedema, coarse hair and skin, puffy facies. The signs and symptoms can vary greatly between patients and is influenced by the rate of onset. Anemia is a clinical sign that can also be present at time of diagnosis (1).

Anemia can be defined as a reduction in red blood cell mass or blood hemoglobin concentration. For the pediatric population, normal ranges for hemoglobin vary with age and sex. Thresholds for defining anemia is a hemoglobin below the 2.5th percentile for age and sex based upon normative data from healthy individuals (2).

The diagnostic approach starts with assessing the mean corpuscular volume of the red blood cell (MCV). Anemia is classified in microcytic (MCV < 2.5th percentile for age and sex), normocytic (MCV 2.5th-97.5th percentile for age and sex) and macrocytic anemia (MCV > 97.5th percentile for age and sex). Consideration of the reticulocyte response can be helpful in differentiating the normocytic anemias. The reticulocyte response shows the reaction of the bone marrow to the anemia. In an anemia due to hypothyroidism, normocytic anemia with a low reticulocyte count is expected (2).

In this case report, we describe an unusual presentation of hypothyroidism with anemia in an adolescent girl. In the narrative review of autoimmune thyroiditis, we want to raise awareness of the diversity in clinical presentation. Especially in children with developmental disability diagnosis can be a challenge (3).

Method

We present clinical and biochemical data of a thirteen-year-old Caucasian girl with an acquired primary hypothyroidism and a profound anemia due to autoimmune thyroiditis. Additionally, a brief narrative review on the hypothyroid phenotype of autoimmune thyroiditis is presented.

Case report

We report the case of a 13-years old girl known with autism spectrum disorder (ASD), for which she is attending a school for children with special needs. She is not taking any medication.

She consulted a general practitioner (GP) because of pain and important blood loss during her periods. The GP assessed the girl as rather pale and decided to do an exploratory blood test. Two striking results were found: a normochromic anemia with a hemoglobin of 4.8 g/dl (12.1 – 14.6 g/dl) and an MCV of 100 fL (80 – 100 fL).and a severe primary hypothyroidism with a TSH of > 950.5 mIU/l (0.51 – 4.3 mIU/l) and an FT4 of < 1.5 pmol/l (12.6 – 21.0 pmol/l). Hepatic function tests were normal. Creatinine was slightly elevated. An increase of total cholesterol and triglycerides was seen. The GP transferred the patient to the pediatric ward of a regional hospital for further elaboration and blood transfusion.

At presentation in the hospital, we found a very pale girl. Her blood pressure was 85/55 mmHg with a heart rate of 90 bpm. During the inspection dry hair and puffy facies were noticed. There was no goiter in the region of the thyroid gland. Her tanner stage was 4.

It was only possible to have very little interaction with the adolescent girl. When we asked the parents, they did not notice any change in behavior. They said she has always been very slow, tired, withdrawn, and introverted, but parents framed this in the context of ASD and intellectual disability. No deterioration of these symptoms was noticed. She was having little appetite, but this has been the case for a long time. No cold intolerance, constipation, or weight gain was present. Further inquiry revealed that the maternal grandmother had a thyroid problem, but the exact diagnosis could not be reported.

Further laboratory test were done in the hospital. Blood tests confirmed primary hypothyroidism, and severe anemia. Very low vitamin D, folic acid deficiency and hypercholesterolemia were also found. On the other hand, iron status was normal, as well as vitamin B12 level.

To determine the cause of the hypothyroidism, autoimmune antibodies were obtained. Thyroperoxidase antibodies (TPOAb) were normal (12.3 IU/ml, ref value < 34 IU/ml), but thyroglobin antibodies (TgAb) were raised (351 IU/ml, ref value < 115 IU/ml). A blood transfusion with two units of packed cells was given to treat the severe anemia. Vitamin D and folic acid supplementation were also started.

Although little growth data were available, plotting data on the growth curve, showed a height declining from the mean at the age of 5 years to -2.5 SDS. Weight started around -1 SDS, and diminished to below -2.5 SDS. Bone age, according to Greulich and Pyle was 11 years, at a calendar age of 13 years. Ultrasound examination of the thyroid region demonstrated a heterogeneous thyroid gland with cystic and hypoechogenic zones, indicating thyroiditis. Diagnosis of autoimmune thyroiditis with severe hypothyroidism was made.

Treatment with L-thyroxin substitution was started with a low dose, approximately 1 µg/kg/day, assuming a long-standing hypothyroidism. During outpatient follow-up, L-thyroxin was gradually up-titrated. Two weeks after diagnosis, the dose was increased to 1.5 µg/kg/day. Normalization of thyroid hormones and TSH occurred within one month (Table 1).

Although character-wise she remained quiet and withdrawn, interaction with her became much more easy.

The tentative explanation of the normocytic anemia was the overt hypothyroidism along with substantial blood loss with her menses and concomitantly a folic acid deficiency.

Discussion

Pathophysiology of autoimmune thyroiditis

The development of autoimmune thyroiditis (AIT) is a multifactorial disease caused by genetic and environmental factors that initiate a complex autoimmune pathway. The onset is marked by lymphocytic infiltration with subsequent cytotoxicity and a humoral immune response producing antibodies against thyroid antigens that leads to inflammation and destruction of the thyroid follicular cells (4).

At the genetic level, mutations in major histocompatibility genes, immunoregulatory genes, thyroid-specific genes, and genes associated with thyroid peroxidase antibody synthesis are described in patients with auto-immune thyroiditis. Familial co-aggregation with Graves' disease, or other auto-immune diseases like celiac disease, diabetes mellitus type 1, vitiligo, or Addison disease is seen (5). In several syndromes, an increased prevalence of autoimmune thyroiditis is seen. Turner syndrome, Down syndrome, Klinefelter syndrome and Noonan syndrome being the most frequent (Table 2) (6). AIT can also be part of autoimmune polyglandular syndrome and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome (1). Regarding the environmental factors, the influence of iodine intake, selenium intake, and vitamin D is suggested, as well as lifestyle factors such as smoking and alcohol (5). Passing through infections in infancy, or therapies which modulate the immune system (e.g., lithium, irradiation) might play a role, but further research is necessary to clarify this (4, 5).

Different phenotypes of autoimmune thyroiditis exist. Distinction can be made based on the concentration of thyroid hormones in the circulation. In this regard, children with auto-immune thyroiditis can present with euthyroidism, subclinical hypothyroidism, overt hypothyroidism, or they can present with subclinical or overt hyperthyroidism. The latter is a temporary phase caused by the release of stored thyroid hormone as the follicles get destroyed. This may also be promoted by the concomitant presence of anti-TSH stimulating antibodies.

The subclinical hypothyroid, euthyroid and hyperthyroid phenotype can evolve to an overt hypothyroid state. de Vries et al. studied 114 children with various clinical presentations leading to diagnosis of auto-immune thyroiditis and referral to a tertiary hospital. The reason for referral was thyroid gland enlargement in 39.5%, clinical symptoms of hypothyroidism in 28.9 %, incidental finding of thyroid dysfunction in 22 %, finding of thyroid dysfunction at routine screen of high-risk group and, hyperthyroid symptoms in 2%. At the moment 37% was hypothyroid, 42% was subclinical hypothyroid, 21% was euthyroid and 1% was hyperthyroid at time of diagnosis (reversed to hypothyroidism within weeks) (7). A German study of 43 children with severe acquired hypothyroidism, all due to Hashimoto thyroiditis, showed 66% of the children had a goiter, 2% had a hypoplastic thyroid and 32% did not have any palpable changes (8). Another study described the presence of a goiter in 40% of children with severe hypothyroidism due to autoimmune thyroiditis (9).

Usually, children with acquired hypothyroidism present with symptoms of fatigue, a remarkably decreased growth velocity and a modest weight gain (1). Other clinical findings that can be present are cold intolerance, dry rough skin and poor tolerance to cold. As mentioned before, goiter is a common finding. Occasionally loss of head hair, hypertrichosis, delayed tendon reflexes, myxedema of the face and extremities is noted. Precocious pseudopuberty (breast development in girls or testicular enlargement in boys, both without virilization), precocious menarche, as well as delayed puberty, irregular menses, excessive menstrual bleeding are described. The most frequent biochemical disturbance in severe hypothyroidism (TSH > 100 U/L, low fT4) are anemia (38%) and lipid disorders. In some cases liver and

Table 1: Thyroid hormone levels at follow-up

Day	Day 0	Day 3	Day 9	Day 26	Day 47	Day 79	Reference value
TSH (mIU/L)	950.5	950.1	349.9	22.02	2.41	1.57	(0.51 – 4.3)
FT4 (pmol/L)	< 1.3	4.7	10.48	17.85	18.41	15.54	(12.6 – 21.0)
Dose	1 µg/kg/d	1 µg/kg/d	1 µg/kg/d	1.5 µg/kg/d	1.5 µg/kg/d	1.5 µg/kg/d	

Table 2: Prevalence of autoimmune thyroiditis by syndrome (6)

Syndrome	Prevalence of autoimmune thyroiditis
Turner syndrome	10-42%
Down syndrome	13-46%
Klinefelter syndrome	5.4-10%
22q11.2 deletion syndrome	5%
Williams syndrome	Rare
Prader-Willi syndrome	Rare
Noonan syndrome	14.3-60%
Neurofibromatosis type 1	2.5%

kidney function tests are impaired. The degree of disturbance correlates with the degree of hypothyroidism (4, 9). Hyperprolactinemia has also been found with hypothyroidism (9). Unexpectedly, severe hypothyroidism can also be found on a random blood check in asymptomatic children (8).

Going back to our patient with hypothyroidism and a severe anemia. Anemia is an underestimated clinical condition that can accompany thyroid diseases. It can be the first and most prominent clinical sign of hypothyroidism (10). Anemia can either be microcytic, normocytic or macrocytic, because of different mechanisms which can play a role in the etiopathogenesis. Thyroid hormones stimulate the proliferation of erythrocyte precursors both directly and via erythropoietin production enhancement (11). Kucharska et al. found a positive correlation between fT4 and red blood cell count, as well as a positive correlation between fT4 and hemoglobin level (9). Uncomplicated mild anemia due to hypothyroidism can recover by starting thyroid hormone supplementation alone (10).

Questioning if the autism spectrum disorder of the patient plays an important role in the diagnostic process, a phenomenon of diagnostic overshadowing is described. In patients with intellectual disability, symptoms can sometimes be mistakenly attributed to the intellectual disability, which can cause a delay in the diagnosing of coexisting somatic disorders. In this regard, people with intellectual disability should be regularly screened for somatic comorbidity, and be re-evaluated in case of behavioral changes (3).

Diagnosis of hypothyroid auto-immune thyroiditis in children

Diagnosis is made by determining TSH and fT4 in the blood, as well as antithyroglobulin antibodies (TgAb) and antithyroid peroxidase antibodies (TPOAb) (12). Antithyroid peroxidase antibodies

are present in 90–95% and antithyroglobulin antibodies 20–50% of patients (1). An ultrasound of the thyroid has a typical appearance, but does not change the treatment, clinical course or outcome of children with AIT (7). Bone age is usually delayed correlated to the duration and degree of hypothyroidism (9).

Treatment of hypothyroid auto-immune thyroiditis in children

Levothyroxine is indicated for hypothyroidism. The treatment of choice are tablets, administrated daily 15-30 minutes prior to food intake. Levothyroxine should not be given at the same time with soy containing foods, iron or calcium supplements. The recommended dose is based on age, weight, and severity of hypothyroidism. For children around the age of 12, a dose of 2-4µg/kg/day is recommended (13). In cases of long-standing hypothyroidism, it is important to uptitrate the dose slowly. Pseudotumor cerebri or changes in behavior can occur when correcting the thyroid axis too quickly (14). Regular outpatient follow-up is necessary every 3 to 6 months and 4 to 6 weeks after dose adjustment. The goal of treatment is to maintain TSH in the age-specific normal range (1)

Prognosis of hypothyroid auto-immune thyroiditis in children

When focusing on growth, the severity of growth retardation has a significant correlation with the severity of hypothyroidism at the time of diagnosis. When starting adequate thyroid hormone supplementation, catch-up growth occurs in most children. The time of initiation of thyroid supplementation in relation to puberty has a major impact. There is a superior catch-up growth when starting thyroid hormone supplementation before the start of puberty (8). When starting thyroid hormone supplementation, the time to euthyroidism does not influence the final adult height. Trials with growth-promoting therapy were not effective (15).

Currently, research considering the association between autoimmune thyroiditis and thyroid cancer is ongoing (16-18). In children and adolescents, some studies show a growing coexistence between autoimmune thyroiditis and Papillary Thyroid Carcinoma (PTC) (17). As a result, some studies suggest an annual thyroid ultrasound in patients with autoimmune thyroiditis. More research is needed to clarify the link between autoimmune thyroiditis and PTC, and to determine the value of ultrasound in follow-up of children with autoimmune thyroiditis (18).

Conclusion

We presented a case of a 13-year-old with acquired overt hypothyroidism with an impressive initial presentation with severe anemia. The diagnosis seemed in this case to be delayed because of the lack of complaints of the girl with ASD. Awareness should be raised about the heterogeneous clinical presentation of autoimmune hypothyroidism. Therefore a check of the thyroid status should be performed in children with vague complaints, especially in children or adolescents with ASD and/or intellectual disabilities for whom anamnesis is more difficult.

Conflict of interest

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

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LABORATOIRE

Neurodevelopmental outcome of preterm infants with isolated grade I intraventricular hemorrhage: a matched case-control study

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Keywords

Preterm, intraventricular hemorrhage, neurodevelopmental outcome, ultrasound

Abstract

Background: Germinal matrix and intraventricular hemorrhages remain one of the most common complications along preterm infants, detected by cranial ultrasound. Especially the impact of low-grade intraventricular hemorrhages on neurodevelopmental outcome has been the source of debate.

Objective: To determine the neurodevelopmental outcome of preterm infants (≤32 weeks) with isolated grade I intraventricular hemorrhage at 24 (19-30) month's corrected age.

Methods: A single-center matched case-control study of preterm infants born at ≤32 weeks' gestation between January 1, 2011 and December 31, 2016 and diagnosed with an isolated grade I intraventricular hemorrhage on cranial ultrasound. Cases were matched with their corresponding control (without intraventricular hemorrhage) based on gestational age (same week), birth weight (±250g), sex and year of birth (born within 2 years after birth of the corresponding case). Neurodevelopmental outcomes were compared at 24 (19-30) months' corrected age.

Results: The final study cohort consisted of 52 cases and 52 matched controls. Sixty-six point three percent of eligible survivors completed follow-up. Infants with grade I intraventricular hemorrhage had significantly lower mean psychomotor developmental index (PDI) scores and a higher rate of motor delay (PDI <85) than those without intraventricular hemorrhage. Furthermore, significantly less preterm infants with grade I intraventricular hemorrhage received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I intraventricular hemorrhage group.

Conclusions: At 19-30 month's corrected age, preterm infants with isolated grade I intraventricular hemorrhage had a significantly poorer motor outcome than their matched controls with normal cranial ultrasound.

Introduction

Germinal matrix and intraventricular hemorrhages (GMH-IVH) remain one of the most common complications among preterm infants with rates varying between 25% and 35% in extremely low birthweight (ELBW, birthweight < 1000g) or extremely preterm infants (<28 weeks' gestation) (1). Grading of IVH is still most frequently based on the Papile classification in which grade I IVH refers to GMH, grade II to an IVH without ventricular dilatation, grade III to an IVH with ventricular dilatation and grade IV to an IVH with parenchymal involvement (2). Nowadays grade IV IVH is less used and grade I-III with or without periventricular hemorrhagic infarction (PHI) is more accurate (3). Although survival and neurodevelopmental outcomes of preterm infants have improved in recent decades, the rate of infants at risk of developmental delay remains high, even for those born moderately preterm (4). High-grade (III-IV) IVH are known to be associated with an adverse neurodevelopmental outcome, but the impact of low-grade (I-II) IVH is more controversial (5–7). The germinal matrix is a source for proliferation of oligodendroglial precursor cells from which these subsequently migrate to the cortical layers. Here, they will differentiate and start producing myelin in the post term period (8) . The peak of migration is situated between 23 and 28 weeks' gestation (9). It is therefore suggested that even low-grade IVH have the potential to destroy these precursor cells and affect migration and myelination, especially in extremely preterm infants (6,8,10). This could result in impaired neurodevelopmental outcome. Nevertheless, several papers described different outcomes. Some studies report significant neurodevelopmental disabilities in preterm infants with low-grade IVH, while others rejected this hypothesis particularly those who utilized MRI as adjuvant neuroimaging (1,5,6,7,9,10–22). The aim of this study was to examine the impact of isolated grade I IVH on neurodevelopmental outcome at 24 (19-30) months' corrected age (CA).

Materials and Methods

Eligibility Criteria

This study was approved by the Research Ethics Committee UZ/KU Leuven, approval number [MP018241]. It is a matched case-control study on prospectively collected data of preterm infants admitted to a level III NICU at Leuven, Belgium. Preterm infants born at a gestational age of ≤ 32 weeks, between January 1, 2011 and December 31, 2016 and diagnosed with a grade I IVH on cranial ultrasound (cUS) were eligible for this study. Infants with grade II-IV IVH, other intracranial hemorrhages (lobar cerebral hemorrhages, thalamoventricular hemorrhages and cerebellar hemorrhages), focal infarction and/or cystic/non-cystic white matter disease on cUS were excluded as were infants with genetic disorders or neonatal meningitis. Cystic white matter disease was scored using the grade classification (grade II-IV) by de Vries et al (23). Non-cystic white matter disease was defined as periventricular echogenicity present for more than 7 days, isolated ventriculomegaly or irregular echodensities without ventriculomegaly. Controls without IVH were also retrieved from the neonatal database and were matched with cases based on gestational age (GA, same week), birth weight (±250g), sex and year of birth (born within 2

years after birth of the corresponding case). As 4 cases could not be matched with a corresponding control based on these criteria, these were excluded from the study.

Variables

Perinatal and neonatal characteristics were collected from the neonatal database or medical record. Perinatal data included antenatal corticosteroid use, defined as both complete (2 doses at 24-hour interval) and incomplete therapy, and chorioamnionitis/funisitis whose diagnosis was based on the anatomopathological report of the placenta. For this latter variable, both groups were slightly smaller because of the absence of a pathology report in 13 cases and 14 controls. Neonatal variables included small for gestational age (SGA, birth weight < 10th percentile), hypotension (defined as need for inotropic support), postnatal surfactant therapy (1 dose or more), necrotizing enterocolitis (NEC, defined as modified Bell stage IIA or higher), retinopathy of prematurity (ROP, defined as stage 3 or higher according to the International Classification of Retinopathy of Prematurity), patent ductus arteriosus (PDA, defined as clinical significant when medical and/or surgical treatment was necessary) and bronchopulmonary dysplasia (BPD, defined as oxygen dependence at 36 weeks' gestation (± 3 days) or at discharge, whichever came first). The presence of early (≤ 72 h) or late-onset (> 72 h) sepsis was determined using clinical characteristics and/or positive microbiology.

Imaging

IVH was diagnosed by cranial ultrasound and classified based on Papile criteria (2). This examination was performed, according to local standard procedure, on days 1, 3 (only when born at GA ≤28 weeks), 7, 14 and biweekly until term equivalent age (TEA). When abnormalities were seen, cUS was repeated weekly. In case of sepsis, NEC and postoperatively, an extra cUS was performed. Coronal and sagittal views were obtained from a transfontanellar approach. Mastoid fontanelle imaging was not routinely performed. All ultrasound images were reviewed by one neonatologist (G.N.) to exclude additional lesions. Standard MRI assessment was not performed.

Assessment of neurodevelopmental outcome

Neurodevelopmental outcomes were evaluated between 19 and 30 months' CA by a multidisciplinary team of trained psychologists, speech-language pathologists, physiotherapists and pediatricians at the Centre for Developmental Disabilities in Leuven. For assessment of neurodevelopmental outcomes, the Bayley Scales of Infant Development (BSID) and the Communicative Development Inventories, Dutch edition (N-CDI 2A) were used. The BSID second (2011-2013) and third edition (as of 2014) were used to assess motor and cognitive outcomes by the psychomotor (PDI) and mental developmental index (MDI), respectively. In this study the BSID-II PDI and MDI was chosen to work with. Therefore BSID-III scores were converted to their corresponding BSID-II scores by using a conversion table as proposed by A.F. Bos (24). To assess language development, the N-CDI 2A was used, a parent questionnaire. The mean score of PDI and MDI is 100, with a standard deviation (SD) of 15. Neurodevelopmental delay was defined as a PDI or MDI below 1 SD for the BSID-II, and language comprehension or language production < 50th percentile (p50) for the N-CDI 2A. For children who had an MDI or PDI score below 55, the score was set equal to 50 (lowest possible score on the scale) to simplify statistical analysis. A similar simplification was applied to the N-CDI 2A scores. For children with scores below the first or above the 99th percentile, the score was respectively set equal to percentile 0 and 100.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 28. To determine the sample size, a comparison of means was conducted. For the BSID a standard deviation of 5 was accepted. In this case a minimum of 45 patients in each group (cases and controls) was required to prove a difference of 3 points on the Bayley scale with a power of 80% and a statistical significance of 0.05. To compare categorical data, $\chi 2$ test or Fisher's exact test was used and t test was performed for continuous data. All tests were 2-sided and a p value of <0.05 was considered to be statistically significant.

Results

The complete database consisted of 776 preterm infants born at ≤32 weeks' gestation between January 1, 2011 and December 31, 2016. 24.7% of these infants developed some grade of IVH: 15.1% was diagnosed with a grade I IVH, 4.4% with a grade II IVH, 4.1% with a grade III IVH and 1.4% with a PHI. After exclusion of infants with associated abnormalities on cUS (hyperechogenic focus in the thalamic region, thalamic hemorrhage, posthemorrhagic hydrocephalus and frontal infarction), associated grade II IVH on the contralateral side, doubtful cUS findings (doubtful grade I IVH on first cUS with negative serial cUS and non-specific findings) and associated conditions (white matter disease, neonatal meningitis, genetic disorders) known to be possible contributing factors to poor neurodevelopmental outcome in preterm infants, 95 preterm infants with isolated grade I IVH were identified. Sixty-six point three percent of eligible survivors completed follow-up. Children with grade I IVH who were lost to follow-up had a significantly higher GA at birth, were less frequently intubated in the delivery room, received less frequently surfactant and systemic corticotherapy, and were less often diagnosed with BPD and ROP (shown in table 1). The final cohort consisted of 52 cases and 52 controls. A flowchart of the study enrollment is shown in Figure 1.

Baseline characteristics

Perinatal and neonatal characteristics are reported in table 2. As expected from matching, there were no significant differences in sex, birth weight or GA between groups. Significantly less preterm infants with grade I IVH received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I IVH group. There were no statistically significant differences in diagnoses of BPD, NEC and ROP between groups.

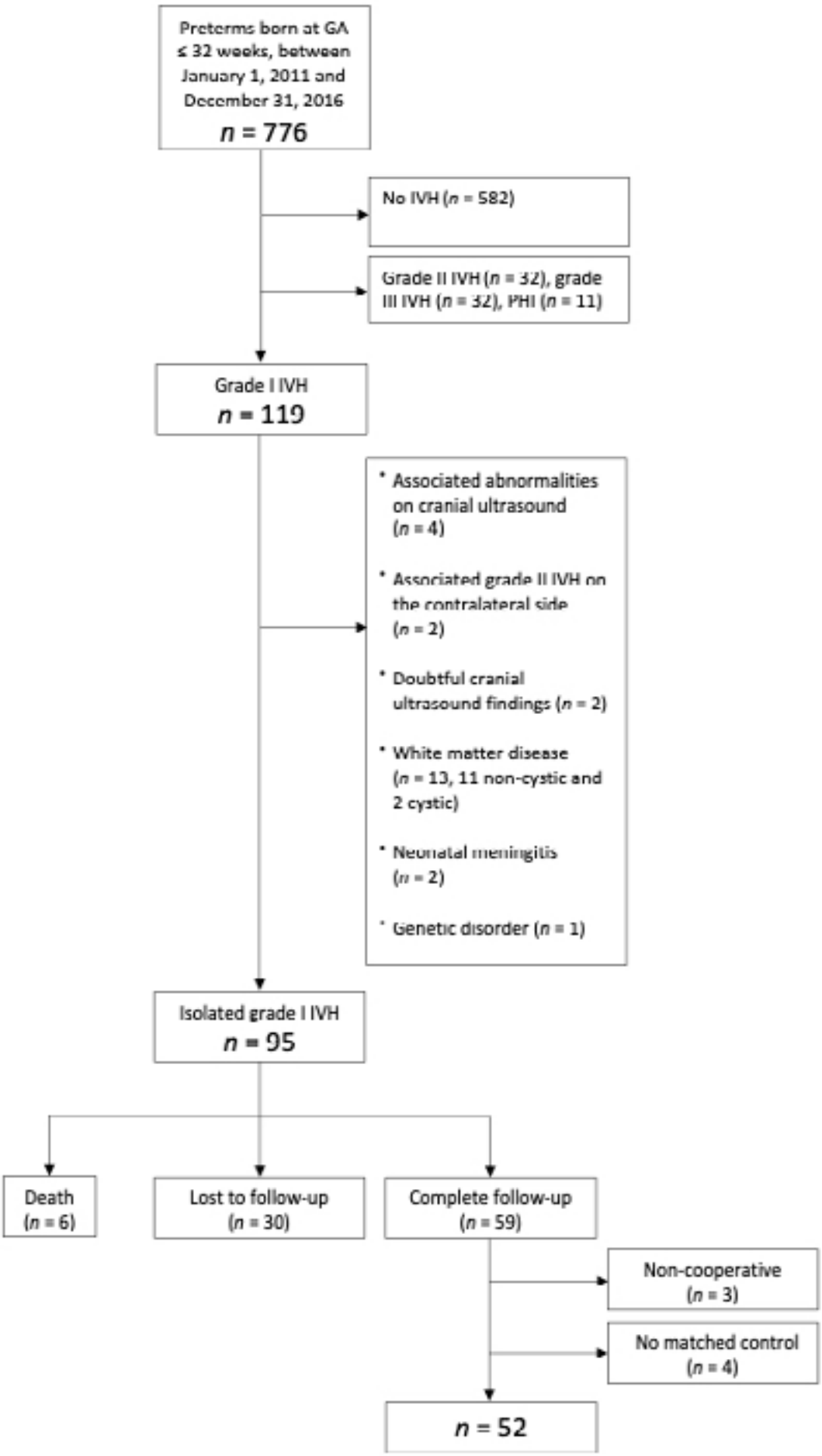
Neurodevelopmental outcomes

Infants with grade I IVH had significantly lower mean PDI scores and a higher rate of motor delay (PDI <85) than those without IVH (shown in table 3). Among these infants, two were diagnosed with cerebral palsy (CP): one with spastic diplegia, GMFCS level II and one with spastic monoplegia of the left lower limb, GMFCS level I. Among the controls with PDI below 85 there were no diagnoses of CP. Furthermore, there were no significant differences in cognitive scores between infants with and without grade I IVH. When classifying the infants according to severity of neurodevelopmental delay, there were no statistically significant differences between cases and controls (shown in table 3). Concerning language development, there were no statistically significant differences either (shown in table 4).

Discussion

This single-center matched case-control study showed that infants with grade I IVH had significantly lower mean PDI scores and a higher rate of motor delay at 19-30 months' CA than those with a normal cranial ultrasound. Furthermore, significantly less preterm infants with grade I IVH received antenatal corticosteroids and were inborn, while vaginal delivery occurred significantly more in the grade I IVH group. The findings of this research are consistent with several previous studies that reported significantly worse neurodevelopmental outcome in preterm infants with low-grade IVH (6,7,9,11–15). Bolisetty et al. and Patra et al. showed that extremely preterm and ELBW infants with low-grade IVH had increased rates of cognitive and motor

Figure 1: Flowchart of the study enrolment



impairment at 2-3 years' CA (6,12).These poor neurodevelopmental outcomes persisted up to 5 years of age, especially in the extremely preterm group, as stated by Klebermass et al. In addition, Pfahl et al. revealed that low-grade IVH in preterm infants of < 32 weeks' gestation was significantly associated with poor motor outcome at 20-24 months' CA (9,13). This was also the case in the study performed by Futagi et al. in which the rates of CP were significantly elevated in preterm infants (mean GA 28.1 weeks) with grade I IVH (7.2%) (7). Finally, in a population-based cohort study by Hollebrandse et al., it was shown that low-grade IVH in extremely preterm infants was associated with higher rates of CP, but not with intellectual ability, executive function, academic skills or overall motor function at 8 years of age (11). The results of the current study are in contrast to those of several studies that did not find any differences neither in early nor late neurodevelopmental outcomes between preterm infants with and without low-grade IVH (1,5,10,16–18,20–22). The main limitation of this study is the use of cUS without additional assessment by MRI at TEA. cUS was performed by different radiologists and there was no measure of interobserver reliability and accuracy among them. Hintz et al. reported that reliability and accuracy between 2 central readers was substantially poorer for low-grade IVH (only 26% agreement for grade I IVH) and PVL (25). The sensitivity of local reader interpretations compared with central readers for grade I IVH was 28% to 53%. Moreover, mastoid fontanelle imaging was not routinely performed. Hence, cerebellar lesions might have been missed. Previous studies reported an incidence of focal cerebellar hemorrhage (CBH) detected by cUS that increased from 3.7% in infants of ≤ 30 weeks' gestation to 9% in infants of < 32 weeks' gestation when using the mastoid fontanel window (26,27). This incidence further increased to 19% when MRI was used (27). Therefore, assessment by MRI at TEA is indispensable to detect cerebellar injury which may be associated with delayed mental and psychomotor development, and higher rates of CP as described in a meta-analysis performed by Villamor-Martinez et al. (28). On the other hand, routine neuroimaging with MRI at TEA in infants with low-grade IVH allows the recognition of additional white matter abnormalities, missed with cUS (29). GMH-IVH are in fact commonly associated with white matter injury that may impair normal development in preterm infants (19,30). Additional standardized assessment by MRI was performed in the study conducted by Reubsaet et al. in which they found that additional lesions were revealed in 54% of the infants with low-grade IVH and 38% of those with normal cUS findings (17). In 2 out of 5 infants these additional lesions could indeed explain subsequent development of CP (17). Other limitations of this study involve the retrospective design and a small sample size. However, the goal sample size of 45 infants per group was reached so that adequate power for the primary outcome could be achieved. There was also a relatively high rate of loss to follow-up (33.7%), which may have resulted in a selection bias. When comparing both groups, infants with grade I IVH who were lost to follow-up had a significantly higher GA at birth, were less frequently intubated in the delivery room, received less frequently surfactant and systemic corticotherapy, and were less often diagnosed with BPD and ROP. Another possible bias is the lack of data concerning parental socioeconomic status and age. Since these factors (especially maternal level of education and age) have a well-known influence on a child's neurodevelopmental outcome, the absence of this information may affect the results of the current study (31–33). Finally, the follow-up period up to 30 months' CA is also a limitation of this study. Behavior and/or cognitive deficits may only present beyond this age. Accordingly, Vohr et al. didn't find any differences in outcome between infants with and without low-grade IVH at 24 months of age nor at 3-5 years of age, but they did find that preterm adolescents with a history of low-grade IVH were at increased risk of neurocognitive deficits (14,31,34). The strengths of this study include the fact that cases and controls were matched so that it was possible to adjust for known risk factors for IVH such as GA, birth weight and sex. Furthermore, this research specifically looked at grade I IVH, while most studies examining the influence of IVH on neurodevelopmental outcome tend to dichotomize the 4 grades into low grades and high grades, which reduces the generalizability of the findings (1). In addition, all children with additional abnormalities on cUS or co-existing disorders that could have an IVH-independent influence on neurodevelopmental outcome were excluded.

Conclusion

This study suggests that preterm infants with isolated grade I IVH had a significantly poorer motor outcome at 19-30 months' CA than their matched controls with normal cranial ultrasound. However, these results should be interpreted with caution because of the lack of additional standardized assessment by MRI at TEA. Therefore, other abnormalities could have been missed. Although this study was sufficiently powered, the sample size was still small and a larger study replicating these analyses is recommended and could be done in the future. Finally, long-term follow-up of these infants is important to determine if these outcomes change at school age.

Conflict of interest

The authors have no conflict of interest to declare.

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Table 1: Perinatal and neonatal characteristics of preterm infants with grade 1 IVH with and without assessment at 19-30 months' corrected age

Total (n = 89)	Followed-up (n = 59)	Lost to follow-up (n = 30)	p value†
Perinatal characteristics			
Multiple gestation	19 (32.2%)	11 (36.7%)	0.67
Antenatal corticosteroids	51 (86.4%)	25 (83.3%)	0.76‡
Inborn	38 (64.4%)	21 (70.0%)	0.60
Delivery			
Vaginal delivery	29 (49.2%)	14 (46.7%)	0.82
Caesarean section	30 (50.8%)	16 (53.3%)	0.82
Apgar score			
1 minute (SD)	6 (2.4)	6 (2.6)	0.91#
5 minutes (SD)	8 (1.6)	8 (1.5)	0.30#
Chorioamnionitis/funisitis (n = 75)	(n = 46) 16 (34.8%)	(n = 29) 6 (20.7%)	0.19
Neonatal characteristics			
Male	30 (50.8%)	14 (46.7%)	0.71
GA at birth, weeks, mean (SD)	28.8 (2.3)	29.8 (1.7)	0.018#*
Birth weight, g, mean (SD)	1214 (384)	1317 (374)	0.23#
SGA	6 (10.2%)	3 (10.0%)	1.00‡
Delivery room intubation	25 (42.4%)	6 (20.0%)	0.036*
Mechanical ventilation, days, mean (SD)	6 (10.5)	3 (7.4)	0.058#
Hypotension – inotropics	6 (10.2%)	0 (0.0%)	0.093‡
Surfactant	34 (57.6%)	10 (33.3%)	0.030*
Systemic corticotherapy	14 (23.7%)	1 (3.3%)	0.015*
PDA	18 (30.5%)	6 (20.0%)	0.29
BPD	25 (42.4%)	6 (20.0%)	0.036*
NEC	3 (5.1%)	3 (10.0%)	0.40‡
ROP	13 (22.0%)	1 (3.3%)	0.029‡*
Neonatal sepsis			
Early-onset	10 (16.9%)	6 (20.0%)	0.72
Late-onset	21 (35.6%)	7 (23.3%)	0.24
Bilateral IVH	21 (35.6%)	12 (40.0%)	0.68
Grade I IVH with BPD, NEC and/or ROP	29 (49.2%)	9 (30.0%)	0.084

† From $\chi 2$ test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences ($p<0.05$)*
GA: gestational age; SGA: small for gestational age; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage

Table 2: Perinatal and neonatal characteristics

Total (n = 104)	No IVH (n = 52)	Grade I IVH (n = 52)	p value†
Perinatal characteristics			
Multiple gestation	24 (46.2%)	18 (34.6%)	0.23
Antenatal corticosteroid use	50 (96.2%)	44 (84.6%)	0.046*
Inborn	51 (98.1%)	31 (59.6%)	<0.001*
Delivery			
Vaginal delivery	10 (19.2%)	25 (48.1%)	0.002*
Caesarean section	42 (80.8%)	27 (51.9%)	0.002*
Apgar score			
1 minute (SD)	7 (2.1)	6 (2.4)	0.76#
5 minutes (SD)	8 (1.3)	8 (1.6)	0.51#
Chorioamnionitis/funisitis (n = 77)	(n = 38) 10 (26.3%)	(n = 39) 12 (30.8%)	0.67
Neonatal characteristics			
Male	26 (50.0%)	26 (50.0%)	1.00
GA at birth, weeks, mean (SD)	29.3 (2.0)	29.2 (2.1)	0.79#
GA < 28 weeks	14 (26.9%)	14 (26.9%)	1.00
Birth weight, g, mean (SD)	1262 (320)	1281 (353)	0.78#
SGA	4 (7.7%)	4 (7.7%)	1.00‡
Delivery room intubation	14 (26.9%)	20 (38.5%)	0.21
Mechanical ventilation, days, mean (SD)	4 (7.8)	5 (9.6)	0.37#
Hypotension – inotropics	1 (1.9%)	5 (9.6%)	0.21‡
Surfactant	30 (57.7%)	27 (51.9%)	0.55
Systemic corticotherapy	6 (11.5%)	11 (21.2%)	0.19
PDA	13 (25.0%)	13 (25.0%)	1.00
BPD	16 (30.8%)	19 (36.5%)	0.53
NEC	4 (7.7%)	2 (3.8%)	0.68‡
ROP	6 (11.5%)	9 (17.3%)	0.40
Neonatal sepsis			
Early-onset	5 (9.6%)	7 (13.5%)	0.54
Late-onset	13 (25.0%)	16 (30.8%)	0.51
Bilateral IVH	-	19 (36.5%)	-

† From $\chi 2$ test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences (p<0.05)*
IVH: intraventricular hemorrhage; GA: gestational age; SGA: small for gestational age; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

Table 3: Cognitive and motor outcomes between 19 and 30 months' corrected age

Total (n = 104)	No IVH (n = 52)	Grade I IVH (n = 52)	p value†
BSID-II			
MDI < 85	20 (38.5%)	25 (48.1%)	0.32
MDI, mean (SD)	89 (20)	88 (22)	0.86#
PDI < 85	7 (13.5%)	16 (30.8%)	0.033*
PDI, mean (SD)	104 (18)	91 (21)	0.001#*
Mild developmental delay			
MDI 70-84	9 (17.3%)	16 (30.8%)	0.11
PDI 70-84	6 (11.5%)	9 (17.3%)	0.40
Moderate developmental delay			
MDI 55-69	8 (15.4%)	6 (11.5%)	0.57
PDI 55-69	1 (1.9%)	3 (5.8%)	0.62‡
Severe developmental delay			
MDI < 55	3 (5.8%)	3 (5.8%)	1.00‡
PDI < 55	0 (0.0%)	4 (7.7%)	0.12‡

† From $\chi 2$ test unless otherwise stated
‡ From Fisher's exact test
 # From independent-samples t test
** Statistically significant differences (p<0.05)*
IVH: intraventricular hemorrhage; BSID-II: Bayley Scales of Infant Development second edition; MDI: mental developmental index; PDI: psychomotor developmental; SD: standard deviation

Table 4: Language development between 19 and 30 months' corrected age

Total (n = 74)	No IVH (n = 37)	Grade I IVH (n = 37)	p value†
N-CDI 2A			
Language comprehension < p50	25 (67.6%)	23 (62.2%)	0.63
Language comprehension, mean percentile (SD)	p38 (34)	p43 (33)	0.53#
Language production < p50	27 (73.0%)	26 (70.3%)	0.80
Language production, mean percentile (SD)	p28 (31)	p33 (31)	0.48#

† From $\chi 2$ test unless otherwise stated
 # From independent-samples t test
IVH: intraventricular hemorrhage; N-CDI 2A: Communicative Development Inventories, Dutch edition; SD: standard deviation

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A qualitative study on the knowledge and attitude of primary school students towards pediculosis capitis

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pediculosis capitis, primary school, qualitative research

Abstract

Background

Pediculosis capitis -or infestation with head lice-is frequent in school-aged children. While the clinical consequences are limited to itchiness and irritation, the social impact of infestation remain high, often due to a lack of knowledge and prejudice. Most research focusses on treatment and prevalence, but rarely on evaluating knowledge, perceptions, and beliefs.

Methods

We used a qualitative methodology (semi-structured interviews) to assess the knowledge and attitude of the students. Ten primary schools in Flanders were included and the opinions of 240 students from fourth, fifth or sixth grade were obtained. The knowledge was tested with ten true/false questions and their perception with an in-depth interview. Data-analysis was performed using the QUAGOL method (Qualitative Analysis Guide of Leuven).

Results

The knowledge test revealed a mean score of 63% (SD ±37%). The topics 'lifecycle', 'symptoms' and 'transmission' scored the worst. The most prominent misunderstanding is the belief that head lice can jump (21% correct). In the reflective part, three main themes occur: misconceptions, attitude (feelings, friendship, behaviour) and disclosure (towards parents, teachers and friends).

Conclusion

This study examined the knowledge and perceptions of primary school students in Flanders concerning head lice. Students failed to assess the transmission route adequately. The main concepts in their reasoning were identified. Accurate health education could be used to counter misconceptions and social stigma

Introduction

Pediculosis capitis, head lice, remains an important and prevalent infestation that affects 8.9 percent of school-aged children, particularly between the ages of three and eleven years old (1,2). It is mainly a paediatric health issue, even though adolescents and adults can also become infected by direct head-to-head contact. Girls tend to be infected more often because of two reasons. Firstly, because of gender-related behavioural differences (girls usually maintain closer contact in groups) and secondly, because of their greater hair length (3). An infestation with head lice can be very unpleasant; but fortunately, the morbidity is mainly limited to itchiness and irritation, while scratching can lead to skin lesions (4).

In contrast to the limited morbidity, a major taboo still exists when someone is infested with head lice. It is often associated with a lack of hygiene, which leads to stigmatisation of the affected children or the so called 'index families' (5). However, research has not found head lice infestation to be significantly reduced by frequent hair washing (1). The negative social consequences (due to a lack of knowledge and prejudice) induces parents not to report when their children are infected. Children on the other hand fear their parent's reaction as they often respond to the news with disgust (6). However, when this information is not disclosed, an outbreak of head lice can spread rapidly.

The majority of research on pediculosis capitis addresses topics like treatment and prevalence while fewer studies have been performed to evaluate knowledge, perceptions, and beliefs. Sidoti et al. showed that there were deficiencies in the knowledge of schoolteachers and students, for instance on the biology of head lice and prevention (7). A study from Thailand demonstrated that adequate health education packages are an effective tool to reduce head lice infestations in schoolgirls (8). This type of research is essential to provide quantitative information on the subject-matter, but an in depth analysis using a qualitative methodology is still lacking. A closer look on perceptions, attitude, and beliefs about head lice in primary school students would be very meaningful as a better understanding of misconceptions, can be used to better educate and mitigate taboo or stigmatisation. This could in turn lead to fewer infections and a better well-being of children in primary schools.

The research question of this study is: 'What is the knowledge and attitude of primary school children in Flanders on pediculosis capitis?'. We hypothesize that there are still many misunderstandings, that children lack a thorough knowledge and that negative emotions (e.g., fear, disgust, shame) are widely present. To investigate this topic we conducted qualitative research using semi-structured interviews with primary school children.

Methodology

Study design

We used a qualitative study design with semi-structured interviews. The strength in this type of research lies in a thorough exploration of thoughts and feelings of participants regarding a specific topic, including personal and even sensitive issues (9). In preparation of the study, an interview guide was designed to guide the discussion and ensure a consistent theme analysis.

In the study the vocabulary and content was adjusted to the level of comprehension and knowledge of primary school children. One school was part of special needs education program, for which we adjusted the formulations to reduce the question complexity, while the content remained the same.

Participants

Primary schools in Flanders were randomly recruited via e-mail using a standard information form accompanied by a personalized message. Schools could reply if they were interested to participate in the study.

Interviews were held in-person in the classroom with the investigating researcher presenting the material and the regular teacher observing the proceedings. Inclusion criteria were: students in the fourth, fifth or sixth grade, physically present in the class and with sufficient mastery of Dutch. In total, 240 children of ten schools met these criteria and were included in this research.

Parents of the participating children were notified at least one week prior to the interview with an information letter. Students received a similar message, explaining the research at their level. These letters were either sent out by the teacher using the online school platform 'Smartschool' or printed and handed out.

Interviews were carried out in Dutch by the same investigator between March and October 2022.

This study was approved by the Ethics Committee UZ KU Leuven (MP018531).

Interviews

The interview guide consisted of ten true/false questions clustered around six topics: prevalence, symptoms, life cycle, treatment, transmission and prevention strategies (2,5,10,17,19,26,27). Students were asked to respond to the statement by showing a true/ false sign. Their answers were counted, and the correct answers were discussed, followed by an explanation of each topic. This survey was followed by the reflective part consisting of six questions to assess their perceptions, feelings and beliefs on head lice (2,10,21,22). Students could raise their hands if they wanted to contribute, and the investigator could explore these topics more in depth.

Data-analysis

We used the QUAGOL method, which is a comprehensive guide for qualitative data analysis (11,12). Interviews were transcribed verbatim, along with a brief summary of practical information describing each participating school.

Next, interviews were read through multiple times, using pen and paper to mark specific statements and write down impressions and thoughts. Each of these fragments were assigned a code manually. A conceptual interview scheme was arranged in preparation of the actual coding process.

During that coding process, the concepts were listed and backed up by representative statements from participants. Results were put into tables for an inter- and intra- dimensional comparison of primary schools. The educational part generated numeric data - for which we created a dataset and used descriptive statistics– next to the qualitative data in the form of quotes. From the reflective part we identified the following main topics: misconceptions, attitude and disclosure paired with their individual subtopics. Analysis of the transcribed data was performed in the original language in which interviews were conducted (Dutch). Quotes from participants in this paper were translated to English.

Results

Socio-demographic characteristics of participants

Thirty-one percent of the schools (10/32) that were contacted, were included in this study. The selection of the schools reflects a balanced representation from the current landscape of free subsidised, free official and the community education in Flanders (Table 1). Each school is denoted with a capital letter. The student's statements are marked by that letter and a number (e.g. Student M.1: first quote from a student in school M).

A total of 240 students from ten schools participated in this qualitative research. Each included school proposed one class from either the fourth, fifth of sixth grade to take part in the interview. One school asked if every grade could be included, which adds up to a total of 12 classes divided over ten schools in Flanders. We included schools of varied sizes with a mean class size of 21 students (SD ±5). One school was part of special education program which explains the small class size of eight students. Geographically, schools were spread across Flanders.

Table 1: characteristics of ten participating primary schools (13,14)

	School network	Class	Class size	School size
School M	Free subsidized education	4th 5th 6th	20 19 17	402
School W	Free subsidized education (Special education)	4th	8	87
School J	Free subsidized education	4th	20	435
School A	Free subsidized education	4th	23	557
School V	Free subsidized education	4th	16	313
School S	Community education	5th	24	201
School L	Community education	5th	17	192
School B	Free official education	5th-6th	25	148
School R	Free official education	4th	26	315
School H	Free official education	5th	25	320

Data overview and identification of important concepts

Knowledge of students

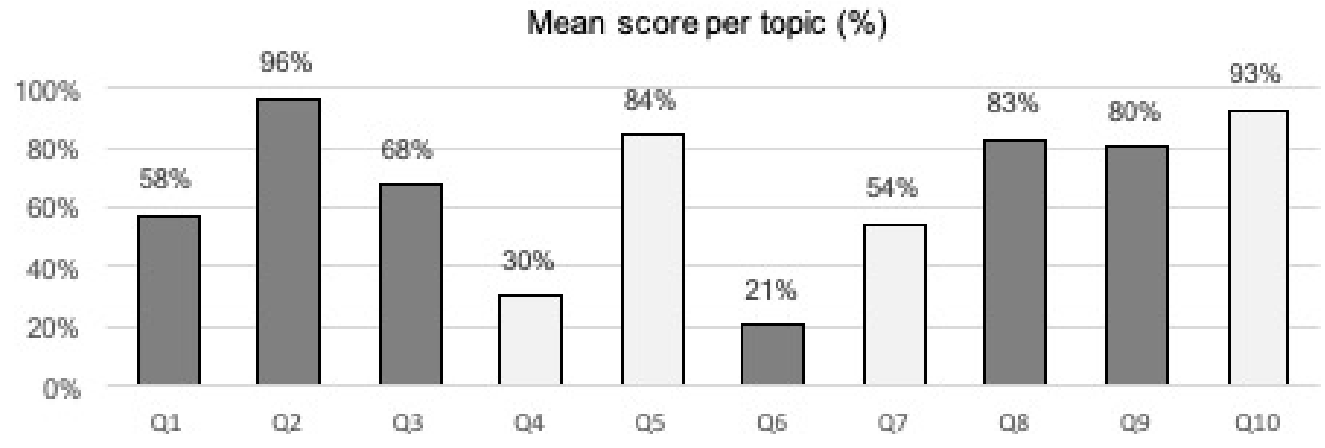
In the educational part of the interview, 240 students participated in a survey with ten true or false statements about six topics concerning head lice (see Table 2). The percentage of correct assessment was calculated using 240 as a total sample size. There was a small drop-out in collected data for one class of 23 students due to technical issues with the recording equipment. Therefore, question five and six could not be accounted for and were calculated with a different total sample of 217 (marked with * in Table 2).

An overall mean score of 63% (SD ±37*)* was achieved. Numerical data and distribution of correct answers are shown in Figure 1. The topics

Table 2: results from knowledge quiz of 240 interviewed primary school students

Topic	True/false questions	N (%)
Prevalence	1) *Head lice are not occurring that frequently any more. A maximum of 2% of primary school children has experienced head lice (false).*	138 (58%)
	2) *Head lice can only occur in children. My parents or grandparents cannot become infested (false).*	231 (96%)
	3) *Girls are more frequently infested with head lice than boys (true).*	162 (68%)
		Mean score 74%
Lifecycle	4) *Most often the heads of children - who wash their hair the least - are the place where head lice like to live the most and reproduce (false).*	73 (30%)
	5) *The eggs of lice are encapsulated in a shell, which is called a 'nit' and the young lice that hatch from it are called 'nymphs'. Those nymphs will grow to become adult lice (true).*	183 (84%) *
		Mean score 56%
Transmission	6) *Head lice can jump from one student to another when they are sitting next to each other on a school bench (false).*	45 (21%) *
		Mean score 21%
Symptoms	7) *The itchiness I experience when I am infested with head lice is because of the crawling of those parasites on the skin of my head (false).*	130 (54%)
		Mean score 54%
Treatment	8) *Without treating the head lice, they will die on their own and disappear (false).*	198 (83%)
	9) *The best way to get rid of head lice is by using a 'louse comb' in hair that is rinsed with conditioner (true).*	193 (80%)
		Mean score 81%
Prevention	10) *It's best to also check my siblings for head lice when I am infested (true).*	222 (93%)
		Mean score 93%
		Total mean score 63%

Figure 1: bar chart of mean scores per topic



of treatment and prevention strategies scored well. The knowledge of head lice prevalence was good. The lower score on the topic of lifecycle was mostly due to the misbelief that head lice infestation is associated with poor hygiene (30% correct answers on question 4).

Most striking were the student's misconceptions about the route of transmission. In almost every class, the majority of students thought that lice could jump from one person to another. This resulted in only 21% correct responses on this topic.

Reflection of students

The following themes were discussed in the reflective part of the interview using six questions: experience with head lice, feelings of shame, fear, disgust, disclosure towards parents, disclosure towards friends/class teacher and lastly the adjustments of daily activities when they were informed that a classmate was infected. The sixth question was if they had been confronted with head lice in places outside of school. This was a concluding question, to open the reflection and to check if they had understood the material. In the analysis three important themes became clear. They are discussed here below, supported by quotes from the interviews.

Misconceptions

Despite the fact that many primary school children have encountered head lice at a given time in their life, several misconceptions still exist. This is illustrated by the quantitative results in table 2, as well as by the following statements and questions.

Student M.1: One time I really knew for sure that I got them from my cat!

Student A.1: I once read this article about a girl who was infected with head lice for about five years and then she died because too much blood had been sucked away.

Attitude

Three subtopics were recurrent during every conversation: feelings of shame, disgust and fear, the value of friendship and behaviour/exclusion.

Feelings

The feeling of shame was not often communicated by students. It was closer to a feeling of fear about the way others would react or the physical experience that accompanied the infestation. Some students stated that the idea of being a host to parasites is not very pleasant. Feelings of fear were mostly grounded in poor understanding and irrational beliefs.

Student M.2: I wouldn't really be ashamed, but I wouldn't find it pleasant either when someone would say 'yuk, that is gross'.

Student S.1: Other children automatically think that they can't come near you because otherwise they might get infected. On the other hand, I do understand them because they just want to be cautious.

Student S.2: I find it gross when I know that there are insects in my hair. When I think about it too much, I get grossed out.

Student A.2: I'm sometimes a bit afraid, 'I hope my hair doesn't fall out because of all the combing and the shampoo, I hope those lice don't make me scratch too much and what if they make scars on my head and start sucking blood…'.

The value of friendship

This value appeared to be a priority to many students. Friendship was a valid consideration when they were asked if they wanted to sit next to a classmate if it was known that he/she was infected.

Student H.1: If it's really one of your best friends with whom you play every day, then I would definitely sit next to them.

Student S.3: I would tell my friends 'I am going to keep my distance now, but we can still be friends, we can still hang out together'.

Behaviour/exclusion

An important consequence when disclosed that somebody has head lice, is the fact that people tend to behave differently. Exclusion of classmates can occur and friendships or even family bonds can be affected.

Student M.3: I would be a bit scared of their reaction that they would refuse to play with me fearing transmission.

Student V.1: I regretted having head lice because we weren't allowed to hug anybody and, on the couch, my family used to always sit together but then they had to keep some distance from me.

Disclosure

It is known that head lice spread readily between young children, especially in primary schools. Regularly, a symptom-free-period of two weeks precedes the onset of pruritus. This can lead to 'silent' transmissions because head lice can freely infect other children if there is close head-to-head contact (15). On top of that, there are - as mentioned above- negative feelings and misconceptions that may interfere with open communication.

We looked into the disclosure of students towards three important actors in this health issue.

Disclosure towards parents

Students seem to know why it is important to be honest to their parents so that they can help. Moreover, it is clear that most parents know how to approach this problem appropriately. On the other hand, a rigorous treatment is time consuming and needs consistency. Guidelines advise to comb the hair for fourteen days straight (using a special comb), which can be a lot of work for parents. As mentioned before, parents can react with disgust which makes it harder for children to confess. Some students impersonated the reactions of their parents in a dramatic way during the interview. Other parents stay very calm and immediately act responsibly.

Student M.4: I would instantly tell my parents because they are the ones who can do something about it. My mother would say 'let's go to the pharmacist to buy a comb or shampoo', but she most certainly would not overreact.

Student H.2: When I tell her, my mom always sighs because she knows how much work it is. But then again, she knows that I can't help it.

Student A.3: My mother always reacts in the same way. Firstly, she's really stressed out and panicked and she begins to call everybody: 'do you have head lice, who has head lice?' and then she calls the pharmacist…

Disclosure towards school (teacher)

A large majority of students stated that they could be honest with their teacher. Only a few individuals stated they would be reluctant to tell their teacher. This largely depends on whether or not they have a good rapport with the teacher. In general, the interviews revealed that it is typically the parents who inform the teacher or school, not the student him/herself.

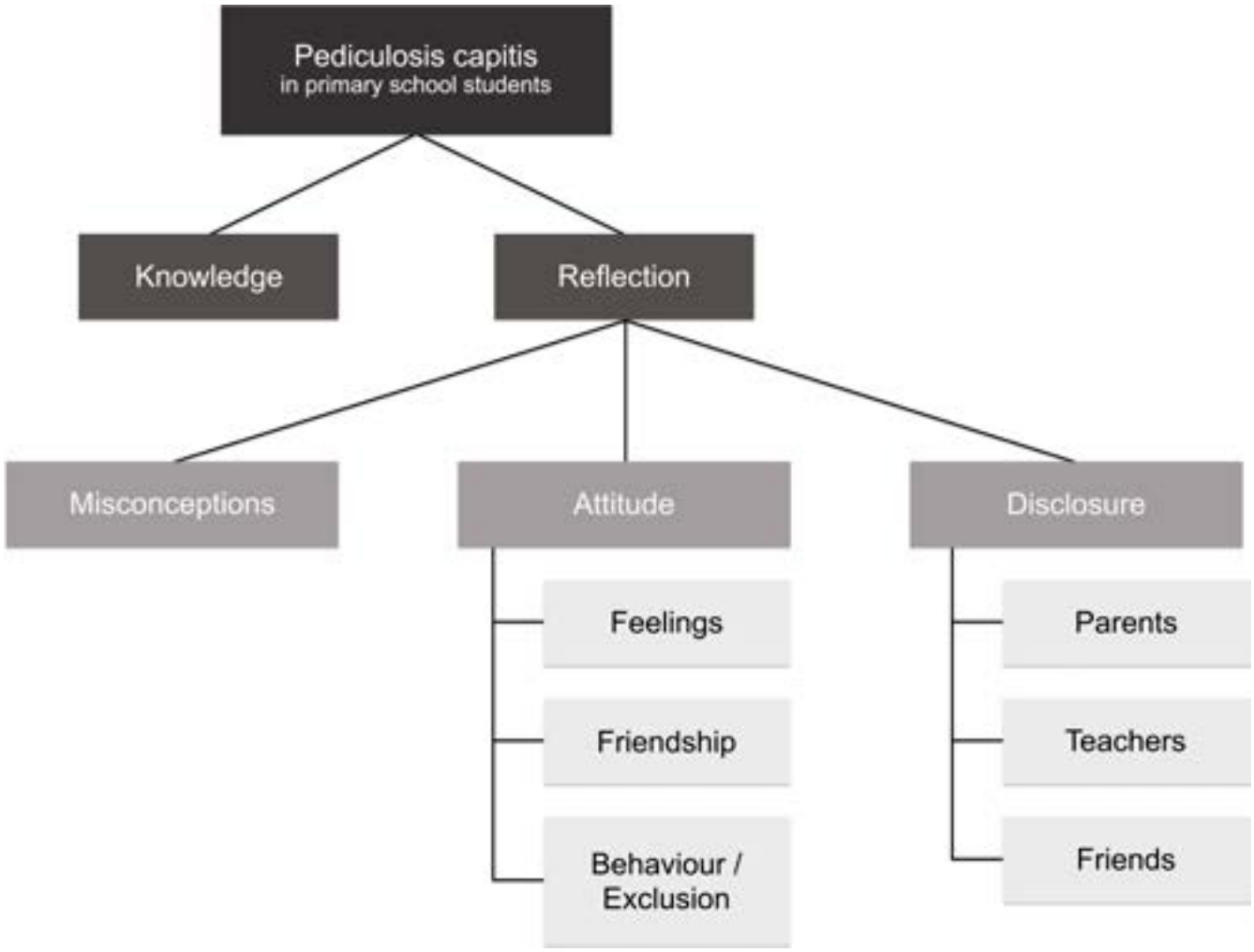
Student M.5: I would only tell her if it has already disappeared, and I no longer have them.

Student W.1: I once told my teacher that I had head lice and she reacted very surprised. Right? And then you immediately told mister X (another teacher at school).

Disclosure towards friends

The friendship with an infested classmate usually minimized their own reaction to the news. On the other hand, disclosing an infestation is not

Figure 2: conceptual overview of the knowledge and perceptions in head lice in primary school children



always easy. When asking them what they would say if a friend came to them with this news, they stated that they would react supportively.

Student S.4: I sometimes find it hard, I have some trouble telling it, because I'm scared of how they might react.

Student H.3: I would not find it gross, I think I would not react in a mean way. I would say 'oh that's too bad, I hope they go away soon.

Discussion

Student knowledge of Pediculosis capitis

The knowledge test showed that participating students are familiar with the subject-matter, oftentimes through their own experiences. Some topics were well understood, such as treatment and prevention strategies. However, the topics 'lifecycle', 'symptoms' and 'transmission routes' of head lice scored poorly, with a 21% correct answer rate in the latter. This heterogeneity in knowledge, was also found in the quantitative study of Sidoti et al (7). Their research used multiple-choice questions and reported only 60% correct answers. Due to the simplicity of their questions a higher score should be anticipated according to the researchers (Sidoti, 2009). In contrast to our finding, Italian students showed less understanding on the topic of prevention. Researchers suggested educational interventions to train students in order to decrease head lice infestations. Yingklang et al. demonstrated this by providing health educational material to an intervention group of schoolgirls compared to a control group (8). Not only did the educated students score better on the questionnaire, but a significant decrease of head lice infestation rate was observed accompanied by a lower incidence of new cases at two months after the intervention.

An important source of misinformation seemed to be cartoons and other media that children watch. The biggest misunderstanding in our cohort was that children believe head lice can jump from one head to another, when in fact they are transmitted by direct head-to-head contact. Head lice cannot fly nor jump, but they keep being presented that way in mainstream media (16,17). For example, an educational magazine used by teachers, principals and school management in Flanders, has an informative video on their website that shows 'jumping head lice' (18). This is rather unfortunate, because the remaining information they supply is correct and they are thought of as a well-established and trustworthy information source for schools. Not a single student was able to correctly answer all ten questions. However, our participants stated that they had gained new insights and talked openly to one another with better understanding than at the beginning of the interview. This indicates that simple interventions on class level could be particularly useful in educating children on head lice.

Student reflections on infestations with Pediculosis capitis: misconceptions, attitude and disclosure.

Misconceptions

Apart from the abovementioned 'jumping of head lice', some other misconceptions were discussed during the reflective part. A recurring

theme was the perception that head lice were able to live on body parts other than the head (i.e. lice crawling over their face or climbing up via hands and arms). Another misconception was that students seemed to be convinced their pet animals could be the source of head lice. This was also listed as a common myth in the article of Clore, et al. (1989), illustrating that false information and insufficient knowledge have been present for decades (19).

Attitude

As a very common and long-existing public health issue, pediculosis capitis had been researched thoroughly over the last decades. The systemic review of Hatam-Nahavandi illustrates this as well, covering topics such as prevalence and worldwide infestation rates (3). However, evidence-based studies about the emotional impact of head lice on school-aged children are scarce. Some research has been conducted to evaluate knowledge and perceptions of schoolteachers or parents (20,21,22). Unfortunately, the population that most often deals with head lice –three- to eleven- year olds – have not often been interviewed. One exception is the research conducted by Purdy & True (23). Using drawings and child-centred interviewing, ten children described feeling sad, embarrassed, dirty, and scared. We hypothesized that students would report feelings of shame when infected, which surprisingly was not often mentioned. Firstly, children did not seem very ashamed overall, as they were most of all concerned with other people's comments. They feared the reaction of their classmates and friends and expected to be excluded by them. Secondly, the physical symptoms accompanying head lice infestations (e.g. itchiness) were reported more often than shame. The itching, tickling feeling and the sometimes-painful treatment strategies (e.g. a fine lined metal hair comb) were reported as 'very unpleasant'. Students sporadically mentioned fear. The idea of hosting a parasite was scary to some because of their blood sucking capabilities. They feared that excessive scratching could lead to scarring.

An important theme was the value of friendship. Students stated their friendship to be most important and did not really mind the infestation in their friends. This is an illustration of the importance of friendship in primary school pupils. Being part of a group and being accepted by your peers is not only vital to the child's wellbeing, but it is also 'one of the most powerful predictors of mental health and behaviour into adulthood' (Sherman, 2000) (24).

An important consequence of head lice infestation is the environment's reaction. Family and friends will behave differently to minimize transmission risk to siblings and avoid major outbreaks at school, respectively. This can lead to exclusion from participating in activities on the playground or in the classroom. Some interviewees answered they would indeed refuse to sit next to an infected classmate to protect themselves. Others talked about the consequences they experienced, from feeling lonely because they could no longer sit close to their family members to enduring bullying by siblings.

In the past decades there has been some controversy on whether to exclude infected children from school. Some literature reports a 'no nit policy', which states that children with nits should be removed from school until they are treated, and all visible nits are removed (25). However, this approach is unscientific because children with nits alone are not infectious (nits are empty eggshells). School exclusion would only harm the students socially and emotionally as it would interfere with their education. In Belgium, the VWVJ (i.e., Flemish scientific association for youth healthcare) clearly states that students should never be excluded from school (5,26,27). Reasons given are the presence of asymptomatic carriers (who are infectious but not diagnosed) and the lack of evidence that would support a 'no nit policy'. Only one interviewee reported to have stayed home from school when infested with head lice.

Disclosure

Van der Wouden, et al. describe the social impact and reaction of parents in particular (6). Apparently, parents often react with shock and revulsion. This response is seated in the deep-rooted misconception that head lice are associated with poor hygiene, which is not the case. The article correctly describes difficulties in tracing the source because shame and social stigma make parents reluctant from disclosing this information. This could complicate contact tracing. However, the results from our research do not indicate that this barrier (informing the parents) is present in Flemish schools. We observed that students stated they would openly tell their parents. We learned that some parents react rather with disappointment to an infestation - especially because of the trouble of treating and combing the hair (based on testimonials of their children). This can take up a lot of time and asks for consistency (28). Some rather panicked reactions have been reported. Yet, most of the parents remained calm according to the children, they consoled them and stated they would take the proper eradicating measures. Parallel with the student's honesty towards their parents, the same statements were made about informing their teachers. Most students did not hold back in telling their teacher, depending on how much they liked their current teacher and if they believed teachers would inform other staff members.

Strengths and limitations

The strength of this research lies in its qualitative nature. The ability to directly ask questions and gain deeper insights behind the reasoning of students, provides a thorough investigation. Furthermore, school-aged children have not been investigated often despite the fact they encounter this health issue most often. The assessment of their knowledge, attitude and perceptions attempts to fill the gap in evidence-based research in this area. The weakness is the possible confirmation bias and peer pressure that occurs when interviewing a group of people - especially children- simultaneously. In the educational part, students could observe which answers their classmates gave. This could make them change their instinctive beliefs – making the results less trustworthy. This problem was observed in the first class we visited. Some adjustments were made to decrease this problem by asking the students to close their eyes before responding in order to be less influenced by their classmates' answers. This method was carried on for the rest of the interviewing process.

Conclusion

By conducting this qualitative research using semi-structured interviews with primary school, we were able to assess their knowledge on the topic of *pediculosis capitis*. A considerable hiatus was observed regarding the head lice's transmission route. We also identified the main concepts in their reflection. These concepts include misconceptions, attitude (feelings, friendship and behaviour) and disclosure (towards parents, teachers and friends).

It is important for children to be well educated and to be able to speak openly about their beliefs and feelings on this topic. Schools should provide them with health education programs, which would benefit not only the student's wellbeing, but can also be of crucial importance in reducing transmission rates.

Conflict of Interest Statement

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

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Autoimmune pancreatitis in Children: Case Report and Review of the Literature

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Keywords

Autoimmune pancreatitis; children; case report

Abstract

Autoimmune pancreatitis (AIP) is a rare entity that is extremely uncommon in children. We report a case of AIP in an 8-year-old boy who presented with severe obstructive jaundice and hepatomegaly. Abdominal ultrasound and Magnetic Resonance Cholangiopancreatography showed a diffuse enlarged pancreas causing compression of the common bile duct with severe dilation of the gallbladder and intra- and extrahepatic bile ducts. Laboratory results revealed positive antinuclear autoimmune antibodies and normal serum IgG4. Based on the clinical findings and imaging the diagnosis of autoimmune pancreatitis was made, which showed excellent response to corticosteroid therapy.

Introduction

Autoimmune pancreatitis (AIP) is a rare chronic disease of the pancreas, first described in 1961 in adults by Sarles et al (1). It was described as a distinct form of chronic pancreatitis, usually characterized by obstructive jaundice and abdominal pain, with or without a pancreatic mass mimicking pancreatic cancer. In 2010, the diagnostic criteria for AIP were established by means of an international panel of experts including pancreas histology, imaging findings, positive serology, presence of other autoimmune or inflammatory organ diseases, and prompt response to corticosteroids. These criteria are otherwise known as the 'HISORt criteria' (2). The AIP entity in adults is divided into two subgroups, IgG4-related AIP (type 1) and non–IgG4-related AIP (type 2) (2). Type 2 is frequently associated with inflammatory bowel disease, whereas type 1 has often signs of extra-pancreatic involvement (3).

In children, AIP is rare and the distinction of two subgroups as described in adults is difficult to achieve. Data on pediatric AIP remain limited with only a few cases reported from all ethnic backgrounds and a median age of 13 years at diagnosis. Most cases show similarity to type 2 in adults (4). In the past pediatricians relied mostly on the adult criteria to diagnose AIP, but new studies and increased recognition of the disease have led to child-specific studies and recommendations (5,6). Here we present a case from our hospital in Curaçao to increase knowledge about this rare entity in the pediatric population.

Case presentation

An 8-year-old boy presented with a 10-day history of abdominal pain in the right upper quadrant, darker urine and pale stools. There was no diarrhea or vomiting and he had no fever. His past medical history was unremarkable. On physical examination he had icteric sclerae, which were present for 10 days as well. The abdomen was slightly distended but not tense, with a significant hepatomegaly for up to 11 centimeters below the costal margin. Biochemically he had elevated transaminases, gamma-glutamyltransferase and hyperbilirubinemia, but the INR, PT, aPTT and lipase were all normal. IgG was elevated as well, but IgG4 levels were normal (see Table 1).

Table 1 : Laboratory data on admission

Laboratory test (SI units)	Result	Normal range
Leukocytes (x10^9/L)	7.3	4.5-13.5
Hemoglobin (g/L)	156.6	127.8- 172.8
Platelets (x10^9/L)	437	150-400
CRP (mg/L)	<4	<10
AST (U/L)	731	13-40
ALT (U/L)	584	10-49
GGT (U/L)	417	<55
Alkaline-phosphatase (U/L)	891	86-315
Total bilirubin (µmol/L)	157	5-21
Direct bilirubin (µmol/L)	121	<5
Lipase (U/L)	56	10-60
IgG (µmol/L)	190	43-106
IgG4 (µmol/L)	1.80	0.15-12.6
PT (sec)	11.9	9.8-12.7
aPTT (sec)	27.3	25-39
INR	1.1	0.9-1.1

(CRP, C-reactive protein; AST, aspartate-aminotransferase; ALT alanine-transaminase; GGT, gamma-glutamyltransferase)

A viral screening was negative. ANA (antinuclear antibodies) screening was positive, with all other antibodies being negative. Abdominal ultrasound showed a distended gallbladder with a length of 11cm and dilation of the intrahepatic bile ducts and a dilated common bile duct (15mm). The pancreas was diffusely enlarged with a head of 2.5cm, body of 2.3cm and an enlarged tail measuring 2.3cm. Other abdominal organs were normal. No enlarged lymph nodes or signs of lymphoma

were observed. Subsequent MRI (magnetic resonance imaging) and MRCP (magnetic resonance cholangiopancreatography) confirmed the diffuse enlarged pancreas resulting in the distended gallbladder and bile ducts. There were no signs of a sclerosing cholangitis (Figures 1 and 2). Altogether this picture was suggestive of a pediatric autoimmune pancreatitis (AIP). Prednisolone was started in a dose of 2 mg/kg/day and within the following days he improved both clinically and biochemically. Because a concomitant autoimmune hepatitis could not be ruled out due to the significant hyperbilirubinemia and elevated liver enzymes, azathioprine was associated in a dose of 2 mg/kg/day. After four weeks, corticosteroids were tapered until eventually they could be discontinued after nine months in total. Azathioprine was continued due to possible concurrent autoimmune hepatitis, unfortunately this could not be confirmed due to the lack of expertise in children's liver biopsy on the island of Curaçao. Repeat MRI after six months of therapy showed no residual signs of pancreatitis and normalization of the gallbladder and liver size. He is currently still in follow-up with frequent clinical and biochemical controls.

Figure 1: Magnetic resonance imaging of the abdomen, showing the dilated gallbladder

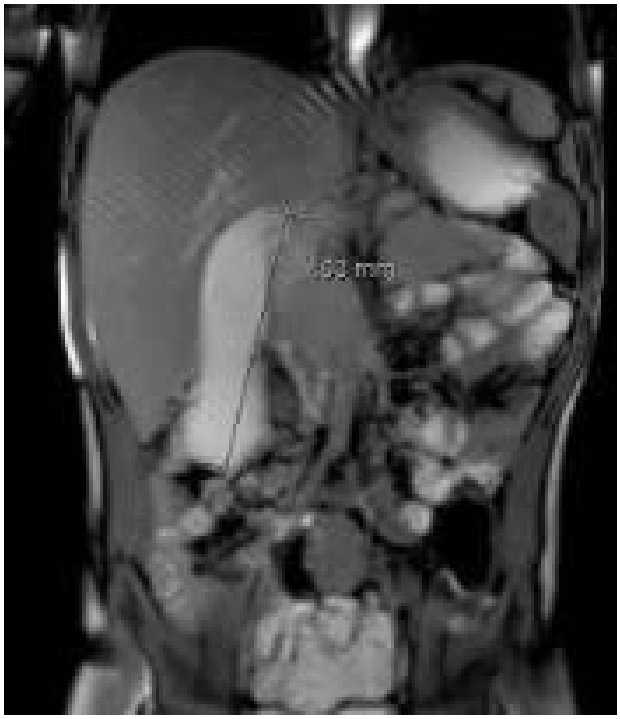
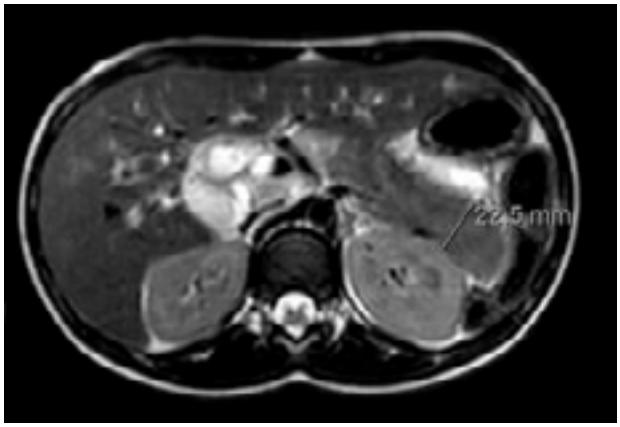


Figure 2: Magnetic resonance imaging of the abdomen, showing the enlarged pancreas with a typical "sausage-like" aspect



Discussion

The worldwide incidence for pediatric AIP is generally unknown, reflected by the previous approach to children with autoimmune pancreatitis, which was largely based on adult data (4). Thanks to the efforts of the INSPIRE group (the International Study Group of Pediatric Pancreatitis: In search for a cuRE) recommendations were made concerning the approach of diagnosis and management of AIP in children. Instead of the HISORt criteria used in adults, which include a pancreatic biopsy to rule out malignancy, the diagnosis in children relies on clinical findings and imaging, given the fact that the risk of pancreatic cancer in children is very low (7).

First step in the approach to a child with obstructive jaundice and/or pancreatitis is usually transabdominal ultrasound. This technique can adequately show pancreatic enlargement or mass formation and rule out other causes of obstructive jaundice. However, if AIP is suspected or when ultrasound resolution is limited, MRCP should be obtained, even in young children who will require sedation for the study (7).

The amylase and lipase levels are not included in the diagnostic criteria in children since these enzymes are normal at the time of diagnosis in 46-57% of children, as was the case in our patient. The same is true for IgG4, which was also normal in our case. Although it has a high diagnostic value in adults, elevated levels are uncommon in children (only in 22%) (4,7). Other autoantibodies have been described in adults with AIP. ANA positivity for example, was identified in up to 40% of adult AIP patients (8). In the pediatric population these autoantibodies have not been systematically studied and since they seem to lack disease specificity, they were not incorporated in the pediatric diagnostic criteria (5,7). Our patient showed positivity to ANA antibodies at presentation.

As for the treatment, current literature favors corticosteroids as first-line therapy in children. The majority of patients with AIP respond to glucocorticoids (80 to 99 percent) and most patients show significant improvement in clinical, biochemical and radiologic abnormalities. Relief of the pancreatic swelling can be observed as early as 2 weeks after the onset of AIP (9). It is suggested to start with oral prednisone, 1 to 1.5 mg/kg/day to a maximum of 40-60 mg given in one or two daily doses for 2-4 weeks, after that the prednisone should be tapered (7). Our 8-year old boy received 2mg/kg/day of prednisolone in two doses for a period of 4 weeks.

Follow-up in all cases is necessary to detect relapse, concurrent auto-immune diseases (e.g. Crohn's, ulcerative colitis, celiac disease, etc.) and possible impaired pancreatic exocrine function (7). Scheers et al. showed that the need for pancreatic enzyme replacement therapy and insulin-dependent diabetes mellitus occurred with a frequency of 16% and 11% respectively during a 21-month follow-up (4). In our patient there was no medical history of autoimmune disorders, nor in his family at presentation, although during his follow-up his mother has been screened for possible auto-immune hyperthyroidism. After 22 months of follow-up, he continues to attend the pediatric outpatient clinic to monitor for relapse or signs of exocrine/endocrine pancreatic insufficiency. Up to date he is doing well without lingering symptoms, although he is still under azathioprine therapy associated with low-dose budesonide since tapering of the corticosteroids resulted in a biochemical relapse of the transaminases. Concurrent autoimmune hepatitis is suspected in this case, which has been described in adult patients, but to our knowledge this has not yet in children been described (10).The signs of autoimmune pancreatitis are as for now completely resolved.

In **conclusion**, autoimmune pancreatitis in children is a distinct entity that responds well to corticoid therapy. Other than in adults, the risk of pancreatic cancer is low, which resulted in recent recommendations to diagnose the disease based on clinical findings and imaging, in particular MRCP.

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Conflict of interest

The authors declare that they have no conflict of interest.

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

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

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

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

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep B vaccin (rDNA, component, geadsorbeerd) EU/1/12/812/001 EU/1/12/812/002 EU/1/12/812/003 EU/1/12/812/004 Farmacotherapeutische categorie: meningokokkenvaccins, ATC code: J07AH09 **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Een dosis (0,5 ml) bevat: Recombinant *Neisseria meningitidis* groep B NHBAfusieeiwit [1, 2, 3] 50 microgram • Recombinant *Neisseria meningitidis* groep B NadAeiwit [1, 2, 3] 50 microgram • Recombinant *Neisseria meningitidis* groep B fHbpfusieeiwit [1, 2, 3] 50 microgram • Buitenmembraanvesikels (BMV) van *Neisseria meningitidis* groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat [2] 25 microgram [1]Geproduceerd in *E. colicellen* door recombinantDNAtechnologie [2]Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3]NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **THERAPEUTISCHE INDICATIES** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **DOSERING EN WIJZE VAN TOEDIENING** Dosering **Tabel 1. Samenvatting van de dosering Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden [a] Primaire immunisatie:** Drie doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c] • **Leeftijd bij eerste dosis: Zuigelingen van 2 tot en met 5 maanden [a] Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c] • **Leeftijd bij eerste dosis: Zuigelingen van 6 tot en met 11 maanden Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c] • **Leeftijd bij eerste dosis: Kinderen van 12 tot en met 23 maanden Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 2 maanden **Booster:** Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c] • **Leeftijd bij eerste dosis: Kinderen van 2 tot en met 10 jaar: Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] • **Leeftijd bij eerste dosis: Adolescenten (11 jaar of ouder) en volwassenen*: Primaire immunisatie:** Twee doses, elk van 0,5 ml **Intervallen tussen primaire doses:** Niet minder dan 1 maand **Booster:** Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] [a]De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b]In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c]Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d]Zie rubriek 5.1 van de volledige SPK. *Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **CONTRAINDICATIES** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen (zie rubriek 5.1 van de volledige SPK). Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosuppressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfuncties (zie rubriek 5.1 van de volledige SPK). Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero.Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. Dit middel bevat minder dan 1 mmol natrium (23 mg) per dosis, dat wil zeggen dat het in wezen 'natriumvrij' is. Terugvinden herkomst Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. **BIJWERKINGEN** Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Bloed- en lymfestelselaandoeningen Niet bekend: lymfadenopathie Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (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** **Luxembourg** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé Site internet : **www.guichet.lu/pharmacovigilance** **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië **DATUM VAN DE GOEDKEURING VAN DE TEKST** 09/2022 (v14) **AFLEVERINGSWIJZE** Op medisch voorschrift. **References: 1.** SmPC Bexsero. **2.** Schmitt JH, Booy R, Astron R, et al. How to optimize the coverage rate of infant and adult immunisations in Europe. BMC Med. 2007;5:11. doi:10.1186/1741-7015-5-11.

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GSK

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

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Keywords

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

Abstract

Background

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

Case

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

Conclusion

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

Introduction

Mercury intoxication is a rare phenomenon that can occur acutely or chronically. Mercury exists in different chemical forms: elemental or metallic (Hg0), mercurous (Hg22+) and mercuric (Hg2+). The mercuric state is found in different inorganic and organic compounds (1). Elemental mercury, also called metallic mercury or quicksilver, is found e.g. in medical measuring instruments (thermometers) and dental amalgam. Inorganic mercury is used as a preservative in vaccines (ethylmercury, thimerosal) and organic mercury is found in seafood (methylmercury) (2).

In industrialised countries, the cause of metallic mercury intoxication in children is usually accidental (2). When a source of liquid mercury breaks, toxic vapours (Hg0) are released. These are absorbed mainly by inhalation into the lungs (80%) and thus into the bloodstream. Also, there is a minimal absorption of metallic mercury via the gastrointestinal system (10%) and the skin (1%). In pregnant women, mercury also passes transplacentally to the foetus. Hg0 preferentially passes through the blood-brain barrier into the central nervous system. In the bloodstream, Hg0 is oxidised to the more toxic Hg2+ state. From there, it spreads to several organs and leads to organ dysfunction. Consequently, organs such as adrenal glands, kidneys, liver, muscles, skin and peripheral nervous system are damaged (1).

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

Case presentation

Patient information

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

Four other family members showed similar symptoms. The 3-year-old brother had insomnia and deteriorating behavioural changes since three months. He also presented with a rash with acral desquamation, tingling legs, pruritus, anorexia with weight loss and hair loss. The

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

Clinical findings

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

Diagnostic assessment

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

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

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

Therapeutic intervention

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

Follow up and outcomes

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

Discussion

Children are vulnerable

The urinary mercury levels were higher in the children than the parents and the children had more symptoms than the parents. Children typically have higher body concentrations at similar exposures than adults. Their vulnerability lies, on the one hand, in increased exposure to mercury vapours. Being heavier than air, they sink to the ground, hence closer to the smaller child. Children also inhale more vapours due to their higher respiratory rate. Also, they come into contact with the peculiar substance more because of their curiosity. On the other hand,

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

children are more susceptible to intoxications due to their still developing nervous system. Consequently, persistent neurological damage is more common in children (2,4)neither children nor adults should have any mercury in their bodies because it provides no physiological benefit. Prenatal and postnatal mercury exposures occur frequently in many different ways. Pediatricians, nurses, and other health care providers should understand the scope of mercury exposures and health problems among children and be prepared to handle mercury exposures in medical practice. Prevention is the key to reducing mercury poisoning. Mercury exists in different chemical forms: elemental (or metallic. Note that the detection of neuropsychiatric changes in a baby can be more challenging.

Diagnosis

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

Chelation therapy and response

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

Conclusion

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

Informed consent

The family provided verbal informed consent for publication.

Acknowledgments

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

Competing interests

The authors state no conflict of interests.

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

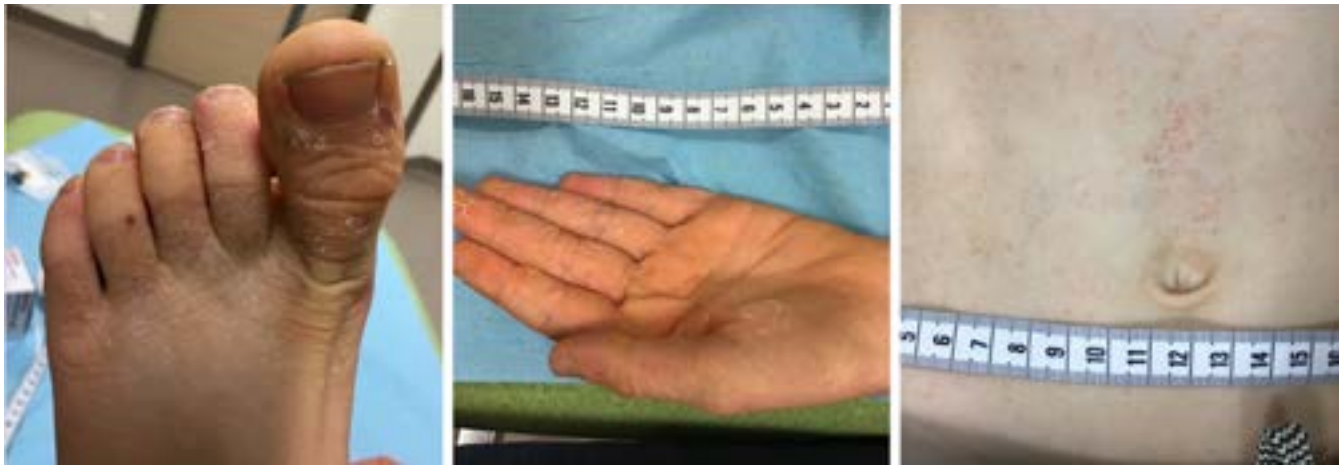

Table 1. Mercury levels in urine and blood pre- and post-chelation therapy.

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

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A complicated course of meningitis caused by *Haemophilus influenzae* serotype a

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Keywords

Meningitis; Haemophilus influenzae serotype a; relapsing fever

Abstract

We describe a case of bacterial meningitis caused by Haemophilus influenzae serotype A with a complicated fever sequence in a 22-month-old otherwise healthy boy. We will discuss the epidemiology of different H. influenzae serotypes and the possible causes of the resurgence of the fever. Surveillance of such invasive infections remains important in order to improve the general vaccination scheme.

Introduction

Bacterial meningitis in young children has become an uncommon, yet life-threatening condition that should be recognized and treated promptly. Since the introduction of generalized vaccination, cases of meningitis caused by the most common bacterial pathogens, such as *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* serotype b, have declined significantly. Other causative micro-organisms remain very rare. We present a case of *H.influenzae* serotype a bacterial meningitis with a complicated fever sequence.

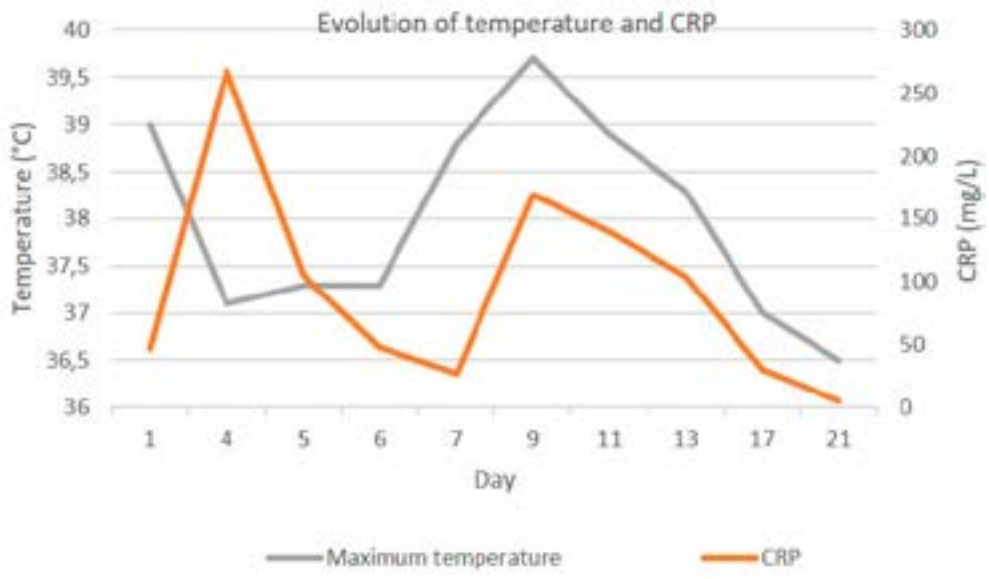
Case presentation

A 22-month-old boy, with no relevant medical history, presented with fever and vomiting since several hours. No other symptoms were reported. Initial clinical examination showed no abnormalities. Laboratory evaluation showed a raised CRP-value (46.8 mg/L; reference value < 5 mg/L) with a normal white blood cell count (5.500/µl; reference value 5.000-15.000/µl). Urine analysis was negative. The boy was admitted to the pediatrics department for observation and supportive treatment. Several hours after admission, his clinical condition deteriorated rapidly with increasing somnolence, global hypotonia and nuchal rigidity. Blood culture and lumbar puncture were performed and empiric treatment, consisting of dexamethasone, ceftriaxone and acyclovir was started.

On day 3, blood and cerebrospinal fluid cultures turned positive for *H. influenzae* (three weeks later, after subtyping in a reference lab, it turned out to be *H. influenzae* serotype a). Ceftriaxone monotherapy was continued, dexamethasone was stopped after 4 days. A central venous catheter was placed on day 4 given prolonged need for intravenous antibiotic therapy and parenteral nutrition.

Initially, the boy improved and defervesced rapidly. However, after 5 days, a second febrile episode occurred with resurging of CRP (from 26.8 mg/l on day 7 to 168.8 mg/L on day 9; figure 1). Urgent neuroimaging (CT-scan) was performed to exclude an intra-cranial abscess. Except for prominent bifrontal subdural effusion of up to 4 millimeters (compared to

Figure 1: Graphical representation of the evolution of CRP-value and maximum temperature.



a CT scan performed 5 days earlier) no abnormalities were found (figure 2). A tertiary hospital was consulted: there were no arguments for subdural empyema and thus no need for immediate therapeutic interventions. In case of persistent fever and/or clinical deterioration, there would be a need for detailed neuroimaging (MRI) and transfer to tertiary hospital.

The central venous line was removed because of a suspected central line infection. However, culture of the catheter tip and blood cultures drawn through the central catheter all stayed negative. Clinical symptoms and additional investigations (microbiological examination of urine, stool and nasopharyngeal samples) did not reveal an alternative cause for the fever. Therefore, we concluded that the fever was based on notable subdural effusion rather than (a new) infection or therapy failure. Hence, antibiotic treatment was continued with addition of systematic acetylsalicylic acid as anti-inflammatory drug.

Antibiotic therapy (ceftriaxone) was continued intravenously for a total of 21 days (cf. antibiotic treatment duration guidelines: treatment duration of 7-10 days in case of uncomplicated *H. influenzae* meningitis, up to 2-4 weeks in case of a complicated course) (1). The fever progressively disappeared within 7 days after the second febrile episode. The boy recovered completely, without neurological impairment at discharge and at follow-up after 2 weeks.

Discussion

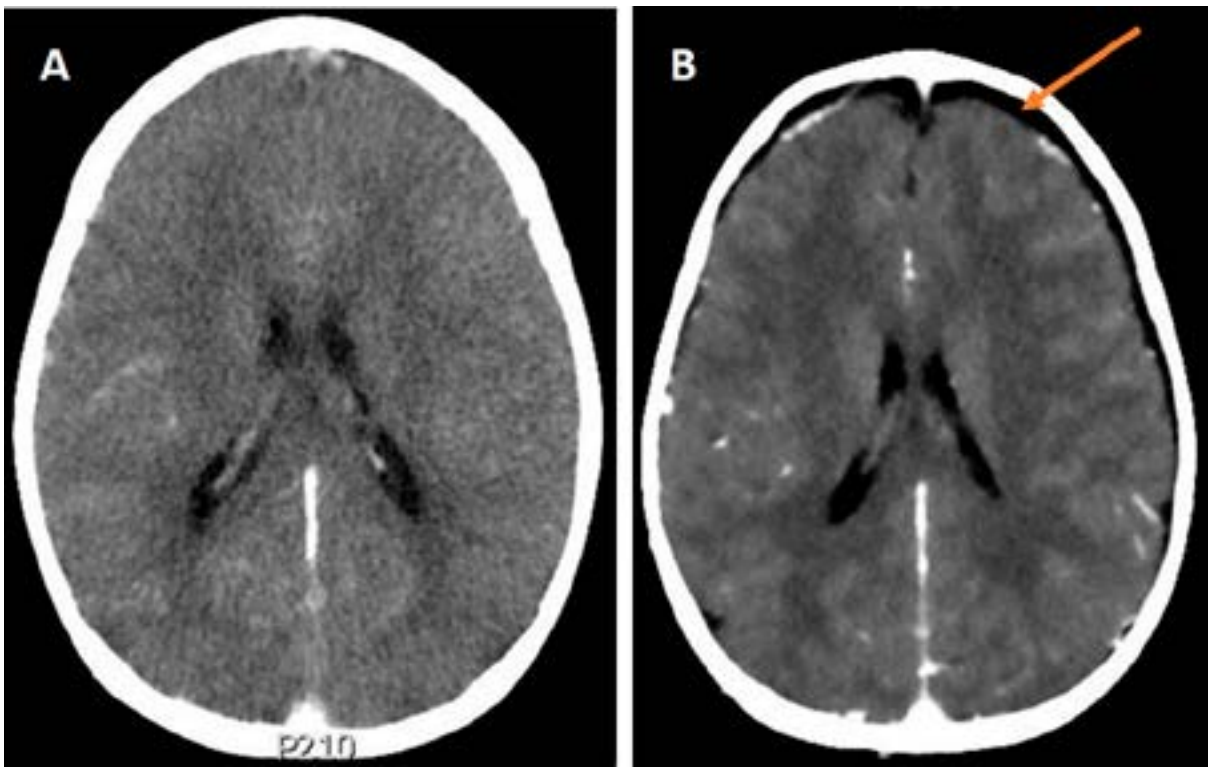
Bacterial meningitis in children older than 3 months has become rare, but it stays important to recognize and treat it rapidly and appropriately. Causative pathogens of bacterial meningitis vary by age group. In children aged 2 months to 10 years the main pathogens are *N. meningitidis, S. pneumoniae* and *H. influenzae* type b. After introducing vaccinations against these 3 main pathogens, a significant decrease was observed in the incidence of bacterial meningitis (2).

This report presents a rare case of meningitis caused by *H. influenzae* serotype a, one of the encapsulated subtypes of the *Haemophilus* strain. The different strains of *H. influenzae* are either encapsulated (6 different serotypes, ranging from a to f) or non-encapsulated (also called 'non-typeable'). The virulence of *H. influenzae* serotype a is comparable to serotype b, given that the capsule has similar characteristics. That is why it equally can cause serious invasive infections, such as sepsis and meningitis (3).

After the introduction of generalized vaccination against *Haemophilus influenzae* serotype b in 1993, there were concerns about a subsequent increase in serious infections with other serotypes. Surveillance of *H. influenzae* invasive infections in Belgium showed a significant decrease in type b infections since generalized vaccination. In 2018, there were 129 invasive *H. influenzae* infections in Belgium, of which only 10 were serotype b (7.8 %). In the remaining cases, the pathogen is non-typeable (74.4%) or serotype f (10.9%). In only 3.8% - i.e. 5 cases including 2 children <5y – of these cases *H. influenzae* type a was involved. This is in contrast to the pre-vaccine period from 1990 to 1992, where there were 250-300 *H. influenzae* type b invasive infections per year. At present in Belgium, we note that there is very limited increase in non-b serotype *H. influenzae* invasive infections (more specifically mainly non-typeable, i.e. non-encapsulated, strains). No absolute numbers are given in the Sciensano report. This has to be monitored closely through ongoing surveillance (4).

A study between 1996 and 2006 in 14 European countries – in which Belgium did not participate – showed an increase in invasive *H. influenzae* infections with non-encapsulated forms, especially in neonates and elderly individuals (relative increase of 3.6% per year in invasive non-b *H. influenzae* infections). Nevertheless, invasive infections with encapsulated serotypes remained very rare, with infections mainly due to serotype e and f (5). Likewise, a population-based study in Utah reveals an increase in non-b invasive infections, with mainly serotype a invasive infection (for invasive *H. influenzae* serotype a in children under 5 years of age: mean incidence increased from 0.8 cases per 100,000 child-years in 1998 to 2.6 cases per 100,000 child-years in 2008) (6). The same observation of increase especially in serotype a invasive infections was seen in a large scale study in The United States and Alaska, with an increase mainly in

Figure 2: Comparison between CT scan of brain at day 2 (A) and day 7 (B), when the second fever episode occurred. The arrowhead on figure B shows a prominent bifrontal subdural effusion, noticeably increased compared to figure A.



young children < 5 years of age (relative increase of 11.1% per year) (7). Although absolute numbers remaining low, worldwide there seems to be an increase of non-b serotype *H. influenza*e invasive infections. A possible explanation for this increase in non-b *H. influenzae* invasive infections may be that *H. influenzae* type b vaccination would reduce carrier status at the throat allowing other strains to establish themselves there. From the throat, these strains can then cause invasive disease. Also, more infections may be reported, due to more accessible surveillance systems

Literature regarding the occurrence of a second febrile episode within the course of a bacterialmeningitis is very limited. The most common reasons for such a relapsing fever are intercurrentnosocomialinfections (viral respiratory tract infections, gastroenteritis, urinary tract infection, infectionsof catheters, ...) and subdural effusions. Rarely, this is due to inadequate treatment, drug fever(diagnosis of exclusion) or subdural empyema. In theory,discontinuation of corticoid therapy may alsobe the cause of the resurgence of fever(8). However, in most cases the exact origin of thesecondaryfever remains uncertain.

There is no well-documented treatment in literature in case of fever due to subdural effusions. Our choice to treat with systematic acetylsalicylic acid as anti-inflammatory drug was hence based on theoretical advantages rather than protocols or evidence based treatment. Given the favorable outcome in our patient, this treatment may be an option in other cases, although we cannot reliably draw conclusions based on one case.

There is no significant difference in the occurrence of a secondary fever among the 3 most important pathogens (*H. influenzae, N. meningitidis and S. pneumoniae*). Persistent initial fever (after starting appropriate antibiotic therapy) > 5 days occurs more in *H. Influenzae* infections than in streptococcal or meningococcal infections (9).

Conclusion

We present a case of *H. Influenzae* serotype a meningitis with a complicated fever sequence in a 22-month-old healthy boy. After 3 weeks of intravenous antibiotic therapy, he recovered completely.

A second febrile period during treatment was noted, causing concern for (re-)infection or therapy failure. We concluded that it was most probably caused by prominent subdural effusion, which is a phenomenon known to occur in bacterial meningitis.

To date, there is limited epidemiological evidence for a slight increase in non-b *H. influenzae* invasive infections in Belgium. Longitudinal studies in the United States of America also show increases in non-b infections, with mostly type a invasive infections. Although serotype a being a rare subtype, concerns are that the prevalence may rise as a result of generalized vaccination targeting serotype b. This should be monitored closely by (inter)national surveillance systems.

Conflict of interest

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

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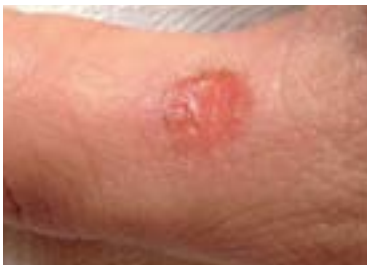
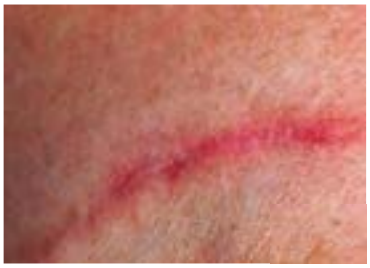

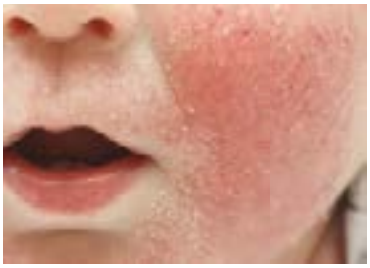
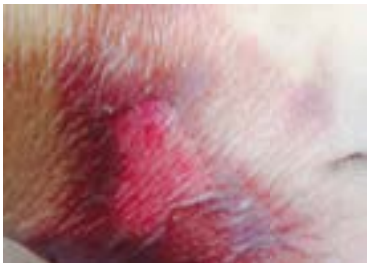


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You have a (paediatric) research idea: How to fund it in Belgium? The 6 Be's of grants-woman-man-ship.

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Keywords

Research grant proposal; research funding

Introduction

If we may dream about environment where research projects are easily financed, the reality if different for everybody, everywhere. Obtaining research funding from local, regional, national or international funding bodies requires dedication and persistence to "survive" peer-review.

Your research proposal will be read, and assessed, by experienced clinician-scientists. Reviewers have been running these kinds of research projects for a long time and know the difficulties in doing so. They can easily see the weaknesses, potential flaws, or foreseen hurdles of your proposal.

Although never easy, possibilities to fund your research idea are greater that one might think. The purpose of this insights paper is to provide reflexions about how the funding process goes together with suggestions to reinforce your research proposal and hopefully make it successful.

1. Be creative: There is no good grant without a good idea (but good idea is not enough)

Modern society apparently loves to run, and our profession is no different. The caricature of a (bad) research project is: it arose from half an idea because you had to publish a paper to get your diploma-contract-promotion, has obviously been written the night before submission, you had no time to discuss it with anybody and could not finalize neither the methods nor the conclusions. This kind of half-prepared submission is easy to identify and has very little chance of success.

Good ideas need time. Discussions. Debates. All which being obviously difficult to organise in our paediatric clinical busy environment. However, with some forward thinking and organization, it is not impossible either. Some projects are "maturing" for years. First, look in the scientific literature for what has been already done on the topic. It will provide you with some background overview and prior attempts to answer your question. Focus on understanding more precisely the issue you want to work on. Who is affected? In what ways are they affected and to what extent? Why is the problem significant? Why is the problem even occurring? It will refine your research question and will pave the way for the appropriate methodology. In terms of methods, you can refer to the 5W questions: **W**ho? **W**hat? **W**hen? **W**here? Ho**w**? Be rigorous and factual in terms of who will do what, when, where and how. Spending more time at the very beginning of a research project is always worthwhile.

2. Be a team: Don't do it alone

Put your good ideas on paper and discuss it with as many people as possible. An idea must be exposed to different people, with different backgrounds and expertise. Present your project to your peers to see if they understand it. Present your project to senior paediatricians to see if they are convinced by it. Look for the opposition, the "other point of view". The useful colleague is that critical one that will provide constructive criticisms and will share her/his experience. Listening to everybody's comments is wise, agreeing with everybody's idea is ineffective. Seeking those discussions will make your grant stronger and will help you learning how to present it best. If you cannot explain well what you want to do, it probably means that you are not ready yet.

3. Be convincing: Precision, rigor and feasibility

A reviewer will never ask you to solve or know everything. What is your actual level of expertise and experience in this specific topic? Don't over pretend, it is most of the time counterproductive. If you are new to the research field, say it and present a convincing collaborative team to support you. There is not much we can do efficiently alone in bio-medical research these days so your collaboration network must be presented in all areas needed for the project success (sustained by identified facts such as co-design of the project, statistical support, previous common publications, …).

One of the key question a reviewer with ask relates to the feasibility of the proposed project to reach its primary objective. How rigorous is the methodology of your proposal? Will the selected study design, the team in place and the overall structure be able to conclude the research? When possible, present potential alternative approaches (plan B) if/when problems happen. Don't hide difficulties, they are inherent to any research process, but show that you have seriously thought about it and have ideas for potential solutions.

4. Be attractive: Your grant needs to be pleasant to read and extremely clear

When sitting in a grant review panel, reviewers receive a large amount of relatively complex grant proposals. Lots of reading for them to do late at night. Many grants are of good quality so your grant must be attractive for the reviewer to become your best advocate in the funding allocation discussion.

You must be clear. Is your grant understandable by a non-specialist? Nobody likes to feel stupid, and grants sometimes are hard to understand. Don't overestimate the knowledge level of any reviewer in your specific topic. What is obvious for you may not be so for the reviewer.

Prefer the use of short sentences (bullet point arguments can sometimes be of great value). Grant proposal are no book literature and long sentences rarely help. Avoid acronyms and abbreviations. They vary according to topic and are unpleasant for the reviewer because unclear. Make your point straight at the beginning of each section/paragraph. Use bolded or underlined font to highlight the key "concluding" sentence of your sections (often a good idea to present in 2-3 clear sentences what you will/have explain/ed in more details in the paragraph). Repetition of the key points is necessary. Reviewer sometimes overlook the proposal and key points should be visually attractive. When reading many grants, the reviewer is attracted by visual pictures, illustrations, font variations, colours, boxes and tables. Adding a graphical abstract that summarize your project is of great value. It takes some time to draw but can really help crossing the funding line. Use boxes and Gantt chart to highlight specific topics and timeline-milestones respectively.

If your grant contains technical of highly specialized data/methods, consider presenting them outside the main text frame. It is good to have different layers of understanding of your grant. The first layer must be very simple (If you have lost the reviewer after the first page, so is your proposal). But you also need to show that you know what you are talking about. So, one trick is to put the "technical" complicated stuff aside (in a figure, a box, a supplementary material -whatever- but visually different from your main text). The interested reviewer can read it, but the non-interested reviewer can easily avoid it. And finally, you must respect the format and recommendations of the funding body. A 5 pages proposal cannot be 6 pages long. Do not expand margins or use lower font but rather simplify the message if needed.

5. Be strategic: Apply for funding with both ambition and reason

You have a great idea, a rigorous and thoroughly designed study protocol, and a beautiful, clear and well-illustrated grant proposal. Where to submit it now? The different funding scheme certainly have variable

Table 1: University related funding foundation or useful websites

University /research agency	Useful Websites
Universiteit Antwerpen	https://www.uantwerpen.be/nl/onderzoek/beleid/financiering-onderzoek/ https://www.uza.be/uza-foundation
VUB Vrije Universiteit Brussel	https://www.uzbrusselfoundation.be https://www.uzbrussel.be/web/onderzoek/fonds-willy-gepts
Universiteit Gent	https://hiruz.be
KU Leuven	https://www.kuleuven.be/fondsenwerving/wat-kunt-u-steunen
Liège université	https://www.fondationleonfredericq.be
UCL Université catholique de Louvain	https://www.fondationsaintluc.be
ULB	https://www.belgiankidsfund.be/fr/ https://www.iris-hopitaux.be/fr/le-reseau-iris/nos-structures/iris-recherche-2
	https://bvk-sbp.be/en/
fwo	https://www.fwo.be/en/
fnrs	https://www.frs-fnrs.be/en/

success rate. In a nutshell, the more international the funding body is, the more competitive the selection will become. It is important to discuss with more experienced colleagues around you, who have a broader vision of funding possibilities and may give you relevant advice and select with you the appropriate funding body. Be ambitious but don't be unreasonable. Build your research career by starting with some local small-scale funding and then expand with more competitive national and international grants. You can often look at the success rate of the grant scheme on the dedicated websites. You can also look at the profile of previous grant recipients to assess whether your experience fit in the "profile" or not. Table 1 summarises a non-exhaustive list of Belgian research foundations. Contact them and discuss your plans and funding strategy. We also have in Belgium many very active sub-specialities foundations that fund research project in specific areas. Contacting the head of sub-specialities will ensure knowing all dedicated funding possibilities. Some, but not all, offer encouraging success rates to emerging researchers.

6. Be persistent: Hang it there

Most funding applications are unsuccessful. Success rates varies from call to call but are overall rather low (some are lower than 5%). Several brilliant research proposals have been rejected a few times by research agencies before being successful. Don't take any negative output personally. Frustration is unfortunately part of the process, but the aim is to be persistent, include any useful reviewer comments and re-apply with a stronger-updated research proposal. If no formal feedbacks are provided by the agency, never hesitate to ask for an explanation about the reasons for rejection. Your either get the research money, or you learn…

Conclusions

Grantsmanship, grantswomanship is an iterative learning process. We try things, often fail but also have some success. It is overall a fun, interesting and creative medical approach. Moreover, the process in itself together with the results that our research deliver are crucial for an innovative, rigorous, and efficient care of the Belgian children we take responsibility for.

Acknowledgments

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Conflicts of interest

No conflict to declare.

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Optimizing diagnosis in drug hypersensitivity

PhD thesis presented on 27/1/2023 at the University of Antwerp, Antwerp, Belgium

Marie-Line M. van der Poorten, MD, PhD[1,2]

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Keywords

Drug allergy, drug hypersensitivity, penicillin allergy, perioperative anaphylaxis, specific IgE quantification, skin testing, drug challenge, diagnosis

Abstract

Drug hypersensitivity reactions constitute an important and increasing health problem with significant morbidity and mortality, associated with both over- and underdiagnosis.

Given the dramatic impact of mislabelling, correct diagnosis is of utmost importance. However, this is not always straightforward, since the available diagnostic tests each carry their own limitations.

Hence this thesis, which aimed to optimize the diagnosis of drug hypersensitivity. In a first objective, the cut-off of specific IgE quantification and potential of a specific-to-total IgE ratio was investigated. Next, we looked at the non-irritant concentrations of skin tests. In the third objective, we objectified the need for drug provocation tests with anaesthetic drugs. Finally, the optimal timing of testing was investigated.

Drug hypersensitivity reactions (DHRs) constitute an important and increasing health problem with significant morbidity and mortality because of misdiagnosis. On the one hand, underdiagnoses carries the risk for re-exposure resulting in life threatening reactions. On the other hand, overdiagnosis, in particular self-reported non-verified allergy comprises severe consequences for the individual patient as well as society. Actually, the false label of a drug allergy is associated with erroneous avoidance and unnecessary substitutions, readmissions, poorer outcomes, prolonged hospitalizations, increased costs and, in case of antibiotic agents, increased rates of antimicrobial resistance. [1-3]

Given the serious, sometimes dramatic impact of mislabelling, it becomes clear that getting the label right is of utmost importance. However, this is not always straightforward.

Diagnosis of immediate drug hypersensitivity generally starts with an in-depth clinical history, followed by skin tests and quantification of specific IgE antibodies. However, no tests are absolutely predictive, each carrying their own limitations.

First, the quantification of specific IgE antibodies displays varying sensitivity and specificity, as shown in our in depth review concerning specific IgEs in the first part of this thesis. [4]

Hence one of the main aims of this thesis was to optimize the performance of these tests.

In the context of rocuronium allergy, we showed that a specific-to-total IgE ratio for rocuronium, pholcodine and morphine did not benefit diagnosis. Whether application of such ratios would benefit diagnosis of other drug allergies, remains an interesting area of research.[5]

In the context of a suspected penicillin allergy, our data show that diagnosis of a non-severe penicillin allergy should not rest upon low specific IgE results between 0.10 and 0.35 kUA/L. We propose an amended algorithm for the diagnosis of beta-lactam hypersensitivity, in which all these patients should be offered a drug provocation tests to confirm or refute diagnosis. [6]

Second, skin testing might be unreliable, such as in patients with cutaneous anergy, dermographism or in patients using antihistamines. Moreover, for many the drugs, the maximal non-irritant concentrations have not been established, entailing a risk for over- and underdiagnosis if set too high or too low respectively.

Hence the second main aim of this thesis: optimizing non-irritant concentrations in drugs in which they have not yet been validated. We chose to do this in populations that relate as closely to clinical practice as possible, that is actual beta-lactam allergic patients instead of healthy controls. Here we show for the non-irritant concentrations for immediate readings for ceftazidime to be a tenfold higher than recommended at the start of this thesis. Moreover, for aztreonam and ceftaroline, we are the first study to propose a non-irritant concentration supported by robust research. We are the first study propose different non-irritant concentrations for immediate and non-immediate hypersensitivity reactions respectively. This shows that non-irritant concentrations should not be generalised and that there is a need to further establish drug-specific non-irritant concentrations in a population representing clinical practise.[7, 8]

A third problem in drug hypersensitivity diagnosis, relates to the absence of a reference test in perioperative hypersensitivity. Indeed, where the drug provocation test is considered the gold standard in allergy diagnosis, it has not been recommended in perioperative hypersensitivity reactions, mainly because of the profound effects of anaesthetic drugs. Hence our objective to explore the need for provocation tests with hypnotics, opioids and neuromuscular blocking agents. By examining re-exposures during subsequent anaesthesia after allergic work-up, we concluded that provocation tests with anaesthetic drugs are not systematically warranted nor absolutely critical for correct diagnosis patients with a suspected perioperative hypersensitivity reaction. [9]

Lastly, we performed research examining the optimal timing of testing for drug hypersensitivity. In this study, which was deemed a practice changer by the American Academy of Allergy, Asthma and Immunology, we challenges the dogma to postpone diagnostic work-up for suspected perioperative hypersensitivity for at least 4-6 weeks. When needed, such as in case of urgent re-intervention, early testing should not be excluded.

Moreover, we refute the too generic recommendation that in vitro testing should never be performed more than 3 years after the index reaction.[10]

In conclusion, this dissertation covers unprecedented research, with each individual study adding to the big picture of drug hypersensitivity diagnosis. Our data have contributed to clinical practice, with value to both the scientific society and the individual patients.

Of course, there is still room for improvement and further efforts are required to optimise the diagnostic approach in drug hypersensitivity.

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Prognosis following a first unprovoked seizure

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Question

What is the risk of further unprovoked seizures and the risk of premature death in people presenting with a first unprovoked seizure?

Context

Approximately one in 25 people will have at least one unprovoked seizure during their life,. A single unprovoked seizure does not signify one has epilepsy as such diagnosis requires two or more unprovoked seizures, usually more than 24 hours apart. However, since a single unprovoked seizure is such a common event, it is important that clinicians can effectively counsel patients and their family on the risk of further unprovoked seizures (and therefore an epilepsy diagnosis) and the risk of premature mortality following their first seizure.

This Cochrane review therefore aimed to provide accurate estimates of the number of individuals going on to have further unprovoked epileptic seizures at certain timepoints following a first unprovoked seizure of any seizure type (or a cluster of epileptic seizures within a 24-hour period or a first episode of status epilepticus). Additionally, it also aimed to provide accurate information on the risk of premature death.

Criteria for study selection

The review included both retrospective and prospective studies of people of all age groups (except neonates) with a single unprovoked seizure of any type who were followed up for at least 6 months. Studies had to include at least 30 participants. Moreover, studies on mortality had to report a proportional mortality ratio (PMR) or a standardized mortality ratio (SMR) at a specific timepoint to be included.

As unprovoked seizures are the focus of this review, studies on people who had seizures that occurred due to precipitant or provoking factors, or in close proximity to a neurological insult were excluded. Studies on situational seizures such as febrile convulsions were also excluded.

Summary of the results

The authors identified 58 studies with a total of 12,160 participants (median 147, range 31 to 1443) of which 26 studies were pediatric studies, 16 were adult and the remaining 16 combined pediatric and adult populations.

In this Cochrane Corner we will focus on the results of the pediatric population and the mixed (children and adults) populations and less on the adult-only population.

Only studies that reported seizure recurrence data at 6, 12 and or 24 months were included in meta-analysis. This was the case for 46 studies of which 23 were pediatric, 13 adult and 10 had a combined population. Seizure recurrence estimates for time points beyond two years could not be provided as most studies had short follow-ups and too few reported data at a single time point after two years.

At six months the estimated overall seizure recurrence for the whole population (mix of adult and children) is 27% (95% CI*: 24% to 31%; 27 studies, 7111 participants, moderate-certainty evidence). At one year the recurrence is 36% (95% CI: 33% to 40%; 34 studies, 6843 participants, moderate-certainty evidence) and it is 43% at two years (95% CI: 39% to 47%; 27 studies, 6908 participants, moderate-certainty evidence).

In the children subgroup analysis, the seizure recurrence estimates are slightly higher: 30% at six months (95% CI: 23% to 37%; 14 studies, 2232 participants, moderate-certainty evidence), 38% at one year (95% CI: 31% to 44%; 16 studies, 2313 participants, moderate-certainty evidence) and 45% at two years (95% CI: 36% to 54%; 12 studies, 2172 participants, moderate-certainty evidence). In the adult subgroup the recurrence estimates were slightly lower than the mixed population.

The included evidence was of moderate certainty. The main limitation was the clinical and methodological heterogeneity caused by some studies that had quite extreme results compared to others. The clinical heterogeneity was somewhat expected as there was variation in the age groups that were included in the studies and treated and untreated individuals were usually combined. However, most studies did show consistent results and the review authors thought the heterogeneity did not impact on the overall results too much.

Results relating to mortality following a first unprovoked seizure were reported in nine studies including 2373 participants, but the data could not be combined in a meta-analysis due to the variability in the reported results. The data did seem to support the consensus that the underlying etiology is the main driver determining the risk of mortality with a first unprovoked seizure, however the authors did not undertake any formal assessment of prognostic factors for mortality in this review.

Conclusion and implications for practice

Seize recurrence estimates after one unprovoked seizure ranged from 30% at 6 months, 38% at 1 year to 45% at 2 years in children. Clinicians can use this information when counselling patients and their families. However, long-term recurrence data, especially beyond 10 years, is still lacking.

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