BJP
Belgian Journal of Paediatrics
Publication of the Belgian Society of Paediatrics

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

2020 - Volume 22 - number 2 - June

Articles

Case Report

Made in Belgium

Paediatric Cochrane Corner

Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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

V.U./E.R. S. Cadranel (ULB), M. Raes (KUL)
UZ Leuven, Herestraat 49, 3000 Leuven
E-mail: BJ-Ped@hotmail.com

SPA® REINE
l'eau et le microbiote du bébé

Dès les premiers mois de la vie, le microbiote intestinal joue un rôle important. **Entretien avec le conseiller en nutrition humaine Jean-Pierre Mans** qui explique le rôle du microbiote et la nécessité d'en maintenir la richesse pour prévenir, à terme, le développement d'infections ou de maladies comme le diabète, l'obésité et l'asthme[1].

L'IMPORTANCE DU MICROBIOTE À LA NAISSANCE

JP MANS *Le microbiote du bébé se constitue dès la naissance au contact de la flore vaginale après un accouchement par voie basse. La colonisation bactérienne se déroule progressivement et dans un ordre précis. Les premières bactéries intestinales ont besoin d'oxygène pour se multiplier (entérocoques, staphylocoques,...). Viennent ensuite les bactéries qui se développent en l'absence de ce gaz (bactéroïdes, clostridium, bifidobactérium...)[2]. Sous l'influence de l'allaitement, de la diversification alimentaire, des traitements médicaux et de l'environnement, la composition du microbiote va évoluer pour se stabiliser vers l'âge de 3 ans.*

UNE BONNE HYDRATATION POUR UN BON MICROBIOTE

JP MANS *Chez le petit enfant, l'hydratation est particulièrement importante puisque le corps du nourrisson est constitué à presque 80% d'eau contre 60% à l'âge adulte[3]. Dès lors, les besoins en eau du bébé sont très élevés: 150ml/kg/j[4]. L'eau faiblement minéralisée et surtout l'allaitement maternel vont jouer de nombreux rôles dont celui du transport des nutriments, des vitamines et des minéraux vers le microbiote pour faciliter leur assimilation.*

RESTAURER UN MICROBIOTE ALTÉRÉ

JP MANS *En cas de diarrhée ou de gastro-entérite chez le bébé, un des risques est la déshydratation (jusque 15% du poids du bébé, en particulier avant 6 mois). Dans ce cas et si l'enfant est nourri au sein, l'allaitement doit être poursuivi. Par ailleurs, une solution de réhydratation reconstituée avec une eau faiblement minéralisée doit être administrée. De plus, si une antibiothérapie a été initiée, il faudra recoloniser le microbiote intestinal[5]. En effet, 80% des cellules immunitaires du corps humain se situent au niveau du tube digestif. Un microbiote intestinal altéré va augmenter le risque de développer par la suite des infections ou des maladies[1]. Dans ce contexte on pourra recourir aux probiotiques dont certaines souches ont démontré leur utilité.*

(1) Harstra et al: Insights into the role of the microbiome in obesity and type 2 diabates, Diabetes care 2015; 38 : 159-65.
(2) Rémy Burcelin, unité INSERM 1048 / Université P. Sabatier & Institut des maladies métaboliques et cardiovasculaires, Hôp. Rangueil, Toulouse.
(3) Fusch et al Water turnover of healthy children measured by deuterated water elimination, Eur J Pediat. 1993; 152 : 110-4.
(4) Conseil Supérieur de la Santé, N° 8309, Recommandations nutritionnelles pour la Belgique, révision 2009.
(5) Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children; J Pediatr Gastroenterol Nutr. 2001 Oct;33 Suppl 2: S17-25.

www.spa.be

Spa soutient la
SOCIÉTÉ BELGE DE PÉDIATRIE

SPA® NATURAL SINCE 1583 éternellement pure

Editorial Board

Founding editors
L. Corbeel, W. Proesmans

Chief Editors
S. Cadranel, M. Raes

Co-Editors
N. Francotte, M. Wojciechowski,
A. Rochtus, Ch. Barrea
S. De Rechter, C. Chantrain
A. Vuckovic

Secretariat
N. Meignen

Universities
G. Buyse (UZL), MC Seghaye (ULG),
P. Smeesters (ULB), S. Van Daele (UZG),
Y. Vandenplas (UZB), S. Verhulst (UZA), St. Moniotte (UCL)

BVK-SBP Executive Committee
M. Raes, President
F. Smets, Vice-president
G. Buyse, Secretary
P. Smeesters, Secretary
D. Dewolf, Treasurer
A. Malfroot, Past-president
D. Van Gysel, International societies

Associations
A. Bael (VVK)
P. Philippet (GBPF)

Belgian Academy of Paediatrics
Ann De Guchtenaere - President
Stéphane Moniotte - Vice-president
Tyl Jonckheer - Secretary
Pierre Philippet - Treasurer

Contents

DE BVK BEDANKT ZIJN PARTNERS VOOR HUN STEUN

LA SBP REMERCIE SES PARTENAIRES POUR LEUR SOUTIEN

---

gsk

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

BIOCODEX
Benelux

SPA

NUTRICIA
early life nutrition

abbvie

Pampers

What's up doc

EXPANSCIENCE
LABORATOIRES

We care for children

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE

SOCIETE BELGE DE PEDIATRIE

Editorial BJP June 2020

The SARS-CoV2 virus is still threatening and dominating our society. Due to a serious flare-up of the number of infections, precautionary measures have to be extended. Planned activities have to be postponed or even cancelled.

Indeed, we have to announce you the sad news that the 48th annual BVK/SBP congress, postponed from March to October 2020 will be canceled. For different reasons it was believed this was the best option. Reimbursement of all registered participants will be arranged. We want to express our very sincere thanks and appreciation to Pierre Smeesters and his HUDERF scientific committee. They had prepared for us a marvelous and very attractive program with some new and original sessions about the central theme: *"Innovations for better health in Paediatrics"*. Arrangements are already started to prepare the March 2021 meeting, organized by the team of Sabine Van Daele, UGent, in close collaboration with the colleagues of HUDERF. Could they have chosen a better and more appropriate title than: "*The Changing Face of Paediatrics* "? Much will be told about a virus that changed not only Paediatrics but most health care systems all over the world. Our knowledge about Covid-19 is increasing every minute. The demand for an effective vaccine was never so intense. Save this date in your agenda! Hopefully we can meet each other face to face.

While being overwhelmed daily with nothing else than corona-related literature, in this BJP issue we offer you solid, traditional scientific contributions in the domain of general pediatrics.

You can read about hepatosplenic complications in cat scratch disease, respiratory problems in pseudohypoaldosteronism type 1B, management of neonatal hypertension, unusual causes of neonatal seizures: inborn errors of metabolism with specific treatment.

In our current Made in Belgium authors focuses on the role of fluoroquinolones in children, bone geometry and bone mineral density by peripheral quantitative computed tomography in healthy and diseased children, new insights in thyroid function in preterm infants.

In the Cochrane Corner section alarm interventions for nocturnal enuresis are critically evaluated.

You might be surprised by the image as cover of this issue of the BJP. It illustrates a very interesting letter to the editor. For those who are familiar with the world of comics it will be easy to recognize in this comic strip the famous Blake and Mortimer Adventures, from the work of Edgar P. Jacobs, one of our most talented Belgian authors. But, furthermore, it is quite relevant to the worldwide pandemic that has completely disturbed our lives.

The report of the BVK/SBP board meeting on February 20th, 2020 is also published.

The JOY-project: a national well-being campaign is announced.

We invite you to visit the website where a lot of up-to-date information can be found about many aspects of the Covid-19 pandemic useful for your daily practice.

We hope you will enjoy reading this issue.

On behalf of the entire editorial board,

We wish you a nice, relaxing and above all a healthy summer!

Samy Cadranel and Marc Raes, editors-in-chief

Dear colleagues

No need to tell you that the previous and current Covid-19 period was and is very stressful not only for most adults but perhaps even more for our children.

Not in the least the most vulnerable ones were threatened in many ways. Key areas of concern were safety, education and the general wellbeing of children.

To counter balance the negative impact of the Covid-19 crisis for children and adolescents, the **Wellbeing working group** of The Belgian Pediatric Covid-19 Task Force will start up a national campaign to focus on the needs and rights of all the children living in Belgium during this crisis period and afterwards. One the one hand, they want to create a positive image of society and give children the feeling and reassurance that they can still move free and develop safe and unrestrained in all aspects of their development. On the other hand, they want to help parents and professional caregivers like teachers, childcare workers and educators to feel themselves comfortable and reassured, so they can fully help to optimize the bio-psycho-social well-being of their children, despite certain risks that never might be possible to be avoided in life. An informative platform with website will be developed with scientific substantiated data, advices and answers to many questions. A Webinar will be organized for different professionals. The creation of a balance between risks and benefits must be the objective. They also want to convince decision makers and the whole society to always consider children's needs and rights whatever decision is taken. Society must be **child-adapted**.

By working together, across borders, with official organizations and authorities e.g. Children's Rights Commissariats, departments of Education, instances for Youth policies, the working group wants to offer professional support to help them to realize their objectives and specific goals.

In the coming weeks and months, the concept of this project will be announced and explained to all those involved and to the general public. A spectacular eye-catching child-oriented **kick-off event** is under preparation.

The rainbow-colored logo illustrates the importance of all different aspects of the psycho-social wellbeing and developmental benefits for children

On behalf of all the members of the Belgian Pediatric Covid-19 Task force
Marc Raes,
President BVK/SBP

ERRATUM

Concerning: Manuscript published BJP March 2020; 22(1), 20-23

"Seizures are not the major issue in selflimited focal epilepsies: focus oncognitive disorders

Elodie Juvené, Audrey Van Hecke, Sophie Galer, Simon Baijot, Maud Brichet, Xavier De Tiège , Charline Urbain, Alec Aeby

Hereby, the editorial board confirms that Elodie Juvené and Audrey Van Hecke contributed equally to this work.

The author contributions will be correct in our next issue.

Kind regards

On behalf of the editorial board

Mustela®

Nouvelle **gamme certifiée BIO**

Huile d'Olive et Aloe Vera issus de culture biologique

99%[2] d'ingrédients d'origine naturelle

Gamme certifiée vegan[3] Sans parfum

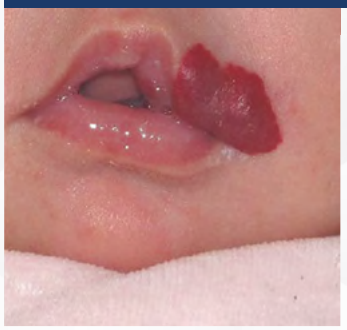
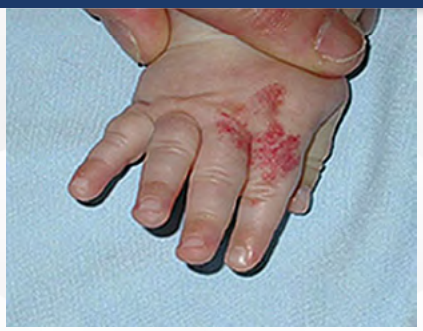
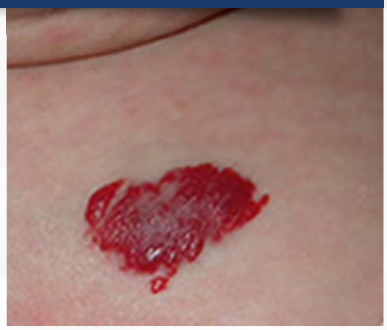
disponible en pharmacie à partir de mi-juin 2020

Dès **la naissance**[1] et **pour toute la famille**

Entreprise B Certifiée

1 Bébés sortis de néonatologie – 2 En moyenne – 3 Sans ingrédients d'origine animale.

MOET IK MIJN PATIËNT DOORVERWIJZEN VOOR DIT HEMANGIOOM?

IHReS

Infantile Hemangioma Referral Score

ONTDEK EEN SNELLE EN GEMAKKELIJKE SCORE
OM U TE HELPEN PATIËNTEN TE IDENTIFICEREN
DIE DOORVERWIJZING NODIG HEBBEN

DIGITALE VERSIE

Met de ondersteuning
van Pierre Fabre
Dermatologie

http://www.ihscoring.com

20200181

Pierre Fabre
DERMATOLOGIE

NOUVELLE MISE À JOUR DU SCHÉMA DE VACCINATION !

Prix public Belgique	86,52€
Prix public Luxembourg	84,07€

BEXSERO

Vaccin méningococcique groupe B (ADNr, composant, adsorbé)

Le **premier** vaccin contre le méningocoque de **sérogroupe B**.[1]

Le **seul** indiqué dès l'âge de **2 mois**.[1,2]

2+1

pour les nourrissons à partir de **2 mois**.[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 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) **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	Primovaccination	Intervalles entre les doses de primovaccination	Rappel
Nourrissons de 2 à 5 mois	Trois doses de 0,5 ml chacune	1 mois minimum	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]
	Deux doses de 0,5 ml chacune	2 mois minimum	
Nourrissons de 6 à 11 mois	Deux doses de 0,5 ml chacune	2 mois minimum	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]
Enfants de 12 à 23 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c]
Enfants de 2 à 10 ans	Deux doses de 0,5 ml chacune	1 mois minimum	Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique [d]
Adolescents (à partir de 11 ans) et adultes*			

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose 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. **CONTRE-INDICATIONS** 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 vaso-vagales (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 contre-indication 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. 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 post-vaccinales. 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. 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. Traçabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 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 co-administré 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 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 gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané 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 musculo-squelettiques 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 du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale 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 gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance Boîte Postale 97 B-1000 Bruxelles Madou Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 04/2020 (v10) **MODE DE DELIVRANCE** Sur prescription médicale.

1. Medini D, Stella M, Wassil J, Vaccine 2015; 33; 2629-2636. 2. Bexsero SMPC.

PM-BE-BEX-ADV-200001 - Juin 2020 - E.R.: GlaxoSmithKline Pharmaceuticals s.a., av Pascal 2-4-6, 1300 Wavre

Report board meeting BVK – SBP 20/02/2020 - UZ Brussel

Present: RAES Marc, MALFROOT Anne, HAUSER Bruno, DE WOLF Daniel, SMETS Françoise, VAN GYSEL Dirk, SCHEERS Isabelle, MATTHYSSENS Lucas, BUYSE Gunnar, WOJCIECHOWSKI Mark, RAES Ann, VAN OVERMEIRE Bart, VUCKOVIC Aline, AEBY Alec.

Excused: BERNIER Vincent, LYSY Philippe, GOUBAU Christophe, DE GUCHTENAERE Ann, GIELEN-Snoeys Marie-Laure, VERHULST Stijn, PHILIPPET Pierre, VANDEWALLE Johan, BIARENT Dominique, HOUTEKIE Laurent, VAN DAMME An, COOLS Filip VANDERLINDEN Dimitri, BECKERS Dominique, SMEESTERS Pierre, SEGHAYE Marie-Christine, GOFFIN Laurence, VAN DAELE Sabine, GEWILLIG Marc, Yvan VANDENPLAS.

Report: Natacha Meignen

---

1. Welcome

In Memoriam: We remember Prof Dr Dirk Matthys, former Medical Head Pediatric Department at the University Hospital Gent and former President of the Belgian Society of Paediatrics, who past away recently.

2. Approval last report: last report of 19th December has been approved.

3. Subspecialties

Recognition of the Sub-specialties – "sous/sur-spécialitées" – "subspecialiteiten".

Since years and years we have been fighting for the recognition of the specialized paediatricians. It's a long way to go. But we already want to proceed with an official "certificate". We see 2 possibilities to achieve this.

Via universities/training centers:

Françoise Smets says there is a possibility to hand out official certificates from the universities. She cannot speak for the Flemish universities, but she will shortly see the deans of the ULB-UCL and CHU Liège. If the deans agree it could be arranged. This official university certificate is in particular useful as a recognition abroad.

Via FOD Volksgezondheid/ Santé Publique.

It seems that the procedure at the Riziv/Unami is progressing with larger steps. We cannot force this procedure but Marc Raes and Daniël De Wolf will meet Pedro Facon, President – Director-General Of the FOD to know more about it. This recognition would give each subspecialty its own nomenclature (for the subspecialties without recognition until now).

4. Fusion Belgian Pediatric Societies: (VVK – GBPF – BVK/SBP – VBS/GBS – Academy)

On 22/06/19, 09/11/19 and 09/01/20 there were meetings with the several Pediatric Societies.

They agreed that forces should be united for several things, without losing its own identity and purpose.

They agreed on an "Umbrella" organization/ "Unified" structure ("Academy")

- "Global" secretariat : what and who do we need? (task lists, costs,…)
- "Joint" website : webmaster
- One membership fee? 600 euro?
- 1 "Professional" communication agency?

"Separate" (regional, national) societies: reason of further existence

- Tasks/activities
- Statutes
- Financial support
- Secretary / Website

Feedback from the board:

There has been an evolution in our society: less time, less financial support: unite societies could be an advantage.

Ask pediatricians about their opinion?

Why not organize the VVK and GBPF congresses at the same time as the BVK/SBP congress?

5. Congress BVK/SBP 19/20 March 2020.

Pierre Smeesters was not able to attend the meeting. Aline Vuckovic and Alec Aeby, two members of the scientific congress team were present to inform us about the actual state of the congress. They asked us to search for moderators and help in diffusing the invitation.

6. BJP

The board approved that submission is only accepted in English.

We ask our members to help:

Stimulate "young and old" to submit original articles, case reports, short communications, letters to the editor,…

Made in Belgium (summary of PhD's)

State of the Art, Reviews, What's new, Focus on Symptoms,…

7. Honorary members BVK/SBP:

Chistiane Vermylen (UCL) and Anne Malfroot (UZ Brussel) will be honored this year. For the first time women has been chosen as honorary members!

8. Vaxinfo

Vax Info is a website for physicians, pharmacologists and people working in the health department but can also been useful for others. This site gives actual information about vaccination and infection diseases coming from government services and scientific publications.

At this time, the authors of those information papers are paid.

Financial support for this website has stopped. The structure can be kept. They asks if the BVK /SBP can support it? Financial support for authors can be foreseen.

Are we interested?

If we find authors who are reliable and can make articles on a regular basis?

18/06/2020 – 19U30 - 22/10/2020 – 19U30

Management of neonatal hypertension

Pascaline Cattrysse [1], Djalila Mekahli [2,3], Elena Levtchenko [2,3], Liesbeth Thewissen [4], Anne Smits [3,4]

[1] Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium
[2] Department of Pediatric Nephrology, University Hospitals Leuven, Leuven, Belgium
[3] Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[4] Neonatal Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium

anne.smits@uzleuven.be

Keywords

hypertension, blood pressure, neonate

Abstract

Neonatal hypertension remains a rare condition. However, it is important for pediatricians to be able to interpret blood pressure (BP) measurements in neonates, since unrecognized and untreated hypertension can result in severe organ damage. This narrative review summarizes the current evidence on hypertension in neonates based on the recent literature. The definition of hypertension, considerations on optimal BP measurements in neonates as well as the etiology, diagnostic workup, and briefly the treatment are reviewed.

Overall, neonatal hypertension, is defined as BP above 95th percentile. In neonates, intra-arterial (invasive) measurement is gold standard for BP measurement. Determinants of neonatal BP, including both maternal and neonatal factors, are not yet completely clear. The etiology of neonatal hypertension is variable, with umbilical arterial catheterization, renovascular, renal parenchymal and pulmonary diseases as most frequent causes. Although the general prognosis is good, it is essential to apply a systematic diagnostic workup in which the confirmation of the diagnosis ensuring the right measurement technique should be the first step.

Introduction

With advances in neonatal care, awareness for neonatal hypertension is increasing although it still remains a rare condition. Nevertheless it is important for pediatricians to be able to interpret blood pressure (BP) measurements in newborns since untreated and unrecognized hypertension can result in severe end organ damage including shock, encephalopathy, congestive heart failure and even death[1]. The incidence of hypertension in neonates is difficult to determine given the lack of a standardized definition, and the fact that it often remains unrecognized. The estimated overall incidence is between 0.2 and 3.0% (systolic or diastolic BP > 95th percentile for age)[2,3].

Hypertension seems to be more common in patients with patent ductus arteriosus, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage and umbilical arterial catheterization (UAC)[4]. In a retrospective study of 1987, Friedman and Hustead reported an incidence of hypertension of 2.6% in 650 infants in follow-up after discharge from the neonatal intensive care unit (NICU)[5]. Mean age at diagsis was 2 months post-term. More recently (2018) Kraut et al investigated the incidence of neonatal hypertension from the multicenter AWAKEN database. They reported an incidence of 5.5%[6]. The higher incidence compared to old reports may reflect increased awareness of hypertension in neonates. In addition, neonatal care has changed dramatically last decades. These observations supports the recommendation of the Fourth Report on BP management in children and the American Academy for Pediatrics to routinely monitor BP after NICU discharge[7].

We will first discuss normal BP values, the (physiological) changes in BP during the first days and weeks of life, determinants of BP, as well as optimal BP measurement techniques in neonates. Subsequently, we aim to provide the pediatrician with a current overview on neonatal hypertension, including definition, diagnosis and etiology. We will discuss very shortly the treatment and the long term prognosis for this population.

Definition

Although a consensus definition of neonatal hypertension is currently lacking, it is arbitrarily defined as: a BP >2 standard deviations above baseline for neonates of similar age[1], or a systolic BP (SBP) or diastolic BP (DBP) >95th percentile for neonates of similar size, gestational age (GA) and postnatal age (PNA)[2,8]. When BP is between the 95th and 99th percentile without organ damage, it is considered moderate hypertension. Malignant hypertension concerns a BP above the 99th percentile with or without end organ damage[2].

Optimal BP measurement in neonates

The gold standard to measure BP in neonates is intra-arterial (invasive) BP measurement. This can be done through an UAC or catheterization of a peripheral artery (e.g. radial or posterior tibial artery)[1]. This method is commonly used in unstable preterm, and critically-ill term neonates. Non-invasive BP measurement is usually performed by an automated oscillometric device. This is a reasonable alternative to invasive BP measurement but it may underestimate SBP in small for gestational age (SGA) neonates and overestimate SBP and DBP in critically ill neonates[2]. Although the reason for this misestimation is unclear, König et al speculate that overestimation of arm-measurements and underestimation of leg-measurements can be related to minimal muscle mass in preterm infants, in particular upper limbs[9]. Dionne et al showed that the first BP reading is usually less accurate than subsequent readings. It is therefore recommended to measure BP three times and average the results[8]. If the first reading is elevated, take the average of the following two measurements[2]. An appropriately sized cuff is needed for optimal measurement. The cuff should cover at least 85% of the limb circumference and at least two thirds of the length of the limb segment[10]. Measurements should preferably be taken at the right upper arm[1,10]. The infant should be in supine position and asleep or quietly awake at least 30 minutes after the last feed because crying can increase SBP up-to 17–25 mmHg when compared with quiet neonates[1,10]. Pejovic et al showed lower BP when the infant was asleep compared to awake[10].

Normal BP values in neonates

Defining normative data for BP in neonates is challenging since multiple factors may have an impact. Neonatal BP is determined by postmenstrual age (PMA), birth weight (BW), GA, PNA, appropriateness for GA and neonatal disease. Other factors such as maternal hypertension and maternal drugs influence BP as well[1].

Zubrow et al provided normal BP and 95th percentiles for the first days of life based on BW, PMA and GA for neonates admitted to the NICU[11]. **Figure 1** shows normal trends in SBP, DBP and mean BP (MBP) according to BW and GA on the first days of life, as well as trends according to GA for the first week

PNA, as published by Pejovic et al[10]. **Table 1** represents normative values for neonates older than two weeks of age based on PMA derived by Dionne et al based on literature data[8]. Around the world NICU's are using these reference values to evaluate BP in neonates.

Figure 1. Increase in systolic (a), diastolic (b), and mean (c) blood pressure during the first month of life in infants classified by estimated gestational age: A ≤ 28 weeks, B 29–32 weeks, C 33–36 weeks, D ≥37 weeks. Reproduced from Pejovic et al(10) with permission from Springer Nature.

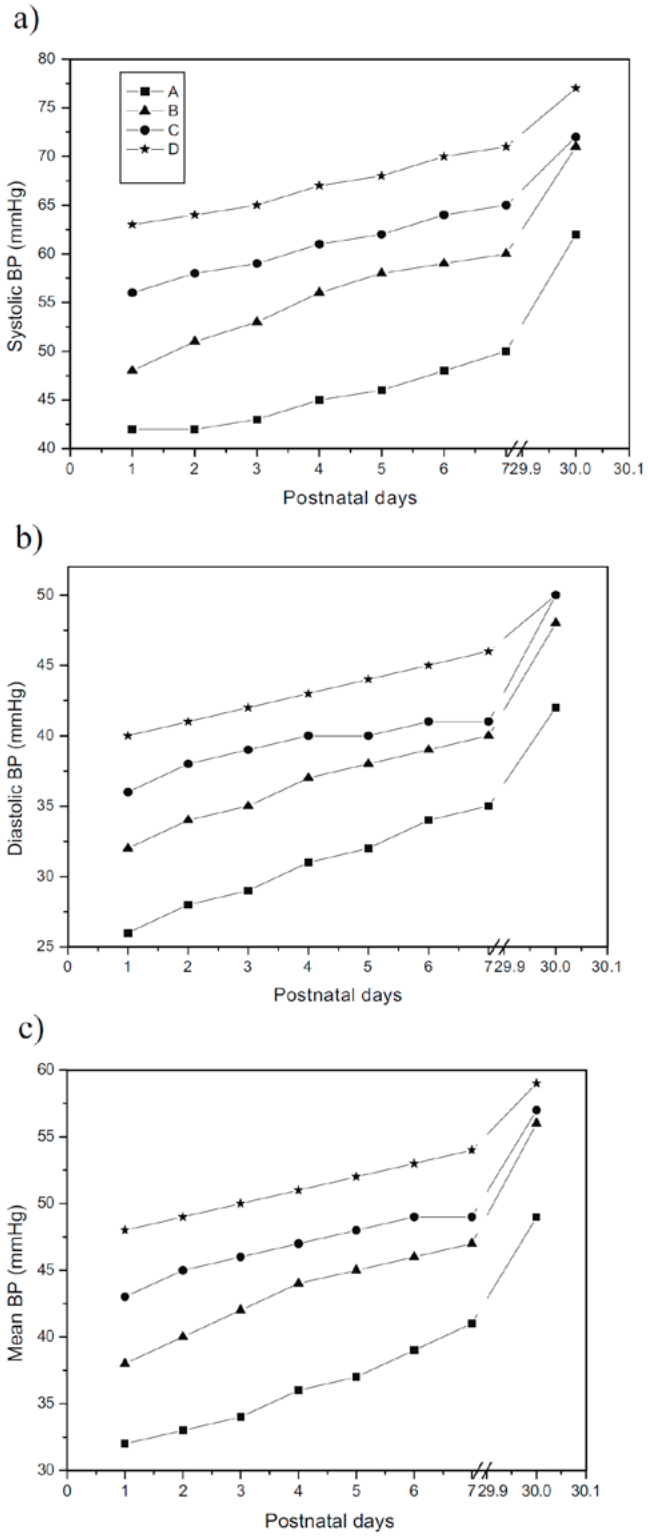


Table 1. Estimated BP values after 2 weeks of age in infants from 26 to 44 weeks postconceptional age. Reproduced from Dionne et al (8) with permission from Springer Nature.

Postconceptional age	50th percentile	95th percentile	99th percentile
44 Weeks			
SBP	88	105	110
DBP	50	68	73
MAP	**63**	**80**	**85**
42 Weeks			
SBP	85	98	102
DBP	50	65	70
MAP	**62**	**76**	**81**
40 Weeks			
SBP	80	95	100
DBP	50	65	70
MAP	**60**	**75**	**80**
38 Weeks			
SBP	77	92	97
DBP	50	65	70
MAP	**59**	**74**	**79**
36 Weeks			
SBP	72	87	92
DBP	50	65	70
MAP	**57**	**72**	**71**
34 Weeks			
SBP	70	85	90
DBP	40	55	60
MAP	**50**	**65**	**70**
32 Weeks			
SBP	68	83	88
DBP	40	55	60
MAP	**48**	**62**	**69**
30 Weeks			
SBP	65	80	85
DBP	40	55	60
MAP	**48**	**65**	**68**
28 Weeks			
SBP	60	75	80
DBP	38	50	54
MAP	**45**	**58**	**63**
26 Weeks			
SBP	55	72	77
DBP	30	50	56
MAP	**38**	**57**	**63**

SBP, Systolic Blood Pressure **DBP,** Diastolic blood pressure **MAP,** Mean arterial pressure

Determinants of neonatal BP

Both maternal and neonatal factors determine neonatal BP. Maternal factors influencing neonatal BP include maternal age, type of anesthesia, mode of delivery, maternal hypertension and preeclampsia. However, evidence on the effect of these factors on neonatal BP is often not conclusive.

A. Maternal factors:

1. Spinal anesthesia during delivery results in lower SBP on day 1 in comparison to epidural, general or no anesthesia, which can cause fetal acidosis[12]. Spinal anesthesia is often associated with maternal hypotension. This sudden decrease in maternal BP results in liberation of maternal moderators which in turn could affect neonatal SBP[12].

2. Maternal BP (such as chronic hypertension or preeclampsia) also seems to influence neonatal BP. A possible mechanism is considered through endothelial dysfunction with reduced production of vasodilators to modify the pressure response. Findings suggest that endothelial dysfunction might be present in the neonate as well, affecting BP similarly as in the preeclamptic mother resulting in higher neonatal BP during the first week of life[13]. Other authors however found that maternal preeclampsia results in higher risk for neonatal hypotension[14]. Further research is needed to explore the impact of maternal BP on neonatal BP, and more specifically, the long term effects into child- and adulthood[15].

3. Administration of corticosteroids prior to preterm delivery results in higher BP in preterms during the first 24-48 hours of life. In 163 neonates, indeed a significantly higher SBP (p=0.04) and mean arterial BP (p=0.04) at birth has been reported in cases with versus without exposure to antenatal steroids[16]. Consequently, there is less requirement for BP support resulting in reduced mortality and morbidity in these preterm neonates[15]. Seliem et al found

an eightfold increase in the risk of neonatal hypertension after antenatal steroid administration[17]. However, results differ between studies. LeFlore et al compared BP in very low birth weight (VLBW) neonates who received antenatal corticosteroids versus VLBW neonates who did not and found no significant difference in SBP, DBP or MBP during the first 72h of life[18].

B. Neonatal factors influencing neonatal BP include GA, BW and appropriateness for GA. In a large multicenter study Zubrow et al recorded BP 8-hourly in 600 NICU patients. They showed that BP on day 1 is strongly correlated with BW and GA[11]. Lower BW resulted in lower BP. However, a large Australian study, including over 400 healthy term neonates, documented that BP on day 1 was not influenced by GA or BW[19].

Pejovic et al observed that GA remains a significant predictor of BP throughout the first 30 days of life[10]. Different mechanisms contribute to the increase of BP with increasing PNA e.g. decreased activity of vasodilators and intrinsic changes in vascular smooth muscle function[10]. Appropriateness for GA has an impact on neonatal BP as well. Smal et al compared BP in SGA neonates with neonates appropriate for gestational age (AGA) and observed a similar BP rise during the first week of life in both groups. In the SGA neonates however, BP was inversely correlated with BW. The SGA neonates with the lowest BW had the highest BP[20]. When the fetus is exposed to high levels of endogenous cortisol to compensate for placental insufficiency, an alteration in hypothalamic-pituitary axis is seen which results in chronic elevation of cortisol levels in the fetus and predisposition for hypertension[20].

Etiology of neonatal hypertension

Most frequent causes of neonatal hypertension are renal etiologies, including renovascular and renal parenchymal diseases[2]. Umbilical arterial catheterization is associated with an increased risk of hypertension, most often due to renal artery thrombosis. Besides this, pulmonary, cardiac, endocrine, exogenous (e.g. drug-induced), neurologic etiologies, or hypertension secondary to neoplasmata can also occur. Nevertheless, in 50% of cases no explanation for hypertension can be found[21].

Renovascular etiologies

Umbilical arterial catheterization is correlated with an increased risk of hypertension. Up to 9% of neonates with UAC develop hypertension[4]. Most often this is due to thrombus formation affecting either the renal arteries and/or the aorta. UAC is associated with a significant increase in plasma tissue factor (TF). Placement of an UAC is associated with mechanical vascular endothelial injury resulting in direct exposure of blood to TF. This initiates the extrinsic coagulation pathway resulting in increased risk for thrombus formation[22]. The thrombus may subsequently embolize the renal parenchyma[2].

However, hypertension can occur even when thrombi cannot be demonstrated[8]. It is recommended to remove the UAC after 5 to 7 days since longer duration is associated with an increased risk for thrombi[1,23]. For each additional day of UAC in situ, adjusted Odds Ratio of developing thrombosis is reported to be 1.2 (95% CI: 1.1, 1.3)[23].

Renal venous thrombosis mostly occurs in a setting with high risk prothrombotic disorders such as maternal diabetes or factor V Leiden mutation. Mechanical compression of one or both renal arteries due to an abdominal mass or severe hydronephrosis can result in hypertension as well. Other vascular abnormalities such as idiopathic arterial calcification, renal artery stenosis due to congenital Rubella infection and aortic coarctation are other well known risk factors for development of hypertension[8,24].

Few case reports have described mid-aortic syndrome as a rare cause of neonatal hypertension[25,26].

Renal parenchymal disease

Renal parenchymal disease causing hypertension can be explained by a combination of mechanisms, including impaired renal sodium and water excretion resulting in volume expansion, activation of the Renin-Angiotensin System (RAS) with excessive release of vasoconstrictors, vasodilator deficiency (e.g. nitric oxide) and sympathetic activation due to increased vascular resistance and cardiac output resulting in vasoconstriction[27].

While these mechanisms are usually common, the underlying disease can differ (congenital or acquired). Polycystic Kidney Disease (PKD) is a well-known congenital cause of neonatal hypertension. Both autosomal recessive and dominant PKD may present with hypertension in the neonatal period.

Less frequently, neonatal hypertension is caused by multicystic dysplastic kidneys[28].

Acquired renal parenchymal disease includes interstitial nephritis, severe acute tubular necrosis, cortical necrosis and rarely unilateral renal hypoplasia. Recently, additional analyses on a multicenter database on neonatal acute kidney injury (AKI) epidemiology (AWAKEN study) showed a significant association with neonatal hypertension and AKI (defined as a rise in serum creatinine of ≥ 0.3 mg/dL or ≥50% from previous lowest value and/or urine output <1ml/kg/h on PNA day 2 to 7)[6,29]. In this study, additional risk factors for hypertension were vaginal delivery, outborn, Caucasian race, congenital heart disease and hyperbilirubinemia[6]. In addition, urologic abnormalities like ureteropelvic-junction obstruction can cause hypertension, which is reported to remain even after correction of the obstruction[30].

Pulmonary disease

Studies demonstrated a possible relationship between neonatal systemic hypertension and chronic lung disease of prematurity or BPD[2]. Alagappan et al found an overall incidence of hypertension of 6.8% compared to 12% in neonates with BPD[31]. More recently, Sahu et al reported BPD as a significant risk factor for development of hypertension with an odds ratio of nearly five[32]. Again, the underlying pathophysiology is considered multi-factorial. Some authors suggest hypoxemia to play a role, while others claim that due to pulmonary hypertension higher SBP is required to maintain pulmonary blood supply[2]. In addition, changes in the angiotensin-renin system due to angiotensin converting enzyme 2 in the lung may play a role in BPD[33]. Furthermore, infants with BPD are often administered steroids which also might contribute to systemic hypertension[34]. In a multicenter study (2017) of preterms with and without chronic lung disease, cases with hypertension presented in both groups around 40 weeks PMA and resolved within another 25 weeks. Resolution of hypertension occurred in all cases[21]. Recently, Farnbach et al explored the etiologic spectrum of hypertension in preterm neonates over time. While high renin-hypertension was more common in the past, they suggested that increasing incidence of transient low-renin hypertension may at least in part be phthalate-induced (e.g. phthalates in respiratory therapy tubing and IV tubing)[35]. However, this topic needs further study.

Other causes

Table 2 provides an overview of known categories of causes of neonatal hypertension. After the major categories described above, some additional, less frequent causes are summarized below. Hypertension due to aortic coarctation may persist or reappear even after surgical correction. Blood pressure in these patients should be monitored closely, even after discharge[36]. Although not fully understood, decreased compliance of the arterial wall after correction of coarctation probably plays a role[37]. Other underlying pathologies such as acute neurologic diseases (e.g. seizures, intracranial hypertension, pain) or tumors (due mechanical compression of the renal vasculature or ureters, or due to catecholamines release) can cause hypertension as well[38,39]. Hypertension in neonates can also be evoked by extrinsic factors such as administration of total parenteral nutrition (TPN) or maternal and neonatal drug (ab)use. Prolonged administration of TPN may induce hypertension due to salt and water overload, vitamin A and D intoxication and hypercalcemia[40]. Maternal use of cocaine or heroin during pregnancy on the other hand has an impact on the developing kidney, resulting in hypertension[41,42]. Drugs administered to neonates evoking hypertension include corticosteroids, bronchodilators and vasopressors[8].

Table 2. Causes of hypertension in neonates

Category	Example
Renovascular[8]	Umbilical arterial catheterization[4]
	Renal venous thrombosis
	Renal artery thrombosis
	Renal artery stenosis (e.g. due to congenital Rubella)
	Aortic coarctation
	Mid-aortic syndrome[25,26]
	Mechanical compression on renal arteries
	Idiopathic arterial calcification[24]
Renal parenchymal disease	Polycystic Kidney Disease
	Dysplastic kidneys[28]
	Unilateral renal hypoplasia
	Severe acute tubular necrosis
	Interstitial nephritis
	Cortical necrosis
	Acute Kidney Injury
	Ureteropelvic-junction obstruction[31]
Pulmonary disease	Bronchopulmonary Dysplasia[31-32,34]
Endocrinologic[21]	Congenital adrenal hyperplasia
	Primary hyperaldosteronism
	Hyperthyroidism
Drugs / exogenous exposures[40]	* Maternal drug use[41-42] - Cocaine, heroin
	* Neonatal drugs[8] - Corticosteroids (dexamethasone), bronchodilators (e.g. beta-agonists, anticholinergics) and vasopressors
	* Other: nutritional (salt and water overload, vitamin A and D intoxication and hypercalcemia due to prolonged TPN), phthalate exposure[35]
Tumors[39]	Wilms tumor
	Nephroblastoma
Neurologic[38]	Seizures
	Intracranial hypertenison
	Pain

Diagnostic evaluation

An overview of the recommended workup is represented in **Table 3**. After a detailed neonatal and familial history, a full physical examination is needed. It can be indicative for underlying etiology, e.g. absent femoral pulses indicating aortic coarctation and specific dysmorphic features in syndromic abnormalities[1,8]. The need for additional laboratory tests, (i.e. blood and urine), and medical imaging investigations usually is limited and indications to perform them in part depend on history and physical examination. Blood analysis should include complete blood count (e.g. thrombosis could present as thrombopenia), electrolytes (hypokalemia, hypercalcemia) and renal function[1,10]. Urine allows to measure urinary protein, creatinine and micro-albumin to diagnose renal parenchymal disease[8]. Renal ultrasound with Doppler has to be obtained in all hypertensive neonates since it is an accurate, inexpensive and noninvasive examination to determine renovascular problems. Cranial ultrasound may exclude intraventricular hemorrhage, due to hypertension. Quantification of cortisol and aldosterone or evaluation of thyroid function should be done in case of clinical suspicion.

Table 3. Diagnostic evaluation of the hypertensive neonate.

Confirming diagnosis (equipment, technique, reference values)
History
Familial history
Personal history (Clinical course)[1,8]
Postnatal interventions (for example umbilical arterial catheterization)
Drugs (current and previous)
Perinatal asphyxia
Meconium aspiration
Physical examination[1,8]
BP in 4 extremities (3 measurements, quietly awake or sleeping)
Femoral pulses
Cardiac (heart murmur, cardiac failure)
Abdominal (masses, epigastric bruit)
Dysmorphic features (Turner syndrome, Williams syndrome, hyperandrogeneity in congenital adrenal hyperplasia)
Blood analysis[1,10]
Complete blood count (thrombosis could present as thrombopenia)
Electrolytes (sodium, potassium, calcium, bicarbonate)
Renal function (BUN, creatinine)
Urine analysis[8]
Proteinuria, micro-albuminuria
Creatinine
RBC
Imaging
Renal ultrasound with Doppler
Chest X-ray: congestive heart failure
Cranial ultrasound: intraventricular hemorrhage
Echocardiography: left ventricular hypertrophy.
Depending on results of previous investigations, additional tests may be advised by pediatric nephrologist: (blood) cortisol, plasma renin activity, aldosterone; (urine) catecholamines, TSH, fT4

BP, Blood Pressure **BUN,** Blood Urea Nitrogen **RBC=** red blood cell count, **TSH=** Thyroid Stimulating Hormone, **fT4 =** Free thyroxine

Treatment

Neonatal hypertension has a low incidence but can result in severe co-morbidity. Consequently, it is recommended to discuss treatment options with experts in specialized centers as soon as hypertension is suspected, to avoid delay in initiation of treatment and to choose the optimal antihypertensive drug. External factors causing hypertension need to be identified and corrected[8]. Complications and end-organ damage should be treated accordingly. In specific cases surgery may be warranted[8]. Recommendations for pharmacological treatment of hypertension in neonates are scarce and mostly based on expert opinion or evidence in older children. The fourth report on BP management in children recommends initiating treatment when BP is consistently above the 99th percentile adjusted for age and weight. One should aim to correct BP to be <90th percentile[7]. Few antihypertensive drugs have been studied in neonates. The final choice of drug is often based on expertise and knowledge of the treating physician according to the underlying etiology[8]. The major drug classes used are diuretics, calcium channel blockers, beta-adrenergic blockers, direct vasodilators and angiotensin converting enzyme inhibitors. Since a detailed discussion on treatment options (i.e. individual compounds and dosing) is beyond the scope of this review, we refer the interested reader to respective references on this topic[7,8,43–51].

Prognosis

Overall, of infants in the NICU diagnosed with hypertension, 41% are discharged with oral antihypertensive treatment[17]. As mentioned above, hypertension associated with BPD almost always resolves[35]. General prognosis of neonatal hypertension is good but depends on underlying etiology and the presence of end-organ damage. Hypertension secondary to UAC usually resolves over time[52,53]. Certain conditions may warrant chronic treatment such as underlying renal diseases. Currently, no studies are available comparing long-term effects of short versus long-term treatment on renal and cardiovascular outcomes.

Mackenzie et al[54] and Keller et al[55] suggested that reduced nephron mass plays an important role in the development of hypertension in adulthood. Observational studies in low birth weight neonates show lower nephron number at birth and an increased risk for development of hypertension later in life[54,55]. Raaijmakers et al. investigated that among young adolescents, extremely low birth weight (ELBW) infants, had higher BP, a 5- to 9-fold higher risk of prehypertension or hypertension, and smaller kidney size with lower glomerular filtration rate derived from serum cystatin C, compared to those born at term. These observations are in line with other reports, but the add-on value of their study was that, in ELBW children, the high BP was associated

with lower plasma renin activity, which was not explained by any difference in the 24-hour sodium excretion. They suggested that the pathogenesis of hypertension after preterm birth is therefore unlikely to be mediated through a RAS-dependent mechanism[56].

Conclusion

Although neonatal hypertension is a rather uncommon condition, it may have a major impact on the child's health. The etiology of neonatal hypertension is highly variable, with UAC, renovascular, renal parenchymal and pulmonary diseases as most frequent causes. Nevertheless, in preterm infants, etiology of hypertension remains unknown in almost 50% of cases. The first step in evaluation of neonatal hypertension is to confirm the diagnosis ensuring the appropriate measurement technique and excluding underlying pathologies. Although prognosis is usually good, both treatment and long-term outcome of neonatal hypertension needs future research.

Acknowledgements

The authors have no acknowledgements to declare.

REFERENCES:

1. Sharma D, Farahbakhsh N, Shastri S, Sharma P, Sharma D, Farahbakhsh N, et al. Neonatal hypertension. J Matern Neonatal Med. 2017;30:540–50.
2. Harer MW, Kent AL. Neonatal hypertension: an educational review. Pediatr Nephrol. 2019;34:1009–18.
3. Baker-Smith C, Flinn S, Flynn J. Diagnosis, evaluation and management of high blood pressure in children and adolescents. Pediatrics. 2018;142:e20182096.
4. Singh H, Hurley R, Myers T. Neonatal Hypertension: Incidence and Risk Factors. Am J Hypertens. 1992;5:51–5.
5. Friedman A, Hustead V. Hypertension in babies following discharge from a neonatal intensive care unit. Pediatr Nephrol. 1987;1:30–4.
6. Kraut EJ, Boohaker LJ, Askenazi DJ, Fletcher J, Kent AL, Selewski DT, et al. Incidence of neonatal hypertension from a large multicenter study [Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates—AWAKEN]. Pediatr Res. 2018;84:279–89.
7. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics. 2004;114:555–76.
8. Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: Diagnosis, management and outcome. Pediatr Nephrol. 2012;27:17–32.
9. König K, Casalaz DM, Burke EJ, Watkins A. Accuracy of non-invasive blood pressure monitoring in very preterm infants. Intensive Care Med. 2012;38:670–6.
10. Pejovic B, Peco-Antic A, Marinkovic-Eric J. Blood pressure in non-critically ill preterm and full-term neonates. Pediatr Nephrol. 2007;22:249–57.
11. Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. J Perinatol. 1995;15:470–9.
12. Sedaghat N, Ellwood D, Shadbolt B, Kecskes Z, Falk M, Brussel T, et al. The effect of mode of delivery and anaesthesia on neonatal blood pressure. Aust New Zeal J Obstet Gynaecol. 2008;48:172–8.
13. Swarup J, Balkundi D, Brozanski BS, Roberts JM, Yanowitz TD. Effect of preeclampsia on blood pressure in newborn very low birth weight infants. Hypertens Pregnancy. 2005;24:223–34.
14. Teng RJ, Wu TJ, Sharma R, Garrison RD, Hudak ML. Early neonatal hypotension in premature infants born to preeclamptic mothers. J Perinatol. 2006;26(8):471–5.
15. Kent AL, Chaudhari T. Determinants of neonatal Blood pressure. Curr Hypertens Rep. 2013;15:426–32.
16. Nair G V., Omar SA. Blood pressure support in extremely premature infants is affected by different courses of antenatal steroids. Acta Paediatr Int J Paediatr. 2009;98:1437–43.
17. Seliem WA, Falk MC, Shadbolt B, Kent AL. Antenatal and postnatal risk factors for neonatal hypertension and infant follow-up. Pediatr Nephrol. 2007;22:2081–7.
18. Leflore JL, Engle WD, Rosenfeld CR. Determinants of blood pressure in very low birth weight neonates: Lack of effect of antenatal steroids. Early Hum Dev. 2000;59:37–50.
19. Kent AL, Kecskes Z, Shadbolt B, Falk MC. Normative blood pressure data in the early neonatal period. Pediatr Nephrol. 2007;22:1335–41.
20. Smal JC, Uiterwaal CSPM, Bruinse HW, Steendijk P, Van Bel F. Inverse relationship between birth weight and blood pressure in growth-retarded but not in appropriate for gestational age infants during the first week of life. Neonatology. 2009;96:86–92.
21. Jenkins RD, Aziz JK, Gievers LL, Mooers HM, Fino N, Rozansky DJ. Characteristics of hypertension in premature infants with and without chronic lung disease: a long-term multi-center study. Pediatr Nephrol. 2017;32:2115–24.
22. Tay SP, Cheong SK, Boo NY. Elevated plasma tissue factor levels in neonates with umbilical arterial catheter-associated thrombosis. Malays J Pathol. 2006;28:41–8.
23. Boo NY, Wong NC, Syed Zulkifli SZ, Lye MS. Risk factors associated with umbilical vascular catheter-associated thrombosis in newborn infants. J Paediatr Child Health. 1999;35:460–5.
24. Milner LS, Heitner R, Thomson PD, Levin SE, Rothberg AD, Beale P, et al. Hypertension as the major problem of idiopathic arterial calcification of infancy. J Pediatr. 1984;105:934–8.
25. Das BB, Recto M, Shoemaker L, Mitchell M, Austin EH. Midaortic syndrome presenting as neonatal hypertension. Pediatr Cardiol. 2008;29:1000–1.
26. Harmon CM, Azzuqa AA, Ranganathan S, Mahmood B, Good M. Mid-Aortic Syndrome in a Preterm Infant: A Rare Cause of Hypertension. J Pediatr. 2015;167:492-e 1.
27. Campese VM, Mitra N, Sandee D. Hypertension in renal parenchymal disease: Why is it so resistant to treatment? Kidney Int. 2006;69:967–73.
28. Susskind MR, Kim KS, King LR. Hypertension and multicystic kidney. Urology. 1989;34:362–6.
29. Jetton J, Booaker L, Sethi S, Wazir S, Rohatgi S, Soranno D, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. Lancet Child Adolesc Heal. 2017;1:184–94.
30. Gilboa N, Urizar R. Severe hypertension in newborn after pyeloplasty of hydronephrotic kidney. Urology. 1983;22:179–82.
31. Alagappan A, Malloy M. Systemic hypertension in very low-birth weight infants with bronchopulmonary dysplasia: incidence and risk factors. Am J Perinatol. 1998;15:3–8.
32. Sahu R, Pannu H, Yu R, Shete S, Bricker JT, Gupta-Malhotra M. Systemic Hypertension Requiring Treatment in the Neonatal Intensive Care Unit. J Pediatr. 2013;163:84–8.
33. Anderson C, Hillman NH. Bronchopulmonary Dysplasia: When the Very Preterm Baby Comes Home. Mo Med. 2019;116:117–22.
34. Abman SH, Warady BA, Lum GM, Koops BL. Systemic Hypertension in Infants with Severe Bronchopulmonary Dysplasia. J Pediatr. 1984;104:928–31.
35. Farnbach K, Iragorri S, Al-Uzri A, Rozansky D, Forbush R, Jenkins R. The changing spectrum of hypertension in premature infants. J Perinatol. 2019;39:1528–34.
36. O'Sullivan JJ, Derrick G, Darnell R. Prevalence of hypertension in children after early repair of coarctation of the aorta: A cohort study using casual and 24 hour blood pressure measurement. Heart. 2002;88:163–6.
37. Suradi H, Hijazi Z. Current management of coarctation of the aorta. Glob Cardiol Sci Pract. 2015;44.
38. Eden O, Sills J, Brown J. Hypertension in acute neurological diseases of childhood. Dev Med Child Neurol. 1977;19:437–45.
39. Weinblatt ME, Heisel MA, Siegel SE. Hypertension in children with neurogenic tumors. Pediatrics. 1983;71:947–51.
40. Koo WWK, Tsang RC. Elevated serum calcium and osteocalcin levels from calcitriol in preterm infants. In: MacDonald M, Seshia M, Mullett M, editors. Avery's neonatology: pathophysiology and management of the newborn 6th edn. 6th ed. Lippincot-Williams and Wilkins, Philadelphia; 2005. p. 847–75.
41. Horn PT. Persistent hypertension after prenatal cocaine exposure. J Pediatr. 1992;121:288–91.
42. Dube S, Jhaveri R, Rosenfeld W, Evans H, Khan F, Spergel G. Urinary catecholamines, plasma renin activity and blood pressure in newborns: effects of narcotic withdrawal. Dev Pharmacol Ther. 1981;3:83–7.
43. Miyashita Y, Peterson D, Rees JM, Flynn JT. Isradipine for treatment of acute hypertension in hospitalized children and adolescents. J Clin Hypertens. 2010;12:850–5.
44. Perlman J, Volpe J. Neurologic complications of captopril treatment of neonatal hypertension. Pediatrics1. 1989;83:47–52.
45. Rose JC, Mayer SA. Optimizing blood pressure in neurological emergencies. Neurocrit Care. 2004;1:287–99.
46. Flynn JT, Tullus K. Severe hypertension in children and adolescents: Pathophysiology and treatment. Pediatr Nephrol. 2009;24:1101–12.
47. Engelhardt B, Elliott S, Hazinski TA. Short- and long-term effects of furosemide on lung function in infants with bronchopulmonary dysplasia. J Pediatr. 1986;109:1034–9.
48. Nakagawa T, Sartori S, Morris A, Schneider D. Intravenous nicardipine for treatment of postcoarctectomy hypertension in children. Pediatr Cardiol. 2004;25:26–30.
49. Tenney F, Sakarcan A. Nicardipine is a safe and effective agent in pediatric hypertensive emergencies. Am J Kidney Dis. 2000;35:E20.
50. Michael J, Groshong T, Tobias J. Nicardipine for hypertensive emergencies in children with renal disease. Pediatr Nephrol. 1998;12:40–2.
51. Treluyer J, Hubert P, Jouvet P, Couderc S, Cloup M. Intravenous nicardipine in hypertensive children. Eur J Pediatr. 1993;9:712–4.
52. Adelman R. Long-term follow-up of neonatal renovascular hypertension. Pediatr Nephrol. 1987;1:35–41.
53. Caplan MS, Cohn RA, Langman CB, Conway JA, Shkolnik A, Brouillette RT. Favorable outcome of neonatal aortic thrombosis and renovascular hypertension. J Pediatr. 1989;115:291–5.
54. Mackenzie H, Lawler E, Brenner B. Congenital oligonephropathy: The fetal flaw in essential hypertension? Kidney Int Suppl. 1996;55:S30-34.
55. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. Vol. 348, New England Journal of Medicine. 2003. p. 101–8.
56. Raaijmakers A, Zhang ZY, Claessens J, Cauwenberghs N, Van Tienoven TP, Wei FF, et al. Does extremely low birth weight predispose to low-renin hypertension? Hypertension. 2017;69:443–9.

NIEUW: PAMPERS® AQUA PURE BABYDOEKJES

De zuiverheid van water in het gemak van een doekje

De nieuwe Pampers® Aqua Pure babydoekjes zijn ontworpen om het meest water bevattende doekje te bieden, en daarbij nog steeds de best mogelijke huidbescherming te waarborgen.

Pampers® Aqua Pure babydoekjes bestaan voor 99% uit gezuiverd water, bevatten biologisch katoen en een lotion met unieke pH-buffer functie voor een milde en beschermende reiniging van de gevoelige babyhuid.

- Dermatologisch getest
- Geschikt voor de huid van de pasgeborene
- Bevat biologisch katoen
- 99% gezuiverd water
- 0% alcohol, parabenen, phenoxyethanol, kleurstoffen, parfum

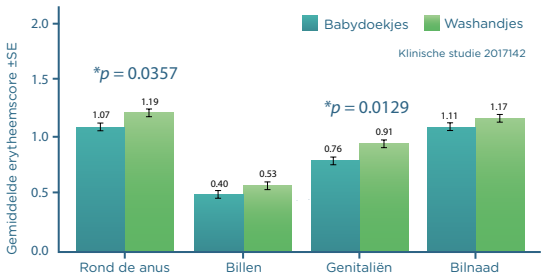
Een nieuwe klinische studie toont aan dat Pampers Aqua Pure-babydoekjes minstens even mild en zacht zijn als een washandje en water

In samenwerking met de ESPD heeft Pampers in een studie bij 130 baby's de invloed van babydoekjes op de luierzone vergeleken met die van een washandje en kraantjeswater.

Dit werd onderzocht in een willekeurig toegewezen, single blind parallel group design studie (dit wil zeggen dat onderzoekers niet weten welke de toegepaste verzorging is). Na een rustfase van één week waarbij enkel washandje en kraantjeswater werd gebruikt, werden de twee verzorgingen vergeleken gedurende een periode van twee weken. De aanwezigheid van erytheem werd daarbij gemeten op vier plaatsen.

Na twee weken gebruik bleken Pampers® Aqua Pure babydoekjes minstens even mild te zijn als washandjes en water. De huid die behandeld werd met babydoekjes, had ook een aanzienlijk lagere pH-waarde dan de huid die verzorgd werd met een washandje en kraantjeswater. Dat zou op lange termijn beter kunnen zijn voor de gezondheid van de huid.

Gemiddelde erytheemscore per meetplaats



Ingrediënten van plantaardige oorsprong die dermatologisch getest werden

- Natriumbenzoaat
- EDTA
- PEG-40 Gehydrogeneerde castorolie
- Citroenzuur
- Natriumcitraat
- Sorbitan Caprylaat

pH-buffer lotion

De lotion bevat een buffer op basis van citroenzuur die het natuurlijke pH-evenwicht van de huid helpt te behouden.[1] Wetenschappelijke studies hebben aangetoond dat de verstoring van het pH-evenwicht door een vuile luier één van de belangrijkste oorzaken van luieruitslag is. De combinatie van urine en stoelgang bevat verteringsenzymen die de huid irriteren. De babydoekjes van Pampers zijn voorzien van een speciaal ontwikkelde lotion die een pH-buffer functie vervult en de pH-waarde van de huid snel herstelt naar het normale niveau van ca. 4,5-6,0.

De Pampers® Aqua Pure babydoekjes bevatten:

Geen alcohol
Geen parfum
Geen parabenen
Geen phenoxyethanol
Geen kleurstoffen
Geen chloorbleekmiddel

[1] Interne gegevens van P&G

OFFICIËLE PARTNER GOLD - 2018

PAMPERS STEUNT DE BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

European Society for Pediatric Dermatology

Goedgekeurd door ESPD

Unusual causes of neonatal seizures: Inborn errors of metabolism with specific treatment

Valérie Leclercq, Joseph P. Dewulf, Bouchra El M'Kaddem, Stéphanie Paquay, Sandrine Marie, Marie-Cécile Nassogne

Service de Neurologie Pédiatrique, Département des Laboratoires Cliniques Cliniques universitaires Saint-Luc, Université Catholique de Louvain Avenue Hippocrate, 10/1062. B-1200 Bruxelles. Belgium

Marie-cecile.nassogne@uclouvain.be

Keywords

vitamin disorders, neonatal seizures, treatable disorders.

Abstract

Neonatal seizures remain a challenge for clinicians, as they involve subtle clinical manifestations, several etiological diagnoses, and treatment difficulties. Although inborn errors of metabolism represent a low percentage of the causes of neonatal seizures, it is important that clinicians keep them in mind in order to consider specific potential treatments and the risk of recurrence. This article summarizes the main metabolic causes of neonatal seizures and describes a practical approach to the diagnosis and treatment of these diseases.

Introduction

Epileptic seizures are described in up to 3/1000 newborns[1]. The major causes of neonatal seizures, accounting for more than 75% of cases, include intraventricular hemorrhage, hypoxic-ischemic encephalopathy, hypoglycemia, electrolyte imbalance, neonatal stroke, and infections of the central nervous system[1]. Seizures may also be due to genetic disorders, such as KCNQ2 mutation and inborn errors of metabolism (IEMs)[2].

IEM-associated seizures may occur as part of multisystem organ failure (as in organic aciduria) or as part of a complex neurological disorder (as in peroxisomal diseases). However, sometimes they are the only sign of the disease. Though IEMs are rare, they should be considered, particularly in case of neonatal seizures. Unclear etiology and therapy resistance should prompt biochemical investigations and specific metabolic treatments. It is important to take a detailed medical history, including the family pedigree, which should

Table 1. Summary of inborn errors of metabolism whose major clinical feature is seizures in the neonatal period.

Disease	Enzyme-protein *Gene* - OMIM	Biological markers
Pyridoxine-dependent epilepsy	- α-aminoadipic semialdehyde dehydrogenase or antiquitin (ATQ) - *ALDH7A1* - OMIM 266100	(B) ↑ αAASA, ↑ P6C, ↑pipecolic acid (U) ↑ αAASA, ↑ P6C (CSF) ↑pipecolic acid
PNPO deficiency	- Pyridox(am)ine phosphate oxidase - *PNPO* - OMIM 610090	(B) PNPO enzyme activity, ↑pyridoxamine (CSF) ↓ PLP
PLPBP deficiency	- *PROSC* - OMIM 617290	No specific marker
Biotinidase deficiency	- Biotinidase - *BTD* - OMIM 253260	(B) ↓ biotinidase enzyme activity, ↑ C3 and C5OH acylcarnitines (U) ↑3-OH-isovaleric acid
Holocarboxylase synthetase deficiency	- Holocarboxylase - *HLCS* - OMIM 253270	(B) ↑ C3 and C5OH acylcarnitines (U) ↑ 3-OH-isovaleraic acid
Defects in serine synthesis	- Phosphoglycerate dehydrogenase - *PHGDH* - OMIM 601815 - Phosphoserine aminotransferase - *PSAT1* - OMIM 610992 - Phosphoserine phosphatase - *PSPH* - OMIM 614023	(B) ↓ serine and glycine (CSF) ↓ serine and glycine
Sulfite oxidase deficiency	- Sulfite oxidase - *SUOX* - OMIM 272300	(B) ↓ total homocysteine, ↓ cystine, ↑ αAASA (U) ↑ sulfocysteine, ↑ αAASA
Molybdenum cofactor deficiency	- *MOCS1* – OMIM 252150 - *MOCS2* – OMIM 252160 - *GPHN* – OMIM 615501	(B) ↓ uric acid, ↓ total homocysteine, ↓ cystine (U) ↓ uric acid,↑ sulfocysteine; ↑ αAASA, ↑ xanthine, hypoxanthine
Nonketotic hyperglycinemia	- *GLDC* – OMIM 238300 - *AMT* – OMIM 238310 - *GCSH* – OMIM 238330	(B) ↑ glycine (CSF) ↑ glycine ↑ CSF/plasma glycine ratio
GLUT-1 deficiency	- Solute carrier family 2, facilitated glucose transporter member 1 - *SLC2A1* – OMIM 606777	CSF/blood glucose < 0.4

B: blood, **U: urine, CSF:** cerebrospinal fluid.* Analysis performed in plasma by Cliniques universitaires st Luc Laboratory and in urine by UZ Antwerpen laboratory, recognized as national reference centres for rare disease biochemical testing »

be followed by a full physical and neurological examination. Some neonatal presentations of IEMs may be accompanied by true birth asphyxia, which can be a misleading confounder[3, 4].

Neonatal seizures require immediate transfer to a neonatal intensive care unit (NICU) in order to exclude the most common causes of neonatal seizures. This should be followed by an extensive urgent routine laboratory work-up to search for hallmarks of IEMs that are associated with systemic

neonatal decompensation. Hypoglycemia may be responsible for seizures, and hyperinsulinism is the major cause of severe neonatal hypoglycemia that leads to intractable seizures[5]. Hypoglycemia should be absolutely excluded as a cause of neonatal seizures[3]. In case of inconclusive work-up, controlled vitamin trials and selective screening tests should be performed, which may confirm the suspected disease. Additionally, accumulating metabolites or lack of substrate can provide useful biomarkers in the diagnostic work-up for these rare disorders. The diagnostic process is not complete until the genetic variants that cause the disease have been identified.

This article summarizes the main metabolic causes of neonatal seizures and proposes a practical approach to the diagnosis and treatment of these diseases. The article focuses on the IEMs that primarily manifest with seizures in the neonatal period (summarized in Table 1).

Main metabolic causes of neonatal seizures

Defects of vitamin B6 metabolism

The diet is the main source of vitamin B6. The B6 vitamers are pyridoxine (PN), pyridoxamine (PM), and pyridoxal (PL), along with their phosphorylated forms pyridoxine 5'-phosphate (PNP), pyridoxamine 5'-phosphate (PMP), and pyridoxal 5'-phosphate (PLP). PLP is the only B6 vitamer that acts as a cofactor for over 100 catalytic functions, including enzymes involved in the metabolism of glucose, lipids, and amino acids. PLP is also important for the synthesis of neurotransmitters, which makes it an essential vitamer for normal brain function. Non-phosphorylated B6 vitamers are absorbed by the intestine and then phosphorylated in the liver. The pyridox(am)ine phosphate oxidase (PNPO) converts PNP and PMP into PLP. This PLP is then exported from the liver to the brain by several steps of dephosphorylation and rephosphorylation, allowing it to cross the blood-brain barrier (BBB) and enter the brain cells. Several mechanisms are involved, of which the protein PLPBP (PLP-binding protein, also called PROSC) seems to play a key function in PLP homeostasis (Figure 1A)[6]. Vitamin B6-responsive disorders are a heterogeneous group of rare conditions, which are mainly characterized by seizures that are exclusively responsive to treatment with the B6 vitamers PN and/or PLP. Recently, several defects have been elucidated in this pathway.

1. Pyridoxine-dependent epilepsy had already been described in 1954 but its genetic background was not elucidated until 2006[7,8]. This disease is the consequence of pathogenic variants in the ALDH7A1 gene encoding α-aminoadipic semialdehyde (αAASA) dehydrogenase (also called antiquitin,ATQ), an enzyme expressed in the brain and involved in the catabolism of lysine (Figure 1B). Clinical manifestations are intrauterine, neonatal, or infantile, including spasms and focal myoclonic, tonic, or bilateral tonic–clonic seizures that are refractory to conventional anti-epileptic drugs (AEDs). About one-third of patients exhibit birth asphyxia or poor adaptation after birth, which misleads clinicians. The electroencephalographic (EEG) pattern is not specific, showing asynchronous bursts of high-voltage generalized epileptiform activity, multifocal discharges, slow spike-wave complexes, burst-suppression pattern, or hypsarrhythmia. Several brain abnormalities have been reported, such as hypoplasia of the *corpus callosum*, cerebellar hypoplasia, cortical atrophy, hydrocephalus, white matter changes, and intraventricular hemorrhage. The response to intravenous PN (100 mg) can be dramatic (in just a few minutes), with disappearance of seizures and normalization of the EEG within 24–48 hours. However, this may be accompanied by severe apnea and coma, which require assisted ventilation. In the case of ineffectiveness, another dose of 100 mg PN may be administered sequentially every 5–10 minutes, up to a total dose of 500 mg. A delayed response to PN is possible, and treatment should be continued at 30 mg/kg/day in three single doses for at least 3–7 days before concluding that the seizures are unresponsive to PN or until ATQ deficiency has been ruled out. Elevated αAASA, piperideine-6-carboxylate (P6C), and pipecolic acid (PA) levels are found in the cerebrospinal fluid (CSF), urine, and plasma[6-8]. The diagnosis is confirmed by molecular analysis of *ALDH7A1*. PN treatment is maintained for life, at a dose of 15–30 mg/kg/d, with a maximum daily dose of approximately 200 mg, divided into 2–3 single doses. Withdrawal of pyridoxine supplementation induces the resurgence of seizures. Since only around 25% of patients have normal cognitive outcomes, despite early seizure control, additional therapeutic strategies have been proposed, including a lysine-restricted diet to lower αAASA levels and high-dose arginine supplementation leading to competitive inhibition of lysine uptake in the gut and at the BBB[6, 9].

2. Pyridoxal 5'-phosphate-sensitive seizures or PNPO deficiency. These neonates present refractory seizures that are resistant to PN but responsive to PLP administration[6, 10]. However, the first administration of PLP can also lead to severe apnea. Within a few days, the patient returns to normal and the seizures stay controlled, provided the therapy is maintained at 30–50 mg/kg/d, administered orally, and divided into 4–6 single doses per day. Patients with PNPO deficiency are frequently born prematurely and display immediate signs of encephalopathy and seizures, as well as lactic acidosis and hypoglycemia. The seizure semiology and EEG findings are indistinguishable from ATQ deficiency, and PNPO deficiency lacks a specific biomarker. An increased blood level of PM and a low CSF level of PLP are both very suggestive, but they have been described in several IEMs. Enzymatic and/or molecular analysis of the *PNPO* gene definitively confirms the diagnosis.

3. Patients with **PLPBP-deficiency (PROSC)** have been reported more recently[11-13]. The clinical picture is variable, with some severe neurological diseases that are dominated by seizures and by global underdevelopment of the cortex (broad gyri and shallow sulci) on cerebral magnetic resonance imaging (MRI). While some patients have acquired microcephaly and developmental delay[11], others have milder disease, which involves the onset of seizures on days 3–9, an absence of microcephaly, and normal brain MRI and development[12]. These patients respond to PN or PLP treatment.

Disorders of biotin metabolism

Biotin (or vitamin B8) acts as a cofactor for enzymes involved in carboxylation reactions, namely propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, pyruvate carboxylase, and acetyl-CoA carboxylase. These enzymes catalyze key reactions in gluconeogenesis, fatty acid synthesis, and amino acid catabolism. Biotin is released from dietary protein by biotinidase. Holocarboxylase synthetase (HCS) catalyzes the biotinylation of apo-carboxylases (i.e., catalytically inactive enzymes). Biotinidase also catalyzes the release of biotin from the peptide products of carboxylase breakdown (Figure 1C). Deficiency of biotinidase or holocarboxylase synthetase leads to multiple carboxylase deficiency[14].

In HCS deficiency, most patients present neonatal seizures with hypotonia, metabolic acidosis, and hyperammonemia. Myoclonic seizures or infantile spasms may be accompanied by a burst-suppression pattern, with a lack of response to conventional AEDs. Subsequent manifestations include ataxia, developmental delay, hair loss, skin lesions, vision impairment, and hearing loss. Testing urine organic acids reveals increased levels of 3-hydroxyisovaleric acid (sometimes alone), 2-methylcitric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycine, tiglylglycine, and propionylglycine, which are secondary to multiple carboxylase deficiency. The blood acylcarnitine profile might also be helpful (see Table 1). Diagnosis is confirmed by molecular analysis of the HLCS gene (21q22.1). Early treatment with biotin, in doses of up to 20–200 mg/d, may lead to complete resolution of the seizures and all clinical symptoms [14, 15].

In biotinidase deficiency, the same symptoms usually occur later (> 3 months)

Figure 1. Summary of some biochemical pathways.

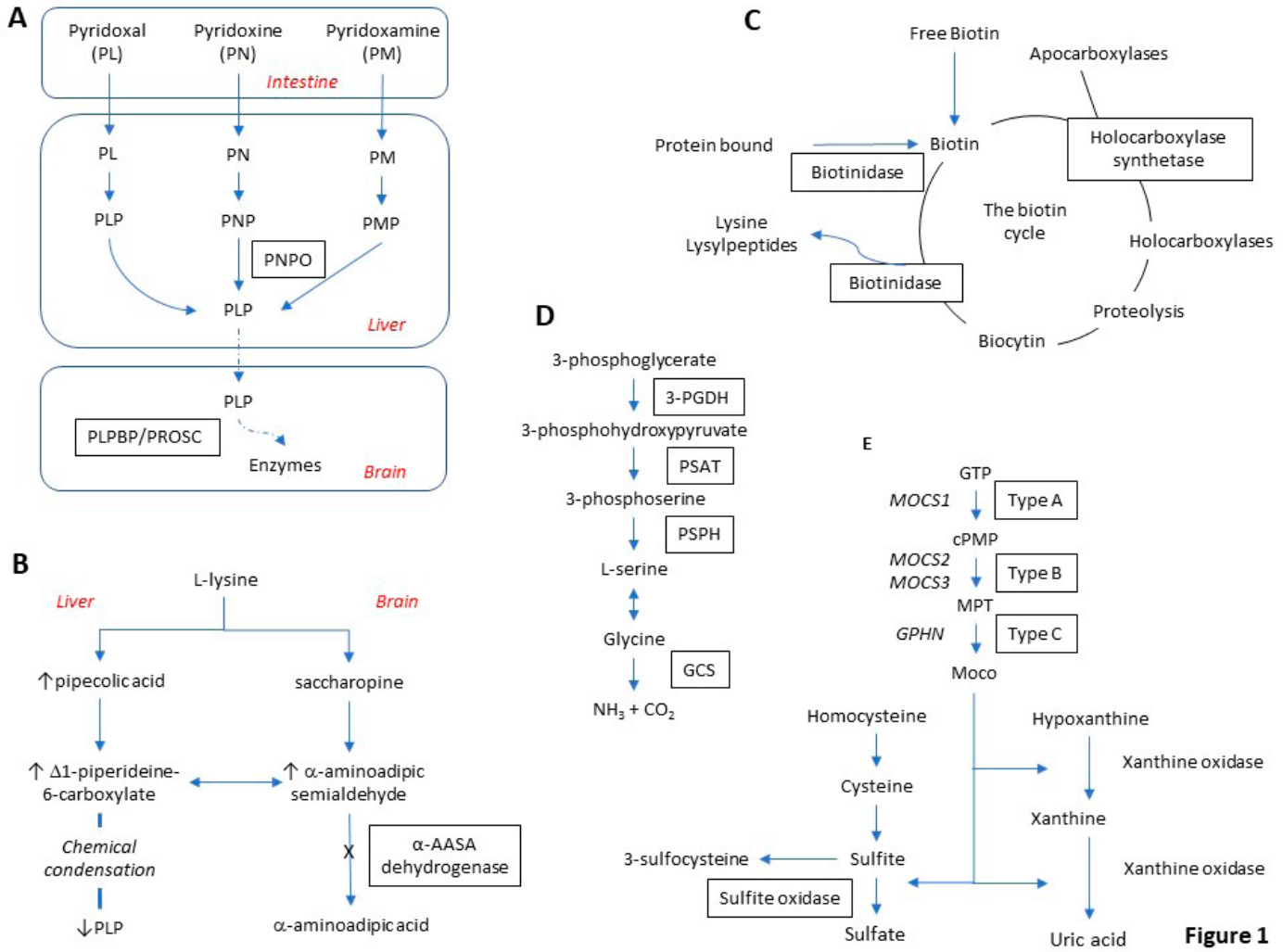


Figure 1

A. Non-phosphorylated B6 vitamers (pyridoxine [PN], pyridoxamine [PM], and pyridoxal [PL]) are absorbed by the intestine and then phosphorylated in the liver. Pyridox(am)ine phosphate oxidase (PNPO) converts pyridoxine 5'-phosphate (PNP) and pyridoxamine 5'-phosphate (PMP) into pyridoxal 5'-phosphate (PLP). PLP is exported from the liver to the brain by several steps of dephosphorylation and rephosphorylation, allowing it to cross the blood-brain barrier and enter the brain cells. Several mechanisms are involved, among which PLPBP (PLP-binding protein-PROSC), an intracellular protein, plays an important role in PLP homeostasis.

B. Biochemical pathophysiology of α-aminoadipic semialdehyde (αAASA) dehydrogenase deficiency: the two pathways of lysine metabolism are in equilibrium: Δ1-piperideine-6-carboxylate (P6C) from the pipecolic pathway and αAASA from the saccharopine pathway. αAASA is converted into α-aminoadipic acid by αAASA dehydrogenase. In αAASA dehydrogenase deficiency, P6C and αAASA accumulate and P6C undergoes chemical condensation with PLP, which results in pyridoxal deficiency. Pipecolic acid accumulates because of black pressure from the enzymatic block.

C. Free biotin enters the cycle from dietary sources or from the cleavage of biocytin or biotinyl-peptides, through the action of biotinidase. The free biotin is then covalently attached to various apo-carboxylases by the action of holocarboxylase synthetase, thereby forming active holocarboxylases. The holocarboxylases are subsequently proteolyzed to biocytin and/or biotinyl peptides, which are then further cleaved by biotinidase, thus recycling the biotin.

D. L-serine is synthesized from the glycolytic intermediate 3-phosphoglycerate via three enzymatic conversions: 3-phosphoglycerate dehydrogenase (3-PGDH), 3-phosphohydroxypyruvate aminotransferase (PSAT), and phosphoserine phosphatase (PSP). Glycine is broken down into NH3 and CO2 by the mitochondrial glycine cleavage system (GCS).

E. Sulfite oxidase, which is involved in the metabolism of sulfated amino acids, leads to oxidation of sulfite to sulfate. This enzyme depends on the molybdenum cofactor (Moco), as do the enzymes xanthine dehydrogenase and aldehyde oxidase. The biosynthetic pathway of Moco involves MOCS1, MOCS2, MOCS3, and GPHN proteins. It can be divided into three steps: synthesis of cyclic pyranopterin monophosphate (cPMP) from guanosine triphosphate (GTP), conversion of cPMP into molybdopterin (MPT), and insertion of molybdate to form Moco.

and are insidious. Urine organic acids and blood acylcarnitine profiles are similar to HCS deficiency. Diagnosis is confirmed by low enzymatic biotinidase activity and molecular analysis of the BTD gene. Biotin supplementation (at a lower dose of 5–10 mg/day) before symptoms appear substantially improves the patient outcome[14].

In HCS deficiency, most patients present neonatal seizures with hypotonia, metabolic acidosis, and hyperammonemia. Myoclonic seizures or infantile spasms may be accompanied by a burst-suppression pattern, with a lack of response to conventional AEDs. Subsequent manifestations include ataxia, developmental delay, hair loss, skin lesions, vision impairment, and hearing loss. Testing urine organic acids reveals increased levels of 3-hydroxyisovaleric acid (sometimes alone), 2-methylcitric acid, 3-hydroxypropionic acid, 3-methylcrotonylglycine, tiglylglycine, and propionylglycine, which are secondary to multiple carboxylase deficiency. The blood acylcarnitine profile might also be helpful (see Table 1). Diagnosis is confirmed by molecular analysis of the HLCS gene (21q22.1). Early treatment with biotin, in doses of up to 20–200 mg/d, may lead to complete resolution of the seizures and all clinical symptoms[14, 15].

In biotinidase deficiency, the same symptoms usually occur later (> 3 months) and are insidious. Urine organic acids and blood acylcarnitine profiles are similar to HCS deficiency. Diagnosis is confirmed by low enzymatic biotinidase activity and molecular analysis of the *BTD* gene. Biotin supplementation (at a lower dose of 5–10 mg/day) before symptoms appear substantially improves the patient outcome[14].

Defects of serine synthesis

Defects in the pathway of serine synthesis were first reported in Belgium by Professors Jaak Jaeken and Emile Van Schaftingen[16]. The major biochemical markers are low levels of serine and glycine in the plasma and CSF. Defects in each of the three steps of serine synthesis produces similar clinical

phenotypes, with phosphoglycerate dehydrogenase deficiency as the most frequent cause (Figure 1D). Children may present with intrauterine growth retardation and congenital microcephaly. After birth, intractable seizures develop within weeks or months, with or without psychomotor development. Congenital cataract is sometimes present. No specific seizure pattern has been observed, and infantile spasms, tonic-clonic seizures, and tonic, atonic, gelastic, and myoclonic seizures have all been reported. This is also the case for associated EEG abnormalities. Cerebral MRI reveals a profound decrease of cerebral white matter volume due to hypomyelination and, sometimes, cerebellar abnormalities.

The identification of low plasma and CSF levels of serine and glycine establishes the diagnosis, which is confirmed by molecular analysis of the specific genes [16, 17]. Treatment consists of high oral doses of L-serine (500–700 mg/kg/day). For children with insufficient responses, glycine (200–300 mg/kg/day) can also be added. This treatment improves wellbeing, behavior, and seizure control, but has little effect on psychomotor development. Treatment can be successful if the amino acid therapy is initiated before symptoms arise, either as antenatal L-serine therapy given to the mother or as immediate postnatal therapy in still asymptomatic patients[18, 19].

Isolated sulfite oxidase deficiency and molybdenum cofactor deficiency

Sulfite oxidase is involved in the metabolism of sulfated amino acids and leads to oxidation of sulfite to sulfate. This enzyme depends on the molybdenum cofactor (Moco), as do the enzymes xanthine dehydrogenase and aldehyde oxidase. Synthesis of Moco consists of three steps (Figure 1E)[20].

Individuals with sulfite oxidase deficiency or Moco deficiency (MocoD) mostly exhibit poor feeding, intractable seizures, characteristic dysmorphic features, and profound intellectual disability in the neonatal period. Bilateral myoclonic or tonic-clonic seizures appear within days of birth and are resistant to common AEDs. As many patients show additional signs of encephalopathy, truncal hypotonia, and brisk reflexes, their condition may be mistaken for hypoxic-ischemic encephalopathy. EEG reveals multifocal spike-wave activity or a burst-suppression pattern. Brain MRI shows generalized brain edema in the early stage and a distinctive pattern of widespread restricted diffusion that involves the cortex at the sulcal depth. This is followed by extensive cystic changes of the white matter and global brain atrophy, which provide some diagnostic clues. Lens subluxation, optic atrophy, and nystagmus have all been reported beyond infancy.

Elevated sulfite in urine occurs in both disorders, but commercial test sticks have returned both false-negative and false-positive results. An increased level of urinary S-sulfocysteine is the gold standard test, while reduced plasma levels of total homocysteine and cystine are good markers of these diseases. Elevation of αAASA has been found in patients with MocoD and sulfite oxidase deficiency, which is most likely due to secondary inhibition of *ALDH7A1* by the accumulating sulfite. In MocoD, impairment of xanthine oxidoreductase leads to increased urinary levels of xanthine and hypoxanthine and low levels of uric acid in urine and plasma[20-21].

Two-thirds of MocoD reported patients have defects in the *MOCS1* gene, involved in the first step of Moco synthesis. This inhibits formation of the first precursor (cPMP) (Figure 1E). These patients, who are referred to as MocoD Type A, may be amenable to intravenous treatment with synthetic cPMP, which should be initiated as soon as biochemical results suggest MocoD [22, 23]. For MocoD Types B and C, as well as for isolated sulfite oxidase deficiency, treatment is purely symptomatic. Dextromethorphan, an N-methyl-d-aspartate (NMDA)-receptor antagonist, and dietary restriction of sulfur-containing methionine have both shown some benefit for individual patients, as has PN in those patients with elevated αAASA.

Nonketotic hyperglycinemia

Glycine is broken down into NH_3 and CO_2 by the mitochondrial glycine cleavage system (GCS, Figure 1D), an enzymatic complex consisting of four proteins (P, H, T, L). Nonketotic hyperglycinemia (NKH) is the consequence of deficient activity of the GCS, which results in accumulation of glycine in all body tissues, including the brain. As L-glycine is an obligatory co-agonist of NMDA receptors, a high level of glycine results in overexcitation of NMDA neurotransmission, which causes excitotoxicity and seizures.

Typically, newborns with NKH present with episodes of apnea, hiccups (often felt by the mother before birth), progressive lethargy, and coma within a few days of birth. This is accompanied by segmental and erratic myoclonus, which may evolve into epileptic spasms and focal motor seizures that are resistant to AEDs. The EEG pattern deteriorates rapidly, with periods of burst suppression and progression toward hypsarrhythmia after three months. MRI demonstrates thin or dysplastic corpus callosum, delayed myelination, and, sometimes, hydrocephalus.

NKH is diagnosed by an increased ratio of CSF to plasma glycine >0.04, with some correlation to phenotype[24]. Diagnosis is confirmed by molecular analysis of the three respective genes involved. For severe NKH, no treatment effectively changes the natural history of developmental delays, spasticity, and intractable epilepsy. Current therapeutic management focuses on reducing plasma concentration of glycine with sodium benzoate and NMDA receptor blockade, as well as symptomatic care. Sodium benzoate (200–750 mg/kg/day in six daily doses) has shown some effect in reducing seizure frequency and glycine levels in plasma[25]. The NMDA receptor antagonist dextromethorphan (10 mg/kg/day in 3–4 daily doses) has also been proposed for attenuated forms of NKH, with improved neurocognitive outcomes and decreased seizure propensity. The response to AEDs is limited. Valproate is contraindicated in NKH, since it raises blood and CSF glycine concentrations and may increase seizure frequency. Vigabatrin has resulted in rapid psychomotor regression, when used to treat West syndrome in NKH[26].

A high level of glycine is also detected in plasma in the case of organic aciduria. Urinary organic acid analysis must be performed to exclude these diseases but, in most cases, other biochemical abnormalities are detected with keto-acidosis and hyperammonemia (ketotic hyperglycinemia). Elevated plasma glycine, accompanied by elevated lactate levels in plasma and CSF, has been described as well in a subgroup of mitochondriopathies related to iron-sulfur cluster defects[27].

Glucose transporter type 1 deficiency syndrome

Glucose transporter type 1 (GLUT-1), a transporter coded by the *SLC2A1* gene, facilitates glucose transport across cell membranes. GLUT-1 deficiency leads to a reduced glucose level in CSF. Clinical presentation varies[28, 29]. The worst phenotype is infantile-onset encephalopathy (before 4 months of age) with epilepsy, developmental delay, progressive microcephaly, abnormal movements, and intermittent symptoms (such as confusion, ataxia, and headache, with post-prandial improvement). Neurological signs may involve the pyramidal, extrapyramidal, and cerebellar systems. Cognitive abilities are variable. Most of the time, seizures are associated with apnea, staring spells, and abnormal eye movements. Seizure control may be difficult to achieve with AEDs. This syndrome is caused by heterozygous mutation in the *SLC2A1* gene (usually an autosomal dominant disease). The diagnosis is suggested by a low CSF/plasma glucose ratio (< 0.4) and confirmed by molecular analysis of the *SLC2A1* gene. A ketogenic diet improves the patient's control of seizures and motor symptoms, but has only a mild effect on cognitive function.

Practical approach to diagnosis and treatment[3, 4, 30]

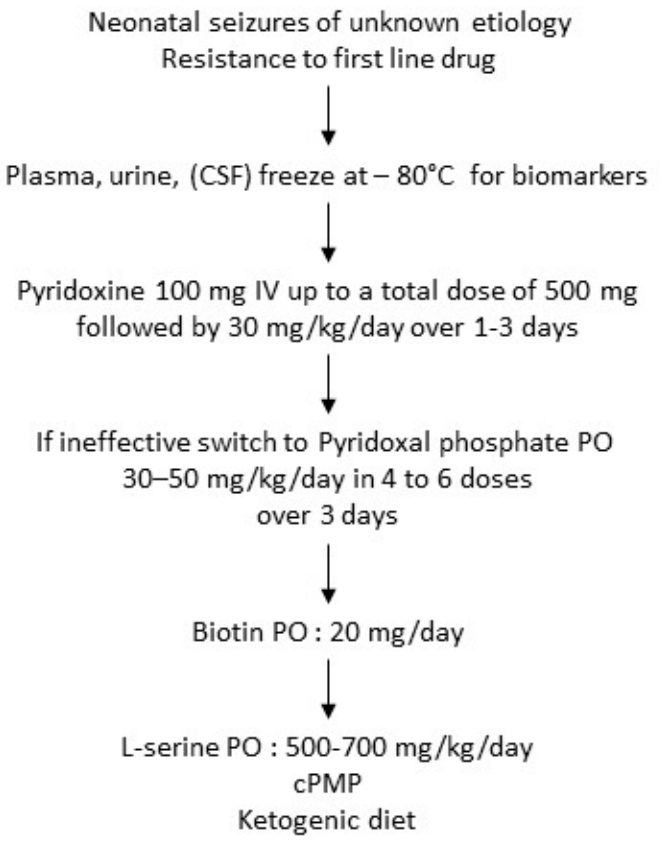
IEMs should be suspected in neonatal seizures that have unclear etiology and are resistant to treatment. Due to the potential existence of a specific treatment, which could dramatically improve the patient's prognosis, it is important to adopt a step-by-step approach. Simultaneously, some metabolic investigations in blood, urines, and CSF should be primarily conducted to support the suspicion of IEM, and, secondly, to highlight the specific biomarkers of the described IEM. The accumulation or lack of metabolites can provide useful biomarkers. These investigations currently remain important, as they deliver rapid results, although molecular analysis is crucial to confirm the diagnosis.

The initial work-up assesses global homeostasis: electrolytes, glucose, pH, lactic acid, NH_3, plasma acylcarnitines and amino acids, urinary ketones, and organic acids. If this first step is inconclusive in determining the cause of the seizures, specific biomarkers should be examined, with particular attention to

those that indicate treatable IEMs. These include amino acids and glucose in plasma and CSF, homocysteine, uric acid, pipecolic acid, P6C and biotinidase in blood, as well as αAASA, P6C, purines, and sulfocysteine in urine. These biomarkers are outlined in Table 1.

Concurrently with biochemical investigations, it is important to initiate specific therapeutic trials, which are summarized in Figure 2. Intravenous PN (100 mg), administered under EEG and clinical monitoring, is the first-line metabolic treatment. If this is ineffective, another dose of 100 mg PN can

Figure 2. Step-by-step algorithm to treat neonatal seizures of suspected metabolic origin.



be given sequentially, every 5–10 minutes, up to a total dose of 500 mg. A delayed response to PN is possible, and treatment should be continued at 30 mg/kg/day in three single doses for at least 3–7 days before concluding that the seizures are not sensitive. In the case of seizures that persist despite 500 mg of PN, this may be replaced with oral PLP (30–50 mg/kg/day in 4–6 doses). In the absence of response to PN and PLP, biotin at 20 mg/day should be tried. Following biochemical investigations, the next step is to consider serine and intravenous cPMP. Low serine and glycine levels in plasma and CSF are suggestive of a defect of serine synthesis. In this case, high doses of L-serine (500-700 mg/kg/day) should be administered. Increased urinary S-sulfocysteine and low levels of uric acid and homocysteine indicate the presence of MocoD. In this case, cPMP (80–160 µg/kg/day, intravenously) must be administrated rapidly. Finally, if GLUT-1 deficiency is suspected, a ketogenic diet must be initiated.

Conclusion

Neonatal seizures require urgent management. IEMs should be considered in the case of treatment resistance, as some are treatable, and a specific treatment may dramatically improve the patient's prognosis. An emergency box of specific drugs (PN, PLP, biotin) should be available in every neonatal ICU.

REFERENCES:

1. Abend NS, Jensen FE, Inder TE, Volpe JJ. Neonatal seizures. In : Volpe J, Inder T, Darras B, de Vries LS, du Plessis A, Neil J, Perlman J, editors. Volpe's Neurology of the Newborn. Philadelphia : Elsevier ; 2018. p. 273-321.
2. El Kosseifi C, Cornet MC, Cilio MR. Neonatal Developmental and Epileptic Encephalopathies. Semin Pediatr Neurol. 2019 ; 32:100770.
3. Saudubray JM, Garcia-Cazorla A. Clinical Approach to Inborn Errors of Metabolism in Pediatrics. In : Baumgartner MR, Saudubray JM, Walter J, editors. Berlin, Heidelberg Springer ; 2016. P3-70.
4. Van Hove JL, Lohr NJ. Metabolic and monogenic causes of seizures in neonates and young infants. Mol Genet Metab. 2011 ; 104(3):214-30.
5. Gataullina S, Delonlay P, Lemaire E, Boddaert N, Bulteau C, Soufflet C, et al. Seizures and epilepsy in hypoglycaemia caused by inborn errors of metabolism. Dev Med Child Neurol. 2015 ; 57(2):194-9.
6. Wilson MP, Plecko B, Mills PB, Clayton PT. Disorders affecting vitamin B6 metabolism. J Inherit Metab Dis. 2019 ; 42(4):629-64
7. Mills PB, Footitt EJ, Mills KA, Tuschl K, Aylett S, Varadkar S, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain. 2010 ; 133(7):2148-59.
8. Plecko B, Hikel C, Korenke GC, Schmitt B, Baumgartner M, Baumeister F, et al. Pipecolic acid as a diagnostic marker of pyridoxine-dependent epilepsy. Neuropediatrics. 2005 ;36(3):200-5.
9. Mercimek-Mahmutoglu S, Cordeiro D, Cruz V, Hyland K, Struys EA, Kyriakopoulou L, et al. Novel therapy for pyridoxine dependent epilepsy due to ALDH7A1 genetic defect: L-arginine supplementation alternative to lysine-restricted diet. Eur J Paediatr Neurol. 2014 ; 18(6):741-6.
10. Mills PB, Surtees RA, Champion MP, Beesley CE, Dalton N, Scambler PJ, et al. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase. Hum Mol Genet. 2005;14(8):1077-86.
11. Darin N, Reid E, Prunetti L, Samuelsson L, Husain RA, Wilson M, et al. Mutations in PROSC Disrupt Cellular Pyridoxal Phosphate Homeostasis and Cause Vitamin-B6-Dependent Epilepsy. Am J Hum Genet. 2016 ; 99(6):1325-1337.
12. Plecko B, Zweier M, Begemann A, Mathis D, Schmitt B, Striano P, et al. Confirmation of mutations in PROSC as a novel cause of vitamin B 6 -dependent epilepsy. J Med Genet. 2017 ; 54(12):809-814.
13. Johnstone DL, Al-Shekaili HH, Tarailo-Graovac M, Wolf NI, Ivy AS, Demarest S, et al. PLPHP deficiency: clinical, genetic, biochemical, and mechanistic insights. Brain. 2019 ; 142(3):542-559.
14. León-Del-Río A. Biotin in metabolism, gene expression, and human disease. J Inherit Metab Dis. 2019 ; 42(4):647-654.
15. Donti TR, Blackburn PR, Atwal PS. Holocarboxylase synthetase deficiency pre and post newborn screening. Mol Genet Metab Rep. 2016 ; 7:40-4
16. Jaeken J, Detheux M, Van Maldergem L, Foulon M, Carchon H, Van Schaftingen E. 3-Phosphoglycerate dehydrogenase deficiency: an inborn error of serine biosynthesis. Arch Dis Child. 1996 ; 74(6):542-5.
17. de Koning TJ, Duran M, Dorland L, Gooskens R, Van Schaftingen E, Jaeken J, et al. Beneficial effects of L-serine and glycine in the management of seizures in 3-phosphoglycerate dehydrogenase deficiency. Ann Neurol. 1998 ; 44(2):261-5.
18. de Koning TJ, Klomp LW, van Oppen AC, Beemer FA, Dorland L, van den Berg I, et al. Prenatal and early postnatal treatment in 3-phosphoglycerate-dehydrogenase deficiency. Lancet. 2004; 364(9452):2221-2.
19. de Koning TJ. Amino acid synthesis deficiencies. J Inherit Metab Dis. 2017 ; 40(4):609-620.
20. Claerhout H, Witters P, Régal L, Jansen K, Van Hoestenberghe MR, Breckpot J, Vermeersch P. Isolated sulfite oxidase deficiency. J Inherit Metab Dis. 2018 ; 41(1):101-108.
21. Schwarz G. Molybdenum cofactor and human disease. Curr Opin Chem Biol. 2016 ; 31:179-87.
22. Veldman A, Santamaria-Araujo JA, Sollazzo S, Pitt J, Gianello R, Yaplito-Lee J, et al. Successful treatment of molybdenum cofactor deficiency type A with cPMP. Pediatrics. 2010 ; 125(5):e1249-54.
23. Schwahn BC, Van Spronsen FJ, Belaidi AA, Bowhay S, Christodoulou J, Derks TG, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. Lancet. 2015 ; 386(10007):1955-63.
24. Swanson MA, Coughlin CR Jr, Scharer GH, Szerlong HJ, Bjoraker KJ, Spector EB, et al. Biochemical and molecular predictors for prognosis in nonketotic hyperglycinemia. Ann Neurol. 2015 ; 78(4):606-18.
25. Bjoraker KJ, Swanson MA, Coughlin CR, Christodoulou J, Tan ES, Fergeson M, et al. Neurodevelopmental Outcome and Treatment Efficacy of Benzoate and Dextromethorphan in Siblings with Attenuated Nonketotic Hyperglycinemia. J Pediatr. 2016 ; 170:234-9.
26. Tekgul H, Serdaroğlu G, Karapinar B, Polat M, Yurtsever S, Tosun A, et al. Vigabatrin caused rapidly progressive deterioration in two cases with early myoclonic encephalopathy associated with nonketotic hyperglycinemia. J Child Neurol. 2006 ; 21(1):82-4.
27. Baker PR 2nd, Friederich MW, Swanson MA, Shaikh T, Bhattacharya K, Scharer GH, et al. Variant non ketotic hyperglycinemia is caused by mutations in LIAS, BOLA3 and the novel gene GLRX5. Brain. 2014 137(Pt2):366-79.
28. Leen WG, Wevers RA, Kamsteeg EJ, Scheffer H, Verbeek MM, Willemsen MA. Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol. 2013 ; 70(11):1440-4.
29. Hully M, Vuillaumier-Barrot S, Le Bizec C, Boddaert N, Kaminska A, Lascelles K, et al. From splitting GLUT1 deficiency syndromes to overlapping phenotypes. Eur J Med Genet. 2015 ; 58(9):443-54.
30. van Karnebeek CDM, Sayson B, Lee JJY, Tseng LA, Blau N, Horvath GA, et al. Metabolic Evaluation of Epilepsy: A Diagnostic Algorithm With Focus on Treatable Conditions. Front Neurol. 2018 9 : 1016.

Hepatosplenic cat scratch disease occurring simultaneously in two siblings

Michaela René[1], Christophe Fricx[2], Anne Massez[3], Frédérique Jacobs[4], Françoise Vermeulen[2]

[1] Candidate for Pediatric Residency, Université Libre de Bruxelles (ULB), Brussels, Belgium
[2] Department of Pediatrics,
[3] Department of Radiology,
[4] Department of Infectiology Hôpital Erasme, Université Libre de Bruxelles (ULB), Brussels, Belgium

Michaela.kleinschmidt@gmail.com

Keywords

systemic cat scratch disease; bartonellosis, hepatosplenic lesions, fever of unknown origin

Abstract

Cat scratch disease (CSD) is a self-limiting cause of lymphadenitis in children following the scratch or bite from a cat or kitten transmitting the gram-negative intracellular bacillus *Bartonella henselae*. An atypical presentation with liver and spleen lesions is rarely reported in an immunocompetent child.
We report about two siblings with simultaneously occurring systemic bartonellosis.

The interest of this case reflects the importance to consider systemic cat scratch disease without previous lymphadenitis in patients with prolonged fever of unknown origin and/or abdominal pain and a history of cat contact. An appropriate treatment could be important to prevent complications and to induce a faster clinical improvement.

Case 1

A previously healthy nine-year-old girl, with unremarkable personal and familial medical history, was referred to the emergency department for an epigastric pain evolving for three weeks associated with prolonged fever, malaise, fatigue and anorexia. She had lost 15 per cent of her weight. Physical examination was unremarkable and no regional adenopathy was seen.

Blood test showed a normal white blood cell count without any abnormal cells, high inflammatory syndrome (C-reactive protein 140 mg/L, normal value <0.5 mg/L) and an accelerated erythrocyte sedimentation rate of 38 mm/h (normal value <20 mm/h). Liver function tests were normal.

Blood and urine cultures were negative. Tuberculin skin test was negative. Stool tests for parasites, and immunodeficiency tests were negative. Serology of *Epstein-Barr-virus (EBV), Cytomegalovirus, Chlamydia, Mycoplasma pneumoniae and Toxoplasma gondii* was negative.

Abdominal ultrasonography (US) and computed tomography (CT) revealed four hypovascular hepatic lesions, ranging from 10 to 16 mm in diameter *(figure 1)*, and one hypovascular splenic lesion measuring 11 mm in diameter *(figure 2)* as well as large adenopathies located in the hepatic and periportal hilum.

Systemic CSD was the first hypothesis. A more detailed anamnesis confirmed the presence of a kitten in the family with possible scratch. Serology of *Bartonella henselae* showed high titers of both IgG and IgM (IgM > 1/400; positive if >1/20, IgG >1/4000; positive if >1/256) which confirms the diagnosis.

Figure 1. Initial US abdominal of the 9-year-old girl (case 1) showing a hepatic lesion.

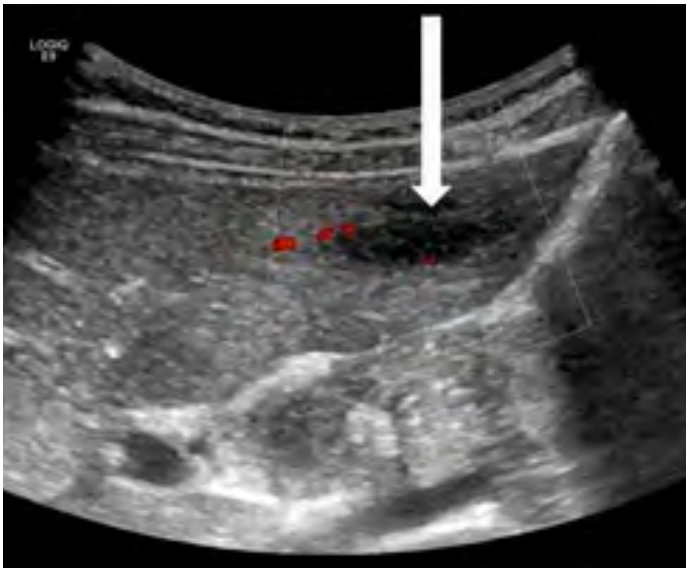
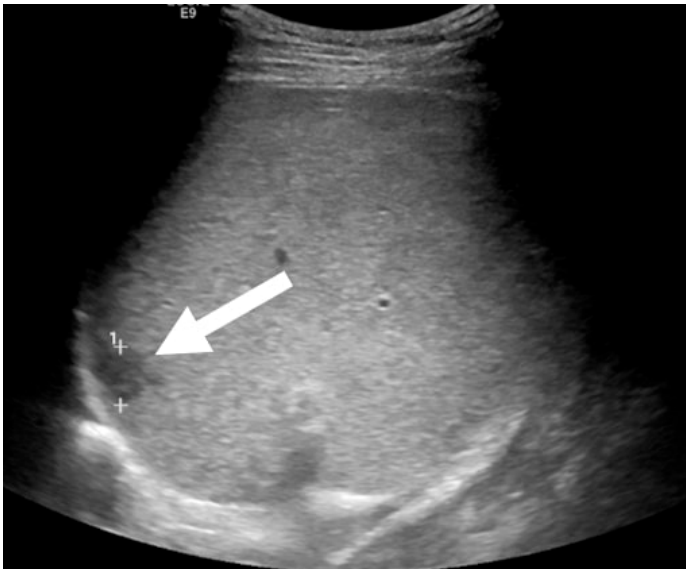


Figure 2. US abdominal of the 9-year-old-girl (case 1) showing the splenic lesion.



Case 2

At the same time, her seven-year-old sister presented with abdominal epigastric pain evolving for 10 days, anorexia and weight loss of 10 per cent of her weight. Physical examination revealed cat scratches on the forehead. Abdominal US showed moderate splenomegaly. Blood test found neutropenia (0.2 x109/L; normal range 1.5 to 8.0 x109/L) as well as a low inflammatory syndrome (C-reactive protein: 26 mg/L). As her sister, she had been exposed to the kitten. Serology of *B. henselae* was also positive for both IgM (>1/400) and IgG (>1/400).

Treatment with azithromycin (10 mg/kg the first day, followed by 5 mg/kg/d) and rifampin (20 mg/kg/j) given orally was started in both children. The kitten received ectoparasitic treatment.

After five days of antimicrobial treatment, clinical and biological improvement was noticed in both girls. Antibiotic treatment was given for 4 weeks in the seven-year-old-girl with full biological and clinical recovery. Her spleen decreased to normal size. No hepatic or splenic lesions were observed in this child.

As the hepatic lesions in the nine-year-old girl remained unchanged after 4 weeks of treatment, the same antibiotic combination was continued. After 3 months, she complained about recurrent abdominal pain and lost again 4 percent of her weight. Previous liver and spleen lesions were still unchanged and a new hepatic lesion of 12 mm in diameter appeared *(figure 3)*. The treatment was then changed to trimethroprim-sulfamethoxazole (TMP-SMZ), dose of TMP 6 mg/kg/d, combined with rifampin for another 3-month-course. Positive clinical evolution was finally observed after two months. Due to loss of follow-up after 6 months, no radiological control could be performed. Several months later, a phone call confirmed the persistent good clinical evolution.

Discussion

Multiple hepatic lesions evoke several differential diagnoses, including acute leukemia, lymphoma, bacterial and mycobacterial infections, histoplasmosis and metastatic disease. CSD was the first hypothesis since the radiological lesions were typical for bartonellosis and compatible with clinical history.

CSD is a known zoonosis caused by *Bartonella*, facultative intracellular Gram-negative bacteria. At least 6 species of Bartonella are responsible for human disease. We will focus on those caused by *B. henselae.*

Cats, especially kittens, are the major reservoir. Infection between cats is transmitted by the arthropod vector *Ctenocephalides felis* (cat flea).

The disease is transmitted to humans by scratches or bites via cat saliva. The typical form is a large and rough regional adenopathy, next to the site of inoculation, with or without skin rash and very mild general signs. Usually, it is self-limiting [1-2].

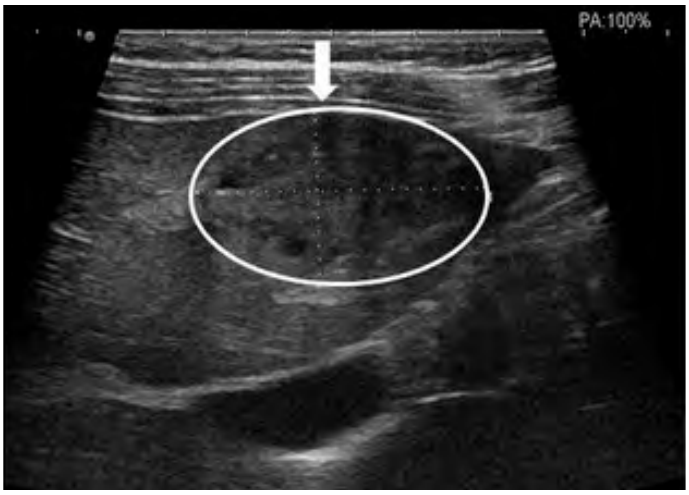
Atypical clinical presentations of CSD without lymphadenopathy include a broad spectrum of clinical syndromes ranging from prolonged fever of unknown origin to disseminated infection including hepatosplenic, ocular, cardiac and neurological manifestations which may mimic more serious disorders such as malignancy. Indeed, bartonellosis is described as the third most common infectious disease among children with fever of unknown origin (FUO), after EBV infection and osteomyelitis. Systemic CSD presenting a more disseminated form usually occurs in immunocompromised children.

Recently, hepatosplenic disease in immunocompetent children is diagnosed more frequently as a result of improvements in serologic and imaging diagnosis and can therefore be classified among the more common of the atypical forms as well as prolonged fever/FUO[2].

Tsujino et *al.* found a frequent association of systemic complication and lack of lymphadenopathy[3]. They proposed two hypotheses. First, a regional lymph node fails to react properly to the entry of *B. henselae* and thus allows systemic infection. Second, *B. henselae* invade the oropharynx or nasopharynx via the contaminated hands and gain access to systemic circulation.

Hepatosplenic CSD is characterized by multiple granulomatous lesions in liver and spleen with possible risk of spontaneous splenic rupture[4].

Figure 3. US abdominal of the 9-year-old-girl (case 1) showing a new hepatic lesion after 3 months of treatment.



These lesions may be demonstrated ultrasonographically in the liver/or spleen as rounded, hypoechoic defects ranging in size from 3 to 30 millimeters of diameter. Lymphadenopathy in the periaortic, periportal, and peripancreatic areas may also be present. Abdominal CT scan shows fairly well defined areas of low attenuation whose margins may enhance following administration of intravenous contrast[5]. The CT of the older sister showed four hypovascular hepatic lesions which enhanced after perfusion of intravenous contrast and one hypovascular splenic lesion as well as hepatic hilar lymphadenopathies. These typical radiological lesions permitted to make the diagnosis.

Diagnosis is made by elevated B. henselae antibody titers that have been reported particularly elevated in patients with the hepatosplenic form of the disease. Positive IgM indicates acute disease. The short duration of IgM antibodies (less than 3 months) makes them infrequently discovered on serology; thus, negative results do not exclude acute disease. IgG titers also decrease over time, with only 25% of patients remaining seropositive after one year[2].

Histopathologic examination of biopsy specimens from liver lesions typically demonstrates necrotizing granulomas. To identify the bacterium, a Warthin-Starry-Silver stain impregnation is necessary. *B. henselae* is difficult to culture, and culture is not routinely recommended.

Polymerase chain reaction (PCR) detection tests have been developed recently with variable sensitivity, according to the amplification target[6].

Usually, the diagnosis relies on the combination of epidemiological, serological, clinical, histological, and bacteriologic criteria.

The commonest form of the disease, isolated lymphadenopathy, recovers spontaneously and usually do not require any treatment. Azithromycin can induce an 80% decrease of the initial lymph node volume but showed no efficacy in systemic CSD[7].

There is no consensus on the management of hepatosplenic CSD by lack of controlled trials.

Macrolides, beta-lactams, expanded spectrum cephalosporins, TMP-SMZ, rifampin, and ciprofloxacine have *in vitro* bacteriostatic activity against *B. henselae*. Only aminoglycosides have demonstrated bactericidal activity *in vitro.* However, these drugs had low *in vivo* efficacy because of lack of bactericidal activity and lack of intracellular penetration[8].

In hepatosplenic disease in the immunocompetent patient, gentamicin, TMP-SMZ, rifampin, and ciprofloxacin have anecdotally been shown to be effective, but because of the variety of antibiotic regimes and study parameters, it is difficult to determine if any single antibiotic regimen is superior in the treatment of hepatosplenic disease[9].

In our first case, because of a possible risk of splenic rupture, prolonged fever and the important weight loss, antibiotic treatment with rifampin and azithromycin was given followed by, initially, a fast clinical improvement. Full clinical and biological recovery was only observed after 6 months of combined

antimicrobial therapy: 3 months of rifampin-azithromycin and 3 months of rifampin and TMP-SMZ.

Since in general, symptoms and visceral lesions tend to regress spontaneously within 6 months, a spontaneous recovery cannot be excluded.

However, rifampin alone or in combination with gentamicin or TMP-SMZ, if a clinical response is not noted to rifampin, is associated with favorable clinical responses in children with prolonged or severe hepatosplenic disease[9].

As domestic cats are responsible for transmission of *Bartonella* to humans, ectoparasitic treatment to prevent flea infestion in cats should be applied[10].

Conclusion

Systemic CSD without previous lymphadenitis should be considered in patients with prolonged fever of unknown origin and/or abdominal pain, and a history of cat contact. An appropriate treatment could be important to prevent complications and to induce a faster clinical improvement. These two cases highlight also the importance of a regular follow-up until full recovery.

Hepatosplenic disease tends to regress spontaneously, but in children with prolonged or severe illness antibiotic therapy by rifampin alone or in combination with gentamicin or TMP-SMZ should be discussed.

A prospective, controlled study of appropriate antimicrobial therapy (type and duration) is still needed.

To avoid transmission of *Bartonella* infection to humans, domestic cats should be treated by ectoparasitic treatment.

REFERENCES:

1. Boiron E, Soto B, Zimmermann B, Jullien M. Atypical presentation of hepatosplenic cat scratch disease in a 3-year-old-child. Archives de pédiatrie. 2012;19:603-606.
2. Florin TA, Zaoutis TE, Zaoutis LB. Beyond cat scratch disease: widening spectrum of Bartonella henselae infection. Pediatrics. 2008;121:1413-1425.
3. Tsujino K, Tsukahara M, Tsuneoka H, Ichihara K, Furuya T, Kawauchi S. Clinical implication of prolonged fever in children with cat scratch disease. J Infect Chemother. 2004;10:227-233.
4. Daybell D, Paddock CD, Zaki SR, Comer JA, Woodruff D, Hansen KJ, et al. Disseminated infection with Bartonella henselae as a cause of spontaneous splenic rupture. Clin Infect Dis. 2004;39.e21-e24.
5. Dangman BC, Albanese BA, Kacia MA, Lepow ML, Wallach MT. Cat scratch disease in two children presenting with fever of unknown origin: imaging features and association with a new causative agent, Rochalimea henseale. Pediatrics. 1995;95:767-71.
6. Vermeulen MJ, Diederen BMW, Verbakel H, Peeters MF. Low sensitivity of Bartonella henselae PCR in serum samples of patients with cat-scratch disease lymphadenitis. Journal of Medical Microbiology 2008:1049-050.
7. Bass JW, Freitas BC, Freitas AD. Prospective randomized double-blind placebo-controlled evaluation of azithromycin for treatment of cat scratch disease. Pediatr Infect Dis J. 1998;17:447-452.
8. Rolain JM, Brouqui P, Koehler JE, Maguina C, Dolan MJ, Raoult D. Recommendations for treatment of human infections caused by Bartonella species. Antimicrob Agents Chemother. 2004;4886:1921-1933.
9. Arisoy ES, Correa AG, Wagner ML, Kaplan SL. Hepatosplenic cat scratch disease in children: selected clinical features and treatment. Clin Infect Dis. 1999;28:778-784.
10. Greco G, Brianti E, Buonavoglia C, Carelli G, Pollmeier M, Schunack B et al. Effectiveness of a 10% imidacloprid/4.5% flumethrin polymer matrix collar in reducing the risk of Bartonella spp. infection in privately owned cats. Parasit Vectors. 2019;12:69.

Methemoglobinemia: One to keep in mind.

Pauline Naessens[1], Stephanie Van Biervliet[2]

[1] Department of Pediatrics, University Hospital Ghent, Ghent, Belgium
[2] Department of Pediatric Gastroenterology, University Hospital Ghent, Ghent, Belgium

pauline.naessens@ugent.be.

Keywords

Methemoglobinemia, central cyanosis, child, infant, methylene blue

Abstract

Methemoglobinemia is rare, but should be considered in cases where central cyanosis occurs without cardiorespiratory distress which does not respond to oxygen therapy.
Methemoglobin is formed by oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}) in hemoglobin. This leads to the inability to bind oxygen and therefore compromises oxygenation of tissues. The signs and symptoms of methemoglobinemia are dose-related. Endogenous reductive pathways control the methemoglobin formation but can be saturated in case of high levels of oxidative stress. Due to an immature defense mechanism, infants are a particularly vulnerable population. Different etiologies are recognized varying from congenital to acquired. A literature research based on a clinical case has been conducted. This case report summarizes possible causes, patient sensibilities and treatment options.

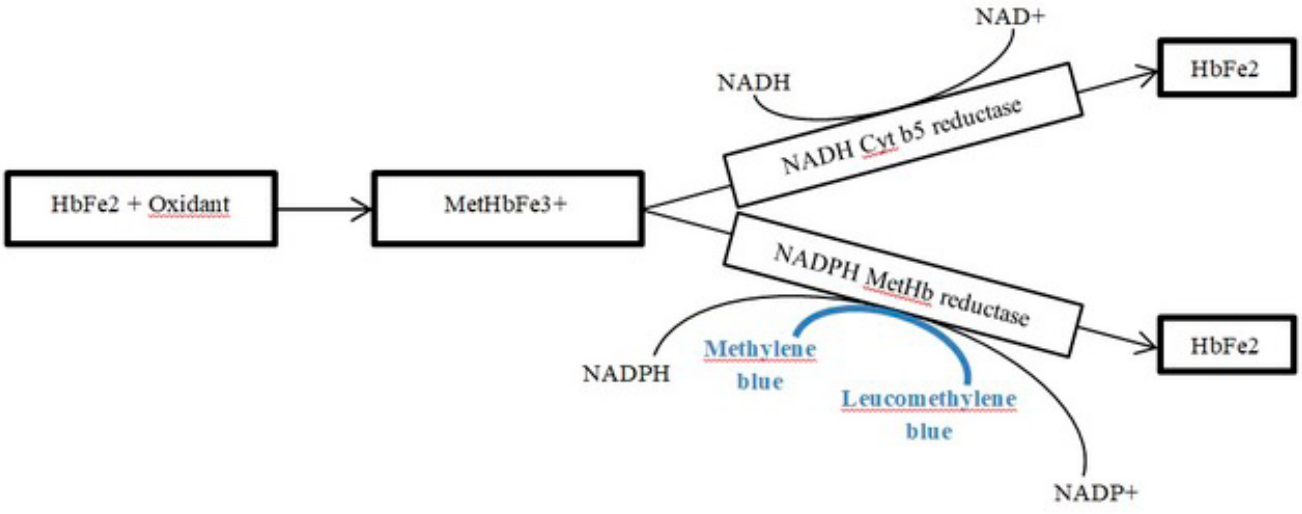
Introduction

Hemoglobin (Hb), a tetramer protein present in red blood cells, binds oxygen to ferrous iron (Fe^{2+}). However, in case of increased oxidative stress, ferrous iron can be oxidized into ferric iron (Fe^{3+}). As a result, the Hb structure will change into methemoglobin (MetHb), which is unable to bind oxygen. Depending on the level of ordinary Hb and MetHb, tissue oxidation will be compromised [1].

Red blood cells are prone to high concentrations of oxidizing chemicals and free radicals. To counter this, the nicotinamide-adenine-dinucleotide-hydride (NADH) cytochrome b5 (cyt b5) reductase enzyme is the main natural defense mechanism responsible for 95% of reductive capacity. This enzyme transfers an electron from NADH to MetHb, reducing ferric (Fe^{3+}) iron into ferrous (Fe^{2+}) iron. The remaining 5% reductive capacity, comes from the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-MetHb reductase pathway. NADPH, formed by glucose-6-phosphate dehydrogenase (G6PD), will also reduce MetHb into Hb by donating an electron *(Figure 1)*. In normal circumstances, the human body maintains the MetHb level at less than 1% of total Hb [2]. Once the enzymatic reducing pathways are saturated, an increase in MetHb and thus methemoglobinemia occurs. The risk of developing a clinically significant methemoglobinemia increases with the amount of oxidative stress but also with impaired oxidative stress defenses.

With this case report, we want to raise awareness of an unfamiliar side effect that may occur when seemingly innocent yet possibly oxidative substances are administered. In addition, we also provide some practical guidelines for the treatment of methemoglobinemia.

Figure 1. The induction of methemoglobin and reducing enzymatic pathways. In case of increased oxidative stress, ferrous iron in hemoglobin is oxidized into ferric iron which changes the hemoglobin structure into methemoglobin. Two natural defense mechanisms are present : NADH Cyt b5 reductase (95% of reducing activity) and NADPH MetHb reductase (5% of reducing activity). In case of methemoglobinemia, treatment with methylene blue facilitates the reducing activity of the NADPH MetHb reductase pathway.



HbFe2 : hemoglobin where ferrous iron is present. **MetHbFe3+** : methemoglobin where ferric iron is present. **NADH** : nicotinamide-adenine-dinucleotide-hydride. **NAD+** : nicotinamide-adenine-dinucleotide. **NADH Cyt b5 reductase** : nicotinamide-adenine-dinucleotide-hydride cytochrome b5 reductase enzyme. **NADPH** : nicotinamide adenine dinucleotide phosphate hydrogen. **NADP+** : nicotinamide adenine dinucleotide phosphate. **NADPH MetHb reductase** : nicotinamide adenine dinucleotide phosphate hydrogen methemoglobin reductase pathway.

Case report

An eleven months girl without prior medical history, arrived at the emergency department with a sudden central cyanosis after her afternoon nap. Her lunch consisted of home-grown turnip and broad beans. The cyanotic girl (saturation 80-85%) displayed no signs of respiratory distress and didn't respond to high flow oxygen. Chest X-ray was normal. A venous blood gas showed a PO2 of 38,4 mmHg, a PCO2 of 38,6 mmHg and a methemoglobin level of 44%. Hemoglobin level was 11,9 mg/dl. She was treated intravenously with 2mg/kg methylene blue and recovered within ten minutes. After a 24 hours observation, she could leave the hospital in good clinical condition. No rebound was observed. Administration of potential oxidative drugs was excluded. There were no deficiencies in G6PD or NADH-cytochrome b5 reductase. The ingestion of home-grown broad beans, known to have a high nitrate content, was the suspected etiology of this particular episode of methemoglobinemia.

Discussion

Methemoglobinemia results in limited oxygen transporting capacity and leads to anemia-like symptoms. The severity of the symptoms depends on the amount of MetHb and the velocity by which the MetHb concentration increases [3].

In a healthy patient, MetHb levels <15% are unlikely to cause symptoms but cyanosis may become apparent [4]. Levels below 30% are associated with symptoms as headache, exercise intolerance and fatigue, evolving towards dyspnea, tachycardia, dizziness and syncope if levels increase to 50%. Finally, levels above 55% may lead to lethargy, seizures, cardiac dysrhythmias, renal failure and stupor. Death occurs in levels above 70% [2,4].

In presence of the above described clinical symptoms, methemoglobinemia should be suspected. Other indicators are chocolate-colored blood and a decreased saturation which is unresponsive to oxygen. A strong argument in favor of methemoglobinemia, is the presence of 'a saturation gap' (a normal arterial oxygen pressure despite low saturation). As MetHb deflects both emitted wavelengths of a pulse-oximeter, it will be reported as desaturation. A CO-oximeter using 4 different wavelengths, however, can confirm the diagnosis since it measures the oxy-Hb, CO-Hb and MetHb percentage [5].

Methemoglobinemia can be a hereditary or acquired trait. Hereditary methemoglobinemia is the result of either a structural Hb abnormality or a deficiency in the anti-oxidative defense system. In Hemoglobin M disease, an autosomal dominant trait, a single amino acid substitution creates a propensity to form MetHb which cannot be reduced [4,5]. NADH-cytochrome b5 reductase deficiency is an autosomal recessive disorder and can also cause hereditary methemoglobinemia by reducing the anti-oxidative defense. Different types are distinguished based on the severity of the deficiency [6]. Patients with hereditary forms of methemoglobinemia can often tolerate higher levels of MetHb before becoming symptomatic [4].

Acquired methemoglobinemia, drug or nitrate induced, is, however, the most frequent cause of methemoglobinemia *(table 1)* [5]. Clinicians who prescribe possible oxidative drugs, should be aware of the risk for methemoglobinemia in order to recognize the problem adequately [2,3,4,7]. Dietary intake of nitrates (for example nitrate contaminated well water or vegetables with high nitrate content as spinach, broad beans, cabbage, endive, beets,…) is also an important cause of methemoglobinemia. Young children are particularly vulnerable due to their limited NADH-cytochrome b5 reductase activity which is only 60% of the adult activity. The presence of fetal-Hb concentrations increases the susceptibility for oxidation [2,3]. Diarrhea in infants can also be sufficient to induce MetHb when the altered intestinal flora causes an increase in nitrite formation [3]. Other vulnerable populations are patients with limited Hb reserve (for example people suffering from anemia, heart or pulmonary disease) or with increased oxidative stress (caused by, for example, liver cirrhosis or systemic inflammation). The increased proportion of MetHb over Hb and the imbalance between oxidative stress and the endogenous defense mechanisms will more readily induce symptomatic methemoglobinemia. Finally, children with G6PD deficiency will more easily have glutathione depleted erythrocytes leading to an increased oxidative damage vulnerability [8].

In suspicion of methemoglobinemia, supportive high flow oxygen should immediately be started to maximize oxygenation of the remaining functional hemoglobin, even in the absence of any clinical effect. Once diagnosed, all potential causes of acquired methemoglobinemia should be eliminated. Further treatment depends on the MetHb-level *(Figure 2)*. In asymptomatic patients a cut-off to start treatment of 30% is used which is lowered to 20% in symptomatic patients or patients with comorbidities [5].

The first-line treatment is methylene blue (methylthioninium chloride), 1-2 mg/kg intravenously in a 1% saline solution over 5 to 10 minutes. The earlier mentioned endogenous NADPH-MetHb-reductase pathway uses methylene blue as a cofactor to increase its reducing activity [4]. Since the half-life of methylene blue is often shorter than the causal oxidative substance, a rebound is possible [6]. It is therefore recommended to follow the MetHb-levels after 2 and 8 hours and to repeat doses if necessary [2]. In case of insufficient available NADPH, methylene blue will act as an oxidant and paradoxically exacerbate methemoglobinemia. Therefore, a total maximal dose of 7 mg/kg should not be exceeded [2,8]. In case of an absent response or even worsening of MetHb concentrations after methylene blue injection, G6PD deficiency should be excluded [8]. If G6PD deficiency is known or suspected, administration of methylene blue should be avoided as it can also, beside worsen the methemoglobinemia, induce hemolysis. If treatment is eminent, before G6PD can be excluded, the effect of lower starting doses (0,3 to 0,5mg/kg) can be considered [2]. Potential side effects of methylene blue include chest pain, shortness of breath, tremor and dysuria. It is also important to warn the patient that urine and feces can have a blue-green color. The renal clearance limits the use in patients with severe renal failure [4].

Alternatives to increase the anti-oxidant defense are vitamin C and Riboflavin. Ascorbic acid (vitamin C) has non-enzymatic antioxidant features but can only be used in non-acute settings as it is slow acting [1]. It has no major side effects and is easily accessible. Although it can be used orally for long-term periods in hereditary methemoglobinemia, in patients with G6PD deficiency or in cases of severe renal failure, the risk of developing kidney stones should be considered. Riboflavin (vitamin B2) can also be used in hereditary methemoglobinemia as it accelerates the reduction of methemoglobin levels through the nicotinamide adenine dinucleotide-flavin reductase system [10].

In life-threatening methemoglobinemia, exchange transfusion or hemodialysis can be considered [6].

The overall outcome of methemoglobinemia is excellent when accurately detected and treated. Late detection will result in prolonged anoxia which causes irreversible organ damage and sometimes death [9]. If there is an excessive reaction (to a normal dosed oxidative agent) or a lack of response to methylene blue treatment, further investigation for potential enzyme deficiencies or Hb abnormalities is strongly recommended [2,6].

Conclusion

Methemoglobinemia should be taken into consideration in cases where central cyanosis occurs without signs of respiratory distress without response to oxygen therapy. Pediatricians should keep the vulnerability of infants in mind when prescribing oxidative agents. The first-line treatment consists of methylene blue but the possible rebound requires at least 24h observation. In case of absent effect, G6PD or hemoglobin abnormalities should be excluded

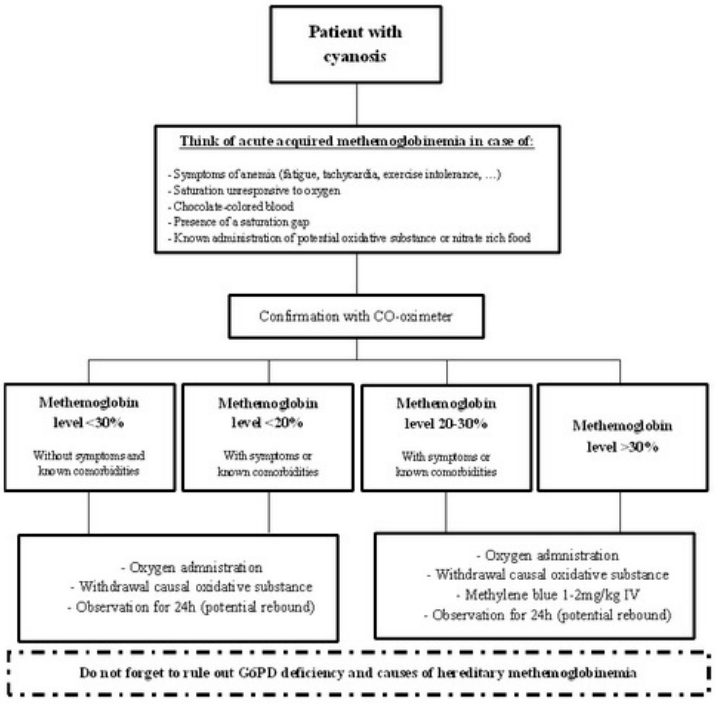
Conflict of interest statement

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

Table 1 : Possible oxidative substances which can cause methemoglobinemia. Based on the presented table in 'Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. Southern Medical Journal. 2011; 104 (11), 757-761'.

Substance type [7-10]	Substance name	Also think about it in
Local anesthetics	Lidocaine Prilocaine Benzocaine	Emla cream
Antibiotics	Sulfamethoxazole/trimethoprim Quinolones 4,4'-diaminodiphenylsulfone Sulphonamides	Prophylactic doses Dapsone
Pain medication	Acetaminophen	Paracetamol
Antimalarial medication	Chloroquine Primaquine Doxycycline	
Vasodilators	Isobutyl nitrite Nitric oxide Nitroglycerin Nitroprusside	
Gastrointestinal prokinetic	Metoclopramide	
Cutaneous application	Silver nitrite	
Nutrition	Nitrate containing foods Fava beans Well-water nitrates Pesticides	Spinach, broad beans, beets, cabbage, endive, …

Figure 2 : Management in case of (suspected) acquired methemoglobinemia. In presence of listed symptoms in patients with cyanosis, acquired methemoglobinemia should be suspected. Treatment depends on the methemoglobin level. Hereditary causes of methemoglobinemia or G6PD should be ruled out in all cases of methemoglobinemia.



G6PD : glucose-6-phosphate dehydrogenase.

REFERENCES:

1. Johnson SF. Methemoglobinemia: Infants at risk. Curr Probl Pediatr Adolesc Health Care. 2019; 49(3): 57- 67.
2. Canning J, Levine M. Case files of the medical toxicology fellowship at Banner Good Samaritan Medical Center in Phoenix, AZ: methemoglobinemia following dapsone exposure. Journal of Medical Toxicology. 2011; 7(2): 139-46.
3. Coughlin K, Flibotte J, Cahill AM, Osterhoudt K, Hedrick H, Vrecenak J. Methemoglobinemia in an Infant After Sclerotherapy With High-Dose Doxycycline. Pediatrics. 2019; 143(2), e20181642.
4. Skold A, Cosco DL, Klein R. Methemoglobinemia: pathogenesis, diagnosis, and management. Southern Medical Journal. 2011; 104 (11), 757-761.
5. Chung NY, Batra R, Itzkevitch M, Boruchov D, Baldauf M. Severe methemoglobinemia linked to gel-type topical benzocaine use: a case report. The Journal of emergency medicine. 2010; 38(5): 601-6.
6. Phillips JD, Nussenzveig R, Lingam B, Koul PA, Schrier SL, & Prchal JT. Molecular basis of two novel mutations found in type I methemoglobinemia. Blood Cells, Molecules, and Diseases. 2011; 46(4): 277-81.
7. Lipton M, Szlam SM, Barker K, Benitez JG. Methemoglobinemia secondary to topical benzocaine application to gastrostomy Site. Pediatric emergency care. 2016; 32(5): 312-4.
8. Berant R, Ratnapalan S. A pale baby with blue blood. Pediatric emergency care. 2015; 31(10): 713-4.
9. Sankar J, Gupta A, Pathak S, Dubey NK. Death in an adolescent girl with methemoglobinemia and malaria. Journal of tropical pediatrics. 2012; 58(2): 154-6.
10. Yamaji F, Soeda A, Shibata H, Morikawa T, Suzuki K, Yoshida S et al. A new mutation of congenital methemoglobinemia exacerbated after methylene blue treatment. Acute medicine & surgery. 2018; 5(2): 199-201.

SPA® REINE
water en het microbioom van de baby

Tijdens de eerste levensmaanden speelt het darmmicrobioom een belangrijke rol. **Gesprek met adviseur menselijke voeding Jean-Pierre Mans,** die uitleg geeft over de rol van het microbioom en over de noodzaak om de rijkdom ervan te behouden om op termijn de ontwikkeling van infecties of van ziektes zoals diabetes of obesitas te voorkomen[1].

EEN GOEDE HYDRATATIE VOOR EEN GOED MICROBIOOM

JP MANS *Bij het jonge kind speelt hydratatie een belangrijke rol omdat het lichaam van de zuigeling voor bijna 80% uit water bestaat, tegenover 60% op volwassen leeftijd[3]. De baby heeft dus zeer veel water nodig: 150ml/kg/j[4]. Licht gemineraliseerd water en vooral borstvoeding vervullen heel wat functies, waaronder het transport van de voedingsstoffen, de vitamines en de mineralen die nodig zijn om de opname ervan te vergemakkelijken.*

HET BELANG VAN HET MICROBIOOM BIJ DE GEBOORTE

JP MANS *Het microbioom van de baby wordt vanaf de geboorte gevormd door het contact met de vaginale flora na een bevalling via de natuurlijke weg. De kolonisatie met bacteriën gebeurt geleidelijk aan en in een welbepaalde volgorde. De eerste darmbacteriën hebben zuurstof nodig om zich te vermenigvuldigen (enterokokken, stafylokokken,...). Vervolgens is het de beurt aan de bacteriën die zich zonder dit gas ontwikkelen (bacteroïden, clostridium, bifidobacterium...)[2]. Onder invloed van borstvoeding, meer variatie in de voeding, medische behandelingen en de omgeving gaat de samenstelling van het microbioom evolueren. Omstreeks de leeftijd van 3 jaar stabiliseert het zich.*

EEN GEWIJZIGD MICROBIOOM HERSTELLEN

JP MANS *Eén van de risico's bij diarree of gastro-enteritis bij de baby is dehydratatie (tot 15% van het gewicht van de baby, vooral vóór de leeftijd van zes maanden). In dit geval, en als het kind borstvoeding krijgt, moet de moeder daarmee doorgaan. Er moet trouwens een rehydratatieoplossing worden toegediend die gereconstitueerd is met een licht gemineraliseerd water. Als er bovendien een antibioticakuur werd opgestart, moet het darmmicrobioom opnieuw worden gekoloniseerd[5]. 80% van de immuuncellen van het menselijk lichaam bevinden zich immers in het spijsverteringskanaal. Een gewijzigd darmmicrobioom verhoogt het risico dat de baby later infecties of ziekten ontwikkelt[1]. In deze context kan men zijn toevlucht nemen tot probiotica, waarvan bepaalde stammen hun nut hebben bewezen.*

(1) Harstra et al: Insights into the role of the microbiome in obesity and type 2 diabates, Diabetes care 2015; 38 : 159-65.
(2) Rémy Burcelin, unité INSERM 1048 / Université P. Sabatier & Institut des maladies métaboliques et cardiovasculaires, Hôp. Rangueil, Toulouse.
(3) Fusch et al Water turnover of healthy children measured by deuterated water elimination, Eur J Pediat. 1993; 152 : 110-4.
(4) Hoge Gezondheidsraad, advies nr 8309 (Herziening 2009).
(5) Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children; J Pediatr Gastroenterol Nutr. 2001 Oct;33 Suppl 2: S17-25.

www.spa.be

Spa steunt
BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

SPA® NATURAL SINCE 1583 Tijdloos puur

A very severe respiratory course in pseudohypoaldosteronism type 1B - Case report and review of the literature

Nathalie Jouret[1], Marleen Moens[2], Stijn Verhulst[3], Dominique Trouet[4], Kim Van Hoorenbeeck[3]

[1] Leuven University Hospital, Department of Pediatrics, Leuven, Belgium
[2] Rehabilitation Center Pulderbos, Department of Pediatric Pulmonology, Antwerp, Belgium
[3] Antwerp University Hospital, Department of Pediatric Pulmonology, Antwerp, Belgium
[4] Antwerp University Hospital, Department of Pediatric Nephrology, Antwerp, Belgium

nathalie_jouret@hotmail.com

Keywords

Pseudohypoaldosteronism type 1B, ENaC, cilia, respiratory, CF like, severet

Abstract

Pseudohypoaldosteronism type 1B (PHA type 1B) is a very rare multi-system salt-wasting disease. Severe life-long salt loss is seen in multiple target organs expressing the amiloride-sensitive epithelial sodium channel (ENaC) including the kidney, sweat glands, salivary glands, colon and lung.

In the lungs, ENaC channels are located on the motile cilia and regulate the osmolarity of the periciliary liquid, necesarry for a normal motile cilia function. The loss-of-function of ENaC in PHA type 1B patients leads to an increase in the airway surface liquid (ASL), resulting in 'intrapulmonary drowning'. Patients present with recurrent episodes of chest congestion, coughing, and wheezing. Despite the different pathophysiology, this pulmonary syndrome with increased sweat and saliva electrolyte can easily be confused with cystic fibrosis (CF).

We report a case of PHA type 1B with a very severe respiratory phenotype.

Reviewing all other PHA type 1B patients with respiratory symptoms, it seems that our patient presents the most severe respiratory course ever described.

Up to now, the pulmonary phenotype in PHA type 1B can not be predicted. Nevertheless, it would be useful for the follow-up of these patients, resulting in a better long-term prognosis. To our knowledge, a respiratory comorbidity like asthma could be such a predictor. More research is needed on this topic.

Introduction

Primary pseudohypoaldosteronism (PHA type 1) is a very rare hereditary salt-wasting disease characterized by peripheral mineralocorticoid resistance. Under normal circumstances aldosterone activates potassium excretion (ROMK channel) in hyperkalemia, whereas it activates sodium reabsorption (ENaC and Na+-K+-ATPase channel) in volume depletion. Despite high levels of aldosterone, PHA type 1 patients can't maintain this electrolyte and water homeostasis [1-3].

PHA type 1 consists of two distinct forms. The classic or renal form (PHA type 1A) is inherited as an autosomal dominant trait by inactivating heterozygous mutations in the NR3C2 gene (4q31) encoding the mineralocorticoid receptor (MR). Mild to modest salt loss is seen in the kidney. The severe or multi-system form (PHA type 1B) is inherited as an autosomal recessive trait by loss-of-function mutations in the genes encoding the subunits of the amiloride-sensitive epithelial sodium channel (ENaC): alpha subunit (SCNN1A; 12p13), beta subunit (SCNN1B; 16p12.2-p12.1), or gamma subunit (SCNN1G; 16p12). Severe life-long salt loss is seen in multiple target organs expressing ENaC including the kidney, sweat glands, salivary glands, colon and lung [1,2,4-12].

Aim

A case of PHA type 1B with a very severe respiratory phenotype will be described and the clinical course will be compared with previous cases described in literature.

Methods

Using the database 'Pubmed', the applied MeSH-term was 'Pseudohypoaldosteronism'. We collected articles about PHA type 1B and checked for other possible articles in the reference lists. The pathophysiology of the pulmonary syndrome in PHA type 1B was analyzed. All cases of PHA type 1B were assembled. Patients with a severe respiratory phenotype were selected using criteria for a cystic fibrosis (CF) like phenotype. Their respiratory illness was compared with that from our patient. We finally looked for possible predictors of the respiratory phenotype in PHA type 1B by comparing data of all the PHA type 1B cases with a non-CF like and CF like phenotype, including our case. If some important clinical data were missing, we contacted corresponding authors.

Results

Case

We report a case of a 16-year-old boy. At his 4th day of life he presented with severe dehydration, vomiting and jaundice. His parents were consanguineous. Biochemical analysis revealed hyponatremia and hyperkalemia with metabolic acidosis. He was treated with intravenous fluids and sodium chloride. Sodium requirement increased and he was presumed to have congenital adrenal hyperplasia. Hormonal therapy seemed ineffective. Further laboratory examinations showed elevated urine sodium, normal 17-hydroxyprogesterone, cortisol and adrenocorticotropic hormone (ACTH), and extremely high aldosterone and renine. At his 19th day of life, he developed cardiac dysrhythmia due to worsening hyperkalemia and needed resuscitation. He was diagnosed as having systemic mineralocorticoid resistance or PHA type 1B. The patient was given oral sodium chloride supplementation, sodium bicarbonate as well as kayexalate at discharge.

During the following months he needed frequent hospital admissions because of acute dehydration, most of the time triggered by intercurrent diarrhea or respiratory tract infections. His skin showed typically a generalized itchy, rough and red eruption, being worse during metabolic acidosis crises. Repeated sweat electrolyte determination revealed markedly elevated sodium and chloride values (Na 133 mmol/L [<60 mmol/L] and Cl 128 mmol/L [<60 mmol/L]), supporting the diagnosis of PHA type 1B. Genetic testing for the frequent CFTR (cystic fibrosis transmembrane conductance regulator) mutations was negative. There was no proof of an underlying immunodeficiency disorder. Important gastroesophageal reflux was excluded by contrast radiographs. Because of poor feeding together with poor growth and to prevent life-threatening salt-wasting episodes, a percutaneous gastrostomy was performed at the age of 1,5 year.

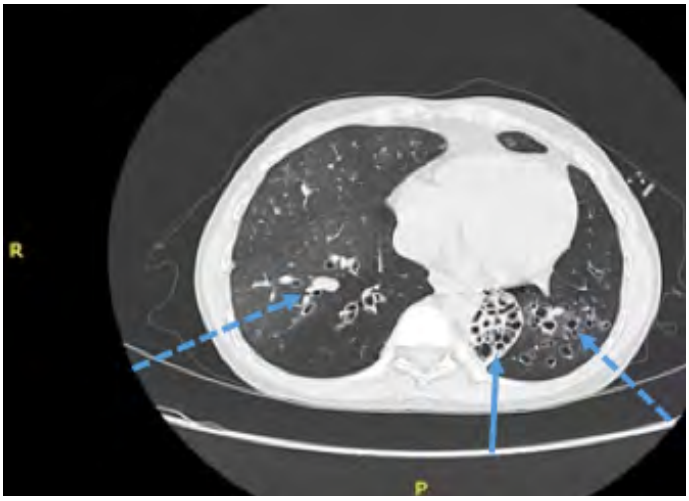
Although metabolic disturbances became less frequent, he had more lower

respiratory tract infections. At the age of 4 years he developed a chronic productive cough and clubbing. Diagnosis of atelectasis of the left lower lung lobe and bilateral bronchiectasis was made. Bronchoscopy showed abundant watery secretions, more present on the left side. Despite intensive therapy, atelectasis persisted. Crackles, rhonchi and wheezing over both lungs together with a productive cough of extremely watery secretions persisted off and on during his diseaese course. In addition he had a chronic nasal drip of clear liquid. Primary ciliary dyskinesia (PCD) was excluded by a nasal brush biopsy. Cultures of sputa did grow pathogens like *Haemophilus influenzae, Serratia marcescens, Enterobacter cloacae, Klebsiella oxytoca and Staphylococcus aureus*. His FEV1 (forced expiratory volume in the first second) declined below 50% with a very obstructive lung function. He received chronic treatment with antibiotics and chest physiotherapy.

From the age of 7 years he needed nocturnal oxygen therapy. Microbiology showed new uncommon pathogens like *Acetinobacter species, Serratia maltophilia, Achromobacter xylosoxidans, Delftia acidovorans, and Pseudomonas species*. A portacath was placed because of the frequent need of intravenous therapy. During respiratory exacerbations he had severe asthma symptoms. An IgE-mediated allergy was diagnosed.

At the age of 14 years, FEV1 predicted was 22%. *Pseudomonas aeruginosa* was isolated in the sputum during a respiratory exacerbation. Bronchiectasis further increased on radiographic studies (figure 1). He was dependent on oxygen, not only during the night but also during exercise.

Figure 1. CT thorax of our patient at the age of 15 years
Bilateral bronchiectasis (striped arrows) together with collapse of the left lower lung lobe (arrow).



Since therapy is started with mepolizumab at the age of 16 years, his respiratory exacerbations are less frequent, FEV1 predicted is stabilized at 30% and his weight shows a more favorable evolution. Moreover, a high-salt diet (12 grams/day) prevents severe salt-losing crises for the last years. Genetic analysis has shown a homozygous region on 16p12.2 (SCCN1B/SCNN1G genes) (7-pointed star symbol in figure 2).

Pathophysiology of the pulmonary syndrome in PHA type 1B

Several authors describe PHA type 1B as a disease mimicking CF because of the increased sweat and saliva electrolyte values and recurrent episodes of chest congestion, coughing, and wheezing. PHA type 1B patients may even require respiratory treatment similar to that for CF. However, there is an important contrasting mechanism of action between these two diseases.

In the lungs, ENaC channels are located on the motile cilia and regulate the osmolarity of the periciliary liquid, necesarry for a normal motile cilia function [14] (figure 3).

In CF, the dysfunction of the chloride transporter CFTR, which is located on the apical side of the airway epithelia, leads to reduced inhibition of ENaC by chloride ions. A subsequently enhanced activity of ENaC contributes to a drastic reduction of airway surface liquid (ASL) together with dehydration of the mucus in the airways.

Figure 2. Family tree of our patient
Genetic analysis has shown a homozygous region on 16p12.2 (SCCN1B/SCNN1G genes), recessively inherited from his consanguineous parents. One brother has the same genetic diagnosis of PHA type 1B with an obviously milder clinical course and not showing any respiratory problems. Another brother died after birth, diagnosed with Pompe disease besides PHA type 1B. One sister is healthy.

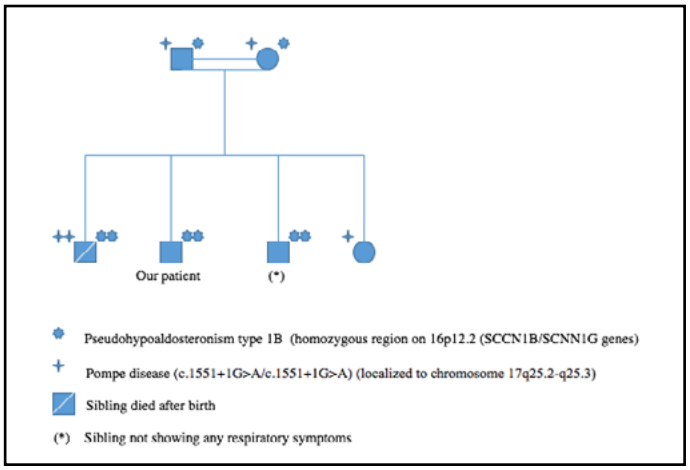
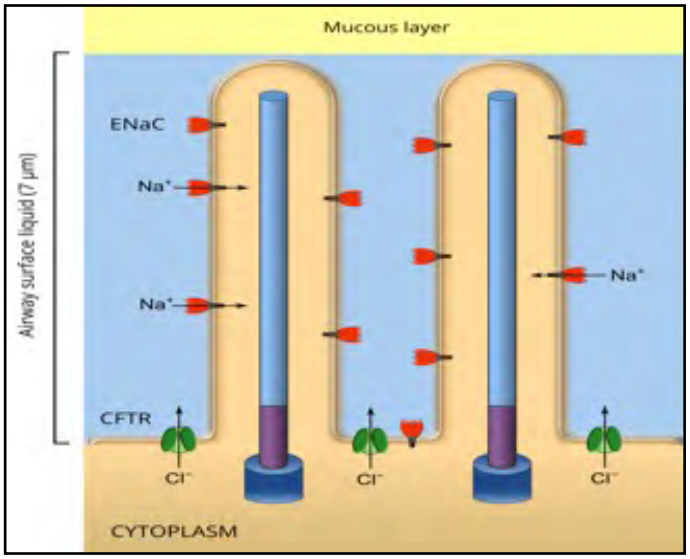


Figure 3. The regulation of the composition of the fluid bathing the cilia, necessary for an adequate transport of mucus
ENaC channels are located along the entire length of the cilia. CFTR channels are located on the apical cel surface.
Source: 14 - Figure drawn by Hanukoglu I (permission achieved to use the figure)



In contrast, the loss-of-function of ENaC in PHA type 1B leads to an increase in the ASL, resulting in 'intrapulmonary drowning'. The mean mucociliary transport rate will be higher trying to compensate. If the surface tension of the air-liquid interface is positive, the pressure drop across the interface produces an additional inward force that can further constrict the airway. Therefore symptoms in PHA type 1B normally become less severe and less frequent with advancing age. The hypothesis is that airway narrowing due to intraluminal liquid may be more prominent in infancy and early childhood when the airway diameter is smaller [5,7,13-16,23].

Does our patient show a unique respiratory course?

We found a total of 74 patients described in literature with the diagnosis of PHA type 1B. Having a respiratory phenotype or not was only mentioned in 57 of these patients. If we count with our patient, only 36 of the remaining 58 PHA1B patients showed a respiratory course, consisting of lower respiratory tract infections whether or not with persistent symptoms of wheezing, rhonchi, crackles and/or cough. As in our case some of the respiratory courses were more severe resembling a CF like phenotype. The criteria we applied to meet a CF like phenotype were 'recurrent low respiratory tract infections' and/or 'persisting symptoms of wheezing, rhonchi, crackles and/or cough', with at least one of the following: 'clubbing', 'persistent oxygen therapy', 'low FEV1',

'rare bacterial pathogens', 'bronchiectasis' and/or 'chronic atelectasis'. Using this criteria, we found 6 other patients ever described with a CF like respiratory phenotype. Table 1 gives an overview of the respiratory illness of each of these latter patients in comparison with that of our patient. Our patient appeared to be the only one with clubbing, low (moreover very low) FEV1, and chronic atelectasis. In addition he was the only one meeting all criteria for a CF like phenotype. We could conclude our patient shows a unique respiratory course within an already very rare disease of PHA type 1B.

Is it possible to predict the severity of the respiratory phenotype in PHA type 1B?

The important short-term risk in PHA type 1B is death from hyperkalemia whereas the long-term prognosis depends on the severity of dehydration episodes and the respiratory course [1]. Up to now, the pulmonary phenotype can not be predicted [17]. Nevertheless, awareness of predictive factors could lead to a more strict follow-up in these patients, resulting in a better long-term prognosis. Therefore we investigated and made an overview of all the possible predictors of the respiratory phenotype in the 36 PHA type 1B patients described with non-CF like and CF like phenotype, including our patient (supplementary table).

Our first chosen possible predictors were 'sex' and 'parental origin', assuming that these parameters would genetically affect the respiratory phenotype. **Male and female sex were more or less equally divided**. If we analyzed for the CF like phenotypes only, male sex was twice as frequent as female sex. 'Male sex' could thus be a predictor of a CF like phenotype. The majority of the PHA type 1B patients, including CF like phenotypes, had a Mediterranean origin. We could conclude a Mediterranean origin is typical in PHA type 1B, but not a predictor of a CF like phenotype.

Besides the obligate severe salt loss in the kidney in the first days of life, PHA type 1B patients show other systemic signs explained by the locus of ENaC. The most frequent symptoms besides the respiratory symptoms are 'persistent clear nasal discharge', 'recurrent diarrhea', and 'mucocutaneous lesions' [1,3,7,8,19]. **The latter present as atopic dermatitis-like rash, miliaria, seborrhea-like lesions or gingivitis, typically worse during salt-losing crises**. We assumed that having one of **the** other systemic symptoms would predict a more dysregulated course of PHA type 1B, and additionally a more severe respiratory phenotype. **We could conclude that most of the patients showed mucocutaneous lesions and persistent clear nasal discharge instead of only a quarter showed recurrent diarrhea**. Too many of these clinical data were missing for the patients with a CF like phenotype, so we could not make further statements. We than made an analysis for 'having three systemic symptoms together' as a possible predictor. We found that **the majority** of the patients had two other symptoms next to the respiratory symptoms. This finding correlates with PHA type 1B being a systemic disease. When we looked for 'having all four systemic symptoms together' only 14% of the patients demonstrated this. Three of the seven CF like phenotypes belonged to this group. We could not say 'having all four systemic symptoms together' is a predictor of a severe respiratory phenotype, but it's notable that the three described CF like phenotypes fell in the small category of 14%.

PHA type 1B patients need life-long therapy with generally very high amounts of sodium supplementation [1,3,9,19,30]. We thought that a higher need of this 'NaCl therapy' would reflect a more severe course of PHA type 1B and consequently a more severe respiratory phenotype. In contrast to this hypothesis, some CF like phenotypes took low doses of salt supplementation. One patient didn't even take any salt supplements [11,16]. Moreover, high doses of NaCl therapy was seen in some patients with little pulmonary involvement.

A sweat test showing Na and Cl of >60 mmol/L is one of the important and useful technical investigations diagnosing PHA type 1B [1,6-8,19]. We supposed that the higher the sweat concentration of Cl and/or Na, the more severe the course of PHA type 1B, including the respiratory course. We directed the amount of Na and/or Cl concentration into groups of <60, 60-90, 90-120, 120-150, and >150 mmol/L. Even though most of the patients belonged to the group of 120-150 mmol/L, the seven CF like phenotypes were equally divided along the different groups. Even one had a Na concentration of 16 mmol/L [17].

As mentioned above, PHA type 1B is inherited as an autosomal recessive trait by loss-of-function mutations in the genes encoding the subunits of the ENaC channel. SCNN1A mutations are the most frequent in PHA type 1B. The loss-of-function mutations consist of nonsense, missense, frame-shift, or abnormal splicing mutations. Although patients with an exactly same mutation show a different pulmonary disease [19], we speculated that 'genotype' could be a good predictor of the respiratory phenotype. For example, alpha-subunit knockout mice have shown death from respiratory distress [1,22]. It is also known that patients having a missense mutation show a milder course of PHA type 1B [1,2,7,19,21,23]. As is shown in the supplementary table we confirmed that SCNN1A mutations are the most frequent, but we could not conclude that these mutations cause a more severe respiratory course. Futhermore the only **SCNN1G** mutation described belonged to one of the CF like phenotypes [11,16]. After analyzing the type of loss-of-function mutation for the CF like phenotypes, we found **the highest prevalence in** frame shift. However, this mutation was also present in patients with a less severe respiratory course. In addition one CF like phenotype showed a missense mutation and this doesn't agree with the description of 'most favorable mutation' [19].

According to the pathophysiology of the pulmonary syndrome in PHA type 1B, it is expected that the respiratory clinic becomes gradually less severe with age, typically from the age of 5-6 years [7,16,23]. Even for CF like phenotypes, we confirmed this improvement over time. Our patient however presented a more severe course of respiratory illness during follow-up. Difficult asthma could explain this severe course. Knowing that inflammation in asthma leads to more mucus secretion and constriction of the bronchial smooth muscle, the recurrent episodes of chest congestion, coughing, and wheezing in our patient can be explained. Analyzing this possible respiratory involvement in the other patients of the supplementary table, no one tested positive for asthma. Asthma could therefore be **an important** risk factor for a more severe respiratory phenotype in PHA type 1B patients.

As a conclusion we regret to confirm it's not easy to predict the respiratory phenotype in PHA type 1B. 'Male sex' and 'having all four important systemic symptoms together' are obviously more present in a CF like phenotype as is the case in our patient. Asthma can be a complementary important predictor of severe respiratory illness.

Conclusion

PHA type 1B is a very rare multi-system salt-wasting chronic disease. We reported a case showing a unique respiratory course mimicking that of cystic fibrosis. It would be useful to predict this severe respiratory phenotype early in the disease course. **To our knowledge, a respiratory comorbidity like asthma could be such a predictor**. More research is needed on this topic.

REFERENCES:

1. Belot A, Ranchin B, Fichtner C, Pujo L, Rossier BC, Liutkus A, et al. Pseudohypoaldosteronisms, report on a 10-patient series. Nephrol Dial Transplant. 2008;23:1636–1641.
2. Tajima T, Morikawa S, Nakamura A. Clinical features and molecular basis of pseudohypoaldosteronism type 1. Clin Pediatr Endocrinol. 2017;26(3):109–117.
3. Güran T, Degirmenci S, Bulut IK, Say A, Riepe FG, Güran O. Critical Points in the Management of Pseudohypoaldosteronism Type 1. J Clin Res Ped Endo. 2011;3(2):98-100.
4. Marthinsen L, Kornfält R, Aili M , Andersson D , Westgren U, Schaedel C. Recurrent Pseudomonas bronchopneumonia and other symptoms as in cystic fibrosis in a child with type I pseudohypoaldosteronism. Acta Paediatr. 1998;87: 472–4.
5. Hanukoglu I, Hanukoglu A. Epithelial sodium channel (ENaC) family: Phylogeny, structure–function, tissue distribution, and associated inherited diseases. Gene. 2016;579:95–132.
6. Hanukoglu A, Bistritzer T, Rakover Y, Mandelberg A. Pseudohypoaldosteronism with increased sweat and saliva electrolyte values and frequent lower respiratory tract infections mimicking cystic fibrosis. The Journal of Pediatrics. 1994;125:752-5.
7. Kerem E, Bistritzer T, Hanukoglu A, Hofmann T, Zhou Z, Bennett W. Pulmonary epithelial sodium-channel dysfunction and excess airway liquid in pseudohypoaldosteronism. The New England Journal of Medicine. 1999;341(3):156-162.
8. Urbatsch A, Paller AS. Pustular miliaria rubra: a specific cuteaneous finding of type 1 pseudohypoaldosteronism. Pediatric Dermatology. 2002;19(4):317-319.
9. Wang J, Yu T, Yin L, Li J, Yu L, Shen Y. Novel mutations in the SCNN1A gene causing pseudohypoaldosteronism type 1. PLoS ONE. 2013;8(6): e65676.
10. Ahluwalia GK, Dasouki M, Lennon A. Clinical Case Reports. 2014;2(6): 326–330.
11. Adachi M, Asakura Y, Muroya K, Tajima T, Fujieda K, Kuribayashi E, et al. Increased Na reabsorption via the Na-Cl cotransporter in autosomal recessive pseudohypoaldosteronism.

1. Clin Exp Nephrol. 2010;14:228–232.
2. Thomas CP, Zhou J, Liu KZ, Mick VE, MacLaughlin E, Knowles M. Systemic Pseudohypoaldosteronism from Deletion of the Promoter Region of the Human B Epithelial Na+ Channel Subunit. Am J Respir Cell Mol. Biol. 2002;27:314–319.
3. Yager D, Butler JP, Bastacky J, Israel E, Smith G, Drazen JM. Amplification of airway constriction due to liquid filling of airway interstices. J Appl Physiol. 1989;66(6):2873-2884.
4. Enuka Y, Hanukoglu I, Edelheit O, Vaknine H, Hanukoglu A. Epithelial sodium channels (ENaC) are uniformly distributed on motile cilia in the ovidcut and the respiratory airways. Histochem Cell Biol. 2012;137:339-353.
5. Widdicombe JH. Regulation of the depth and composition of airway surface liquid. J Anat. 2002;201:313-318.
6. Adachi M, Tachibana K, Asakura Y, Abe S, Nakae J, Tajima T, et al. Compound Heterozygous Mutations in the g Subunit Gene of ENaC (1627delG and 1570-1G3A) in One Sporadic Japanese Patient with a Systemic Form of Pseudohypoaldosteronism Type 1. JCE & M. 2001;86(1):9-12.
7. Welzel M, Akin L, Büscher A, Güran T, Hauffa BP, Högler W, et al. Five novel mutations in the SCNN1A gene causing autosomal recessive pseudohypoaldosteronism type 1. European Journal of Endocrinology. 2013;168:707-715.
8. Schaedel C, Marthinsen L, Kristoffersson A, Kornfält R, Nilsson KO, Orlenius B, et al. Lung symptoms in pseudohypoaldosteronism type 1 are associated with deficiency of the a-subunit of the epithelial sodium channel. J Pediatr. 1999;135:739-45.
9. Nur N, Lang C, Hodax JK, Quintos JB. Systemic pseudohypoaldosteronism type 1: A case resport and review of the literature. Case Reports in Pediatrics. 2017;2017:1-8.
10. 20. Schweiger B, Moriarty MW, Cadnapaphornchai MA. Case report: severe neonatal hyperkalemia due to pseudohypoaldosteronism type 1. Curr Opin Pediatr. 2009;21:269-271.
11. 21. Bistritzer T, Kerem E, Berkovitch M, Rapoport MJ, Evans S, Aladjem M. Erythrocyte Na+, K+-ATPase and nasal potential in pseudohypoaldosteronism. Clinical Endocrinology. 2002;56:575-580.
12. 22. Chang SS, Grunder S, Hanukoglu A, Rösler A, Mathew PM, Hanukoglu I, et al. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. Nature Genetics. 1996;12:248-253.
13. 23. Edelheit O, Hanukoglu I, Gizewska M, Kandemir N, Tenenbaum-Rakover Y, Yurdakök M, et al. Novel mutations in epithelial sodium channel (ENaC) subunit genes and phenotypic expression of multisystem pseudohypoaldosteronism. Clinical Endocrinology. 2005;62:547-553.
14. 24. Bonny O, Knoers N, Monnens L, Rossier BC. A novel mutation of the epithelial Na+ channel causes type 1 pseudohypoaldosteronism. Pediatr Nephrol. 2002;17:804-808.
15. 25. Peters TA, Levtchenko E, Cremers CWRJ, Curfs JHAJ, Monnens LAH. No evidence of hearing loss in pseudohypoaldosteronism type 1 patients. Acta Oto-Laryngologica. 2006;126(3):237-239.
16. 26. Edelheit O, Hanukoglu I, Shriki Y, Tfilin M, Dascal N, Gillis D, et al. Truncated beta epithelial sodium channel (ENaC) subunits responsible for multi-system pseudohypoaldosteronism support partial activity of ENaC. Journal of Steroid Biochemistry & Molecular Biology. 2010;119:84-88.
17. 27. Hanukoglu A, Edelheit O, Shriki Y, Gizewska M, Dascal N, Hanukoglu I. Renin-aldosterone response, urinary Na/K ratio and growth in pseudohypoaldosteronism patients with mutations in epithelial sodium channel (ENaC) subunit genes. Journal of Steroid Biochemistry & Molecular Biology. 2008;111:268–274.
18. 28. Huppmann S, Lankes E, Schnabel D, Bührer C. Unimpaired postnatal respiratory adaptation in a preterm human infant with a homozygous ENaC-a unit loss-of-function mutation. Journal of Perinatology. 2011;31:802-803.
19. 29. Amin N, Alvi NS, Barth JH, Field HP, Finlay E, Tyerman K, et al. Pseudohypoaldosteronism type 1: clinical features and management in infancy. Endocrinology, Diabetes & Metabolism. 2013;ID: 13-0010:1-8.
20. 30. Hanukoglu A, Hanukoglu I. Clinical improvement in patients with autosomal recessive pseudohypoaldosteronism and the necessity for salt supplementation. Clin Exp Nephrol. 2010;14:518–519.

NOUVEAU: LINGETTES PAMPERS® AQUA PURE

La pureté de l'eau avec la facilité d'une lingette

Les nouvelles lingettes Pampers® Aqua Pure ont été développées pour offrir une lingette la plus humide possible qui assure à la fois un soin efficace et la meilleure protection de la peau.

Les lingettes Pampers® Aqua Pure contiennent 99% d'eau purifiée, du coton bio et une lotion à effet tampon de pH unique pour un soin en douceur tout en protégeant la peau sensible de bébé

- Testées dermatologiquement
- Conviennent à la peau des nouveau-nés
- organic cotton — A base de coton bio
- 99% d'eau purifiée
- 0% alcool, parabène, phénoxyéthanol, colorant, parfum

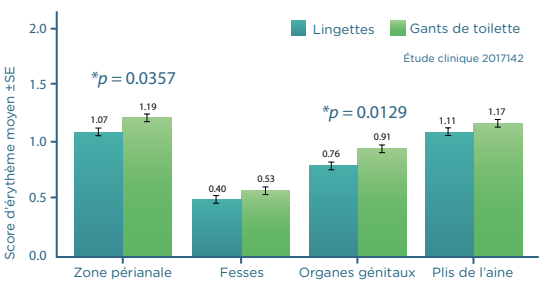
Une nouvelle étude clinique démontre que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau

En collaboration avec l'ESPD, Pampers a mené une étude chez 130 bébés évaluant l'effet des lingettes pour bébé sur le siège en comparaison avec un gant de toilette imbibé d'eau du robinet.

Cette étude a été réalisée en parallèle en aveugle et à répartition aléatoire (ce qui signifie que les examinateurs ignoraient quels étaient les soins appliqués). Après une phase de repos d'une semaine durant laquelle seul l'usage d'eau du robinet et du gant de toilette était autorisé, les deux types de soins ont été comparés pendant une période de deux semaines en mesurant les scores d'érythème sur 4 sites.

Après deux semaines d'utilisation, il a été démontré que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau. La peau nettoyée avec des lingettes a également présenté un pH significativement inférieur en comparaison à la peau nettoyée à l'aide d'un gant de toilette imbibé d'eau du robinet, ce qui pourrait procurer des bénéfices à long terme pour la santé de la peau.

Score d'érythème moyen par site



Composants d'origine végétale qui ont été testés dermatologiquement

- Benzoate de sodium
- EDTA
- PEG-40 Huile de ricin hydrogénée
- Acide citrique
- Citrate de sodium
- Caprylate sorbitan

Effet tampon de pH

La lotion contient un système à effet tampon à base d'acide citrique conçu pour préserver l'équilibre naturel du pH de la peau.[1] Des études scientifiques ont démontré que l'une des principales causes de l'érythème fessier est le déséquilibre du pH qui se produit lorsque le lange est souillé. Les langes sales (combinaison urine et selles) contiennent souvent des enzymes digestives qui irritent la peau. Pour contrer cet effet, les lingettes pour bébé Pampers contiennent une lotion spécialement conçue, dotée d'un effet tampon permettant de ramener rapidement le pH de la peau à des valeurs normales comprises entre 4,5 et 6,0.

Les lingettes Pampers® Aqua Pure sont :

sans alcool
sans parfum
sans parabène
sans phénoxyéthanol
sans colorant
sans blanchiment au chlore

[1] Données internes de P&G

PARTENAIRE OFFICIEL GOLD - 2019
PAMPERS SOUTIENT LA SOCIÉTÉ BELGE DE PÉDIATRIE

European Society for Pediatric Dermatology
Approuvées par ESPD

New Insights in Thyroid Function in Preterm Infants.

An Eerdekens [1]

PhD thesis presented on May 24th, 2019 at Catholic University Leuven, Belgium

Promotor: Christine Vanhole [2]

Co-promotors: Lies Langouche [3], Johan Verhaeghe [2]

[1] Neonatal Intensive Care Unit, UZ Leuven
[2] Department of Development & Regeneration, Faculty of Medicine, KU Leuven
[3] Department of Cellular and Molecular Biology, Faculty of Medicine, KU Leuven

an.eerdekens@uzleuven.be

Keywords

Thyroid hormones – Preterm Infants – Brain development – Transient hypothyroxinemia of prematurity

Abstract

Thyroid hormones are important developmental hormones, in particular for the brain. Until mid-gestation, the fetus is dependent on maternal thyroid hormone supply, mainly regulated by the placenta. From mid-gestation, the fetal thyroid hormone system starts to function, but only after birth, the newborns' thyroid hormone system acts autonomously. Preterm infants often present with transient hypothyroxinemia of prematurity, a temporary decrease in circulating thyroid hormone levels without the expected increase in the pituitary secreted thyroid-stimulating hormone, with controversies about both the clinical relevance and therapeutic approaches. The aim of this PhD project was to gain more insight in this phenomenon.

Main text

Thyroid hormones (TH) are indispensable for fetal development in general, and in particular for the developing brain, where they play an important role in neurogenesis, myelination, dendrite proliferation and synaptogenesis [1]. Until mid-gestation, the fetus is completely dependent on maternal TH supply and the placenta plays a central role in this maternal-fetal TH transfer. From around 20 weeks of gestation, the fetal TH system starts to function, but it is only after birth that the newborns' TH system acts completely autonomously [2]. Preterm infants often present with transient hypothyroxinemia of prematurity (THOP), a temporary decrease in circulating TH levels without the expected increase in the pituitary secreted thyroid-stimulating hormone (TSH)[3]. THOP is already topic of debate for several decades: both the clinical relevance as therapeutic approaches are subject of discussion. This demonstrates the complexity of this phenomenon [4]. The aim of this PhD project was to gain more insight in THOP.

In the general introduction of this thesis, an overview of the general aspects of TH metabolism and actions was given, with focus on the importance of THs in fetal maturation and brain development and the challenges of pregnancy towards maternal thyroid economy and mechanisms of maternal-fetal TH transfer in normal circumstances. Subsequently, the focus shifted towards complicated pregnancies. Histological features of the placenta in conditions of chronic utero-placental hypoxia were described and the current knowledge about the impact of these conditions on placental TH transport and metabolism were discussed. Since preterm birth is the result of a complicated pregnancy, and preterm infants present with THOP, an overview of the knowledge about the etiology of THOP, and discussed controversies about both the impact of THOP on the infants' neurodevelopment and therapeutic approaches, were given[4,5].

We first hypothesized that in preterm birth, the underlying pregnancy complication affects the trans-placental supply of THs to the fetus and therefore, this complication predisposes the preterm infant to THOP. We questioned whether maternal and placental compensatory mechanisms are activated to increase TH transfer to the fetus. An observational case-control study in mother-infant-dyads with complicated pregnancies ending in spontaneous preterm birth (n=31) or indicated preterm birth due to vascular complications (n=45) and normal pregnancies (healthy term controls; n=41) was performed. At delivery, maternal and cord blood and placenta samples were collected. Cord and maternal plasma concentrations of TSH, total thyroxine (T4), free thyroxine (fT4)/free thyroxine index, total triiodothyronine (T3) and Thyroid-Binding Globulin (TBG), and maternal serum concentrations of Thyroid Peroxidase-antibodies were measured. Placental maturity was evaluated histologically and mRNA and/or protein levels of thyroid hormone deiodinases DIO 1, 2 and 3 and transporters monocarboxylate transporter 8 (MCT8) and 10 (MCT10) and organic anion-transporting polypeptide 1C1 (OATP1C1) were quantified. We found that in indicated and spontaneous preterm births, cord plasma T4 concentrations were lower than in healthy term controls ($P \leq 0.001$), whereas T3 was only decreased in spontaneous preterm birth ($P \leq 0.001$). Compared with spontaneous preterm births and healthy term controls, indicated preterm birth was characterized by higher maternal plasma TSH levels ($P \leq 0.05$), earlier placental maturation, higher placental DIO2 gene and MCT10 protein levels and lower DIO3 gene levels (all $P \leq 0.01$). We concluded that low T4 was observed in preterm infants irrespective of the cause of preterm birth, while maternal (TSH) and placental (DIO2, DIO3 and MCT10) compensatory responses were only associated with indicated preterm birth due to vascular complications. This may have mediated the fetal T3 availability in preterm infants born after indicated preterm birth but not after spontaneous preterm birth[6].

Next, the evolution of circulating TH levels during the first week of life in preterm infants was studied. It remains questionable which ranges for circulating TH levels in preterm infants are optimal in relation to gestation and postnatal ages. By studying the evolution of circulating TH levels during the first week of life and expressing it as Δ, i.e. the difference between the end of the first week of life and cord blood, we developed a novel approach in assessing THOP, independent of predefined reference values. This was a single-center prospective observational study. We collected plasma levels of total and free T4, total T3, TSH and TBG in cord blood and at the end of the first week of life in 120 preterm infants (gestational age < 37 weeks). The change over time was calculated (delta, Δ). The association of perinatal and subsequently postnatal variables on Δ was studied by hierarchical multiple regression. The association of Δ on the neurodevelopmental outcome at the corrected age of 9 and 24 months, measured by the Bayley Scale of Infants

Development II, was assessed by logistic regression. Negative Δ(f)T4 values were associated with low gestational age and use of dopamine, whereas low ΔT3 values were only associated with low gestational age (GA). Negative Δ(f)

T4 values were present in 75% of the extremely low gestational age newborns (ELGANs), whereas 23·5 % had a negative ΔT3value. There was an increased risk for an abnormal mental developmental score (<85) with decreasing ΔT3 at 9 months, corrected age, but not at 24 months. We concluded that by this approach, immaturity is the most important contributing factor to THOP, since negative trends in the evolution of TH levels were most prevalent in ELGANs, whereby infants with GA of 24-25 weeks were most affected. Besides, the use of dopamine was another risk factor for these negative trends. Not a negative evolution in the prohormone T4, but in the active hormone T3 was negatively affecting the infants' neurodevelopment at the corrected age of 9 months, but this impact could not be demonstrated anymore at the corrected age of 24 months [7].

Finally, this novel approach of THOP to the evaluation of TH action in the preterm infants' brain was applied by performing a pilot study about the impact of THOP on functional brain development with electro-encephalogram (EEG) measurements. We hypothesized that since THOP is present in a time-frame where important TH-dependent processes occur, brain development is affected and this is reflected by alterations in EEG complexity at term age. In this retrospective single-center study, circulating fT4 levels on day 0 (time 1) and at the end of the first week of life (time 2) were collected and delta (Δ) fT4 (= fT4time2-fT4time1) was calculated in 61 ELGANs. Brain maturation was quantified by measurement of EEG complexity using multiscale entropy at term age. In a subset of 14 infants, EEG recordings in the first weeks of life (range day 6 – 25) were also available. The evolution in EEG complexity was compared between the groups with positive and negative ΔfT4. Relevant clinical data were collected. We found that in the negative ΔfT4 group, EEG complexity was significantly lower in the right central and frontal channels. EEG complexity in the first weeks of life was comparable, but there was a trend towards lower EEG complexity at term age in the negative ΔfT4 group. Although we have to be very careful with interpreting these results, due to the limitations of this retrospective study, we conclude that temporary low TH levels were associated with less EEG complexity at term age, suggesting less brain maturation. Therefore, EEG is a promising tool in studying the effects of temporary low circulating TH levels on the preterm infants' brain.

The results of this thesis might help to develop further research strategies to obtain more insight in the underlying mechanisms and impact of THOP and to design possible future therapeutic trials.

Disclosure of potential conflicts of interest:

None of the authors have a conflict of interest.

REFERENCES:

1. Bernal J. Thyroid hormone receptors in brain development and function. Nature clinical practice Endocrinology & metabolism. 2007;3(3):249-59.
2. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience. 2017;342:68-100.
3. Fisher DA. Thyroid system immaturities in very low birth weight premature infants. Seminars in perinatology. 2008;32(6):387-97.
4. Eerdekens A, Langouche L, Van den Berghe G, Verhaeghe J, Naulaers G, Vanhole C. Review shows that thyroid hormone substitution could benefit transient hypothyroxinaemia of prematurity but treatment strategies need to be clarified. Acta paediatrica (Oslo, Norway : 1992). 2019;108(5):792-805.
5. Eerdekens A, Verhaeghe J, Darras V, Naulaers G, Van den Berghe G, Langouche L, et al. The placenta in fetal thyroid hormone delivery: from normal physiology to adaptive mechanisms in complicated pregnancies. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019:1-10.
6. Eerdekens A, Langouche L, Güiza F, Verhaeghe J, Naulaers G, Vanhole C, et al. Maternal and placental responses before preterm birth: adaptations to increase fetal thyroid hormone availability? The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019;32(16):2746-57.
7. Eerdekens A, Naulaers G, Ortibus E, Verhaeghe J, Langouche L, Vanhole C. Evolution of circulating thyroid hormone levels in preterm infants during the first week of life: perinatal influences and impact on neurodevelopment. Journal of pediatric endocrinology & metabolism : JPEM. 2019;32(6):597-606.

NOUVELLE MISE À JOUR DU SCHÉMA DE VACCINATION !

Prix public Belgique	86,52€
Prix public Luxembourg	84,07€

BEXSERO

Vaccin méningococcique groupe B (ADNr, composant, adsorbé)

Le **premier** vaccin contre le méningocoque de **sérogroupe B**.[1]

Le **seul** indiqué dès l'âge de **2 mois**.[1,2]

2+1

pour les nourrissons à partir de **2 mois**.[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 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) **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	Primovaccination	Intervalles entre les doses de primovaccination	Rappel
Nourrissons de 2 à 5 mois	Trois doses de 0,5 ml chacune	1 mois minimum	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]
	Deux doses de 0,5 ml chacune	2 mois minimum	
Nourrissons de 6 à 11 mois	Deux doses de 0,5 ml chacune	2 mois minimum	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]
Enfants de 12 à 23 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c]
Enfants de 2 à 10 ans	Deux doses de 0,5 ml chacune	1 mois minimum	Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique [d]
Adolescents (à partir de 11 ans) et adultes*			

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose 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. **CONTRE-INDICATIONS** 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 vaso-vagales (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 contre-indication 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. 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 post-vaccinales. 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. 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. Traçabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 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 co-administré 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 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 gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané 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 musculo-squelettiques 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 du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale 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 gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance Boîte Postale 97 B-1000 Bruxelles Madou Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 04/2020 (v10) **MODE DE DELIVRANCE** Sur prescription médicale.

1. Medini D, Stella M, Wassil J, Vaccine 2015; 33; 2629-2636. 2. Bexsero SMPC.

PM-BE-BEX-ADV-200001 - Juin 2020 - E.R.: GlaxoSmithKline Pharmaceuticals s.a., av Pascal 2-4-6, 1300 Wavre

Bone geometry and bone mineral density by peripheral quantitative computed tomography in healthy and diseased children

Inge Roggen

PhD thesis presented on 18th of January 2020 at the Vrije Universiteit Brussel, Jette, Belgium

Promotor: Prof. dr. Jean De Schepper

inge.roggen@vub.be

Introduction

Many chronic diseases and eventually their treatments in childhood, such as leukaemia and chemotherapy, cystic fibrosis (CF) and glucocorticoid use, cerebral palsy and physical activity, type 1 diabetes (DM1) and insulin treatment, and anorexia nervosa (AN) and feeding, affect the mineralization of the skeleton, as well as the locomotor and muscle function. As children with chronic diseases tend to survive longer than a few decades ago, it is of major importance to ensure that every child, despite any underlying disease, can grow up and grow old in optimal conditions, with as little as possible additional burdens on the long-term, including bone fractures due to osteoporosis. The tracking of bone density and muscle strength during childhood and adolescence offers an opportunity for early intervention in children at risk for a poor development of the musculoskeletal system.

Dual-energy x-ray absorptiometry (DXA) at the lumbar spine and hip is considered the gold standard for measurement of bone mineral density (BMD) in adults and is used for fracture risk assessment. The main problem with DXA is that it makes a 2-dimensional projection of 3-dimensional bone data, losing the information on bone thickness. DXA therefore reports an areal BMD, which is highly body size dependent, resulting in under- or overestimation in growing children and adolescents, when their body height is far below or above the “normal” values.

Peripheral quantitative computed tomography (pQCT), introduced in the early 1990s, using a rotate-translate CT technique to generate a transverse slice of the upper or lower limb, made it possible to examine, even with lower radiation dose (1.5-4 µSv per scan) than DXA, the real (3 dimensional) bone density as well as bone geometry (bone area, cortical thickness) in children. As pQCT measures the density of a given compartment reflecting the degree of mineralization of the measured volume of a bone compartment, but not for the bone itself.

Despite its advantages, pQCT is mainly used as a research tool. One of the disadvantages of pQCT is the lack of large population-based reference data (especially for the tibia), the uncertainty of interchangeability between different commercial devices and the lack of consensus of optimal site of measurement (radius vs. tibia; dominant vs. non-dominant limb). Though the advantages of differentiation between cortical and trabecular bone seem useful, currently there are only limited data on the relevancy of the different bone parameters assessed by pQCT in predicting the fracture risk in children and adolescents with or without chronic disease [1].

Recent bone research has also focused on the evaluation of the bone parameters in relation to muscle strength. The use of the muscle-bone strength relation allows to discriminate between primary (a problem with the bone itself) or secondary (as a reaction to decreased physical activity, medication use, disease, …) bone disease.

When it comes to the assessment of muscle force, many surrogates have been used in research: whole body or leg/arm muscle mass by DXA, cross-sectional muscle area or volume by pQCT have all been suggested [2, 3], but maximum muscle force does not only depend on muscle size [4, 5]. The novel technique of jumping mechanography, using different kinds of hopping, has been suggested as a highly reproducible and non-invasive technique for measuring muscle force, showing a strong correlation with several bone parameters at the tibia as measured by pQCT [6]. Of all the different kinds of hopping, forefoot hopping seemed to produce the highest voluntary ground reaction force (fGRF) [7].

In this thesis, both these modern techniques, pQCT and jumping mechanography, were used to study bone mineralisation and muscle force development in both healthy and chronically diseased children presenting different degrees of growth and muscle force failure.

Reference database

A large national database for the development of pQCT reference values at the tibia was constructed, as European reference values were lacking in children. Using pQCT measurements at the tibia in 432 children and adolescents, aged between 5 and 19 years, reference parameters for trabecular BMD at the distal tibia (4%), cortical BMD at the proximal (14% and 38% site) and bone geometry at all sites, were calculated using the LMS method, in relation to age, body height and muscle force, generated during one leg hopping [8].

Chronic disease

Four chronic diseases were investigated cross-sectionally, either with an onset in infancy (cystic fibrosis; CF) or later in childhood (obesity, type 1 diabetes; DM1 and anorexia nervosa; AN). The impact of body size (in all conditions), muscle force (obesity), body composition (CF and obesity) and disease-specific conditions (CF, DM1) on bone geometry at the midshaft, and trabecular BMD at the distal ends of the radius or tibia was studied.

Cystic fibrosis

In a non-selected group of 64 adolescents (> 12 years) and young (< 40 years) adults with CF, a smaller bone size at the radius, based on German reference values, was evident in females, despite only a moderate degree of undernutrition. Cortical bone area deficit was found to correlate positively with lean mass percentage deficit. Beside lower cortical bone areas and cortical thickness parameters, lower trabecular BMD values were present in patients with CF-associated diabetes mellitus [9].

Obesity

In a group of 51 male obese adolescents, aged between 10 and 19 years, at both the forearm and lower leg, larger bones as well as higher trabecular BMD values compared with normal-weight peers were found. Bone geometry results at the tibia correlated highly with the muscle force during one leg hopping [10].

Anorexia nervosa

A decreased trabecular BMD at the radius was the only aberrant finding in a group of 24 underweight adolescent females with a recently diagnosed (mean duration of 1.3 years) AN and characterized by a premenarcheal disease onset. No correlations with anthropometric parameters or any disease related factor were found, such as the age at onset and degree of weight loss [11].

Diabetes mellitus type 1

Finally, smaller cortical bone sizes at the proximal radius in 23 young adult DM1 females, aged between 18 and 23 years old, after a mean disease duration of 10.6 years, when compared to age, height and BMI matched controls were documented. No association between the bone deficit and disease related factors, as metabolic control and disease duration, was found [12].

Conclusions

In this work, the goal was to establish Belgian reference values for pQCT measurements at the tibia in relation to gender, age, height and muscle force, and investigate the contribution of body size (body weight and body height), whole lean mass (as measured by DXA), and real muscle force (not its surrogate muscle area) in chronic diseases. The use of pQCT allowed to evaluate the impact of chronic disease on the two bone compartments (trabecular and cortical bone), since they react differently to changes in body weight, muscle strength and hormonal or metabolic changes.

pQCT measurements at both radius and tibia were performed in children with several chronic diseases during adolescence, when peak bone mineral accretion velocity is greatest. We were interested in quantifying potential bone segment (weight-bearing vs. non-weight-bearing), bone compartment (trabecular vs. cortical bone), bone structure (bone size vs. bone mineral density) changes occurring in chronic disease during this period of maximal bone mineral accretion. The studied conditions, obesity, anorexia nervosa, cystic fibrosis and type 1 diabetes mellitus, differ in body size, body composition and muscle involvement, which all are known to influence the bone mineral accretion, permitting a view on the impact of each of these determinants. Furthermore, age at onset of the disease and additional chronic disease differed between the studied chronic conditions, given the opportunity to study the effect of the moment of disease and possible associated conditions impairing bone health.

Our hypothesis, that in chronic diseases where undernutrition or hormonal or metabolic disturbances prevail, trabecular BMD would be preferentially reduced, and that in diseases where disturbances in body mass and body composition, impacting on muscle mass and force, are predominantly attained, differences would be mainly found in cortical bone size, was only partially confirmed. Major bone geometry disturbances were indeed observed in the studied cohort of female patients with cystic fibrosis (decreased CSA at the radius), and in the group of male adolescents with obesity (increased diameter at the radius), but were also seen in the female type 1 diabetes young adults (decreased values). On the other hand, increased trabecular BMD was present in the male obese patients and a deficit in BMD was only observed in the underweight females with anorexia nervosa.

Future perspectives

First of all, consensus is needed on scan acquisition (desired bone, dominant or non-dominant, radius or tibia) and scan sites, (although most studies included the 4 % metaphyseal site) and scan analysis (placement of reference line) to promote the use of pQCT in clinical practise. The lack of consensus on the desired scan site, as well as the limited availability in commercial devices, and the limited published reference data, put a hold on the further development of pQCT as a clinical tool. Another window on the future might be the choice of HR-pQCT, especially in younger children, as the newest generation HR-pQCT scans even have a resolution of 5-fold greater than the Stratec scanners used in these studies.

Furthermore, there is a need for prospective cohort studies in children with chronic diseases in order to establish the short- and long-term fracture implications of deficits in trabecular and cortical outcome parameters. It could be useful to continue tibia measurements in young adults to analyse the age of peak bone mass attainment, which might be different in children with chronic disease.

Interesting studies in obese adolescents to perform in the future are parallel studies of body fat distribution, muscle force and bone compartments across the adolescent age range, since the effect of fat distribution on bone development may vary with age. Long-term studies up to young adulthood in these children are needed to verify if the beneficial effect on bone size and BMD will have life-long effects or might deteriorate when visceral obesity increases

REFERENCES:

1. Zemel B, Bass S, Binkley T, Ducher G, Macdonald H, McKay H, et al. Peripheral quantitative computed tomography in children and adolescents: the 2007 ISCD Pediatric Official Positions. J Clin Densitom. 2008;11(1):59-74.
2. Ducher G, Courteix D, Même S, Magni C, Viala J, Benhamou C. Bone geometry in response to long-term tennis playing and its relationship with muscle volume: a quantitative magnetic resonance imaging study in tennis players. Bone. 2005;37(4):457-466.
3. Heinonen A, McKay H, Whittall K, Forster B, Khan K. Muscle cross-sectional area is associated with specific site of bone in prepubertal girls: a quantitative magnetic resonance imaging study. Bone. 2001:29(4):388-392.
4. Binkley T, Specker B. Muscle-bone relationships in the lower leg of healthy pre-pubertal females and males. J Musculoskelet Neuronal Interact. 2008;8(3):239-243.
5. Fricke O, Schönau E. The 'functional muscle-bone unit': probing the relevance of mechanical signals for bone development in children and adolescents. Growth Horm IGF Res. 2007;17(7):1-9.
6. Anliker E, Rawer R, Boutellier U, Toigo M. Maximum ground reaction force in relation to tibial bone mass in children and adults. Med Sci Sports Exerc. 2011;43(11):2102-2109.
7. Runge M, Schiessl H, Rittweger J. Klinische diagnostik des regelkreises muskel-knochen am unterschenkel. Osteologie. 2002;11(1):25-37.
8. Roggen I, Roelants M, Sioen I, Vandewalle S, De Henauw S, Goemaere S, et al. Pediatric reference values for tibial trabecular bone mineral density and bone geometry parameters using peripheral quantitative computed tomography. Calcif Tissue Int. 2015;96(6):527-533.
9. De Schepper J, Roggen I, Van Biervliet S, Robberecht E, Gies I, De Waele K, et al. Comparative bone status assessment by dual energy X-ray absorptiometry, peripheral quantitative computed tomography and quantitative ultrasound in adolescents and young adults with cystic fibrosis. J Cyst Fibros. 2012;11(2):119-124.
10. Vandewalle S, Taes Y, Van Helvoirt M, Debode P, Herregods N, Ernst C, et al. Bone size and bone strength are increased in obese male adolescents. J Clin Endocrinol Metab. 2013;98(7):3019-3028.
11. Roggen I, Vanbesien J, Gies I, Van den Eede U, Lampo A, Louis O, et al. Forearm bone mineralization in recently diagnosed female adolescents with a premenarcheal onset of anorexia nervosa. Int J Eat Disord. 2016;49(8):809-812.
12. Roggen I, Gies I, Vanbesien J, Louis O, De Schepper J. Trabecular bone mineral density and bone geometry of the distal radius at completion of pubertal growth in childhood type 1 diabetes. Horm Res Paediatr. 2013;79(2):68-74.

Fluoroquinolones for children- filling the gap

Kevin Meesters [1,2]

PhD thesis presented as a joint-PhD at Ghent University and Vrije Universiteit Brussel on September 5, 2019

Promotors: Johan Vande Walle [1], Yvan Vandenplas [2], Pauline De Bruyne [1,3]

[1] Department of Internal Medicine and Pediatrics, Ghent University Hospital, Corneel Heymanslaan 10, 9000 Ghent, Belgium.
[2] KidZ Health Castle, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
[3] Department of Pediatric Gastroenterology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

kevin.meesters@ugent.be

Introduction

The safety of fluoroquinolones was studied, in the 1990s, in juvenile animals since pediatric data were limited during that time. Unfortunately, it turned out that these animals frequently had severe cartilage tissue lesions after exposure to fluoroquinolones [1]. In 1995, this resulted in a class label warning for the use of fluoroquinolones in the pediatric population. Nevertheless, many children have been prescribed fluoroquinolones since then [2]. Up until today, there is no evidence of irreversible cartilage tissue lesions as a clinical side effect in children [3]. The main aim of this PhD thesis was to enhance knowledge of the developmental pharmacology of fluoroquinolones, as this was limited at the beginning of this project.

Reflections on current fluoroquinolone usage in Belgian children

We analyzed indications for systemic fluoroquinolone prescriptions, and its quality, in a cohort of hospitalized children in two Belgian university children's hospitals, during a three-year period [4]. Main data about the study population and the prescriptions are displayed in table 1. The majority (83.6%) of prescriptions were for off-label indications, but there was at least some evidence available for the majority of these indications.

Meningoencephalitis is the largest group of off-label indications. Cephalosporins are typical first-line agents for this indication, which does not cover Mycoplasma pneumoniae that might account for up to 10-30% of all pathogens causing encephalitis [5]. Fluoroquinolones are effective against Mycoplasma pneumoniae, and attain therapeutic concentrations in cerebrospinal fluid; in contrast to macrolides and tetracyclines which are commonly prescribed against Mycoplasma pneumonia [6-8].

Prophylaxis of febrile episodes in neutropenic patients under treatment for childhood cancer was the second group of off-label indications. In neutropenic adults, fluoroquinolone prophylaxis is part of the standard of care in many centers worldwide. To the best of our knowledge, only one randomized controlled trial has investigated the effectivity of ciprofloxacin prophylaxis in neutropenic children [9]. In this study, ciprofloxacin showed a statistically significant risk reduction of 23.0% (-45.0% to -0.9%) in febrile episodes, no significant short-term adverse effects were observed [9].

18 out of 34 non-CF patients in our population for whom fluoroquinolones was administered for pneumonias, had neurologic comorbidities such as cerebral palsies and muscular diseases. These patients, who often reside in specialized institutions, commonly carry Pseudomonas and Klebsiella strains, which may justify fluoroquinolone prescription.

Approximately a third (30.2%) of all prescriptions were considered underdosed, according to dosing schemes available at the time of prescription. Logistic regression analyses were performed to identify risk factors for this, which results are displayed in table 2. Prescription of non-ciprofloxacin fluoroquinolones seemed to protect against underdosing. An explanation for this might be that these prescriptions were so uncommon that prescribers were more cautious in dosing. However, this risk factor did not reach statistical significance, probably due to the limited number of non-ciprofloxacin prescriptions. Dosing errors were least frequent in adolescents, possibly due to similarities with widely available adult dosing schemes. On contrary, infants and preschool children were at particular risk for dosing errors.

Dosing studies

In an attempt to study drug exposure in children under treatment for complicated urinary tract infection, we performed a pharmacokinetic study in 23 children who took ciprofloxacin, either intravenous or orally. Serial serum and urine samples were collected, in which ciprofloxacin concentrations were measured, and subsequently analyzed in a population pharmacokinetic model. Creatinine based algorithms have been used traditionally for estimating renal clearance. In our population, glomerular filtration rate was best estimated using a formula that combines cystatin C and creatinine [10]. Despite being a superior marker for drug clearance when compared to creatinine, cystatin C is not widely used in clinical practice [11]. Volume of distribution in our population was lower in comparison with previous studies [12-13]. In these studies, patients with cystic fibrosis were included, in whom volume of distribution is usually larger due to their increased lean body mass.

After thorough testing, a population pharmacokinetic model using fat-free mass and standardized kidney function, best described the concentration-time profiles in our population. This model was subsequently used to simulate optimal dosing regimens for Enterobacteriaceae and Pseudomonas aeruginosa. We found that, under conventional doses, all simulated groups reached the pharmacokinetic/pharmacodynamic target for Enterobacteriaceae. On contrary, on average 53% of all children reached the target for Pseudomonas aeruginosa, when dosed at 15 mg/kg PO. This is worrisome, as ciprofloxacin was prescribed as the only PO alternative for treating Pseudomonas aeruginosa in 7/22 of our patients, and subtherapeutic concentrations of fluoroquinolones select resistant Pseudomonas strains [14-15].

In order to better predict disease related differences in ciprofloxacin exposure, the data of our population pharmacokinetic study were further used to construct a physiologically-based pharmacokinetic model in children [16]. The methodology of physiologically-based pharmacokinetic models is complex, this is extensively described elsewhere [17]. In short, physicochemical parameters of drugs and available pathophysiological data are combined to mathematically model drug exposure at different body sites (i.e. organs and tissues). A major advantage of this approach is that it allows to predict drug exposure in the context of major pathophysiological alterations in diseased children. First, a published physiologically-based pharmacokinetic model of ciprofloxacin in healthy adults was transformed, thereby mainly adjusting for developing physiologic parameters, to a model for healthy children. Last, by adapting renal function parameters, our final model was constructed for children with complicated urinary tract infections.

Future perspectives

In this thesis, fluoroquinolones were used as an example of a drug that is regularly prescribed for children despite limited knowledge of its developmental pharmacology. At a global level, multiple initiatives have come

in practice during the last years to stimulate drug research in children [18]. Nevertheless, off-label prescribing remains common in pediatrics [19]. Due to significant progress in analytical methods, drug concentration measurements have become available using very small amounts of body fluids. Additionally, advancements in pharmacokinetic modelling methods have made it possible to construct models with a very limited number of samples per participant. This facilitates pediatric drug research significantly. Yet, to collect adequate data, it is important to create broader support for clinical studies in children in the society.

Table 1. Main demographic data about the study population, and information about the prescriptions. Displayed are either frequencies and percentages, or medians and interquartile ranges.

Population	Age	5.23 year (1.75 - 12.44)
	Weight	18.6 kg (11.3 - 38.7)
	Sex	Male 114 (55%), female 118 (45%)
	Comorbidity	Malignancies: 53 (20.2%) Cystic fibrosis: 14 (5.3%) Benign hematologic disorders: 14 (5.3%) Neurologic disorders: 38 (14.5%) Congenital anomalies of the kidneys and urinary tract: 18 (6.9%) Inflammatory bowel disease: 7 (2.7%) Transplant organ: 3 (1.1%)
	Department	Academic pediatrics ward: 104 (39.7%) Pediatric oncology: 53 (20.2%) PICU: 105 (40.1)
Prescriptions	Drug prescribed	Ciprofloxacin 253 (96.6%) Moxifloxacin 3 (1.1%) Levofloxacin 5 (1.9%) Norfloxacin 1 (0.4%)
	Indication	On-label indications: Respiratory infection in CF patients: 13 (5.0%) Complicated UTI and pyelonephritis: 31 (11.8%) Off-label indications: Prophylaxis of febrile neutropenia: 49 (18.7%) Pneumonia: 34 (13.0%) Multidrug-resistant tuberculosis: 1 (0.4%) Sepsis: 6 (2.3%) Ocular trauma: 1 (0.4%) Intraabdominal abscess and peritonitis: 15 (5.7%) Enteritis: 13 (5.0%) Meningitis and/or encephalitis: 65 (24.8%) Epididymitis: 2 (0.8%) Skin and soft tissue infections: 27 (10.3%) Osteomyelitis: 2 (0.8%) Q-fever: 1 (0.4%)

Table 2. Risk factors for underdosing. Displayed are odds ratios with corresponding 95% conference intervals, and p-values.

	Unadjusted OR	Adjusted OR
Age		
<1 year	0.249 (0.092 - 0.658) p=0.005	0.263 (0.097 - 0.701) p=0.008
1-3 years	0.447 (0.198 - 0.976) p=0.046	0.467 (0.206 - 1.027) p=0.062
3-6 years	0.269 (0.113 - 0.622) p=0.002	0.254 (0.106 - 0.588) p=0.020
6-12 years	0.672 (0.281 - 1.605) p=0.368	0.702 (0.292 - 1.684) p=0.425
12-18 years	reference category	reference category
CF vs. non-CF	1.332 (0.398 - 3.992) p=0.618	-
IV vs. orally	0.816 (0.480 - 1.384) p=0.451	-
Study center	1.294 (0.753 - 2.253) p=0.356	-
Off-label vs. on-label	0.780 (0.357 - 1.597) p=0.512	-
Culture based vs. empiric	1.292 (0.744 - 2.226) p=0.358	-
Other FQ vs. ciprofloxacin	3.556 (0.638 - 66.71) p=0.234	2.601 (0.436 - 49.86) p=0.382
Department		-
Academic pediatrics ward	1.238 (0.686 - 2.248) p=0.479	
Hematology - oncology	1.213 (0.595 - 2.549) p=0.601	
Pediatric intensive care unit	reference category	

REFERENCES:

1. Linseman DA, Hampton LA, Branstetter DG. Quinolone-induced arthropathy in the neonatal mouse: Morphological analysis of articular lesions produced by pipemidic acid and ciprofloxacin. Toxicol Sci. 1995;28(1):59–64.
2. Yang Z-T, Zahar J-RR, Méchaï F, Postaire M, Blanot S, Balfagon-Viel S, et al. Current ciprofloxacin usage in children hospitalized in a referral hospital in Paris. BMC Infect Dis [Internet]. 2013;13(245):(27 May 2013). Available from: http://www.biomedcentral.com/content/pdf/1471-2334-13-245.pdf%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3668209&tool=pmcentrez&rendertype=abstract
3. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child [Internet]. 2011;96(9):874–80. Available from: http://adc.bmj.com/content/96/9/874.abstract?ijkey=d7127fb3f842f6239157d400940d92d4203d4a64&keytype2=tf_ipsecsha
4. Meesters K, Mauel R, Dhont E, Walle J Vande, De Bruyne P. Systemic fluoroquinolone prescriptions for hospitalized children in Belgium, results of a multicenter retrospective drug utilization study. BMC Infect Dis. 2018;18(1):1–8.
5. Christie LJ, Honarmand S, Talkington DF, Gavali SS, Preas C, Pan C, et al. Pediatric encephalitis: what is the role of Mycoplasma pneumoniae? Pediatrics. 2007;120(2):305–13.
6. Scotton PG, Pea F, Giobbia M, Baraldo M, Vaglia a, Furlanut M. Cerebrospinal fluid penetration of levofloxacin in patients with spontaneous acute bacterial meningitis. Clin Infect Dis. 2001;33(9):e109–11.
7. Lipman J, Allworth a, Wallis SC. Cerebrospinal fluid penetration of high doses of intravenous ciprofloxacin in meningitis. Clin Infect Dis. 2000;31(5):1131–3.
8. Alffenaar J, van Altena R, Bökkerink H, Luijckx G, van Soolingen D, Aarnoutse R, et al. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. Clin Infect Dis [Internet]. 2009;49(7):1080–2. Available from: http://www.journals.uchicago.edu/doi/abs/10.1086/605576
9. Laoprasopwattana K, Khwanna T, Suwankeeree P, Sujjanunt T, Tunyapanit W, Chelae S. Ciprofloxacin reduces occurrence of fever in children with acute leukemia who develop neutropenia during chemotherapy. Pediatr Infect Dis J [Internet]. 2013 Mar;32(3):e94-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23080291
10. Chehade H, Cachat F, Jannot AS, Meyrat BJ, Mosig D, Bardy D, et al. New combined serum creatinine and cystatin C quadratic formula for GFR assessment in children. Clin J Am Soc Nephrol. 2014;9(1):54–63.
11. Brou NA, Jacqz-Aigrain E, Zhao W. Cystatin C as a potential biomarker for dosing of renally excreted drugs. Br J Clin Pharmacol. 2015;80(1):20–7.
12. Rajagopalan P, Gastonguay MR. Population Pharmacokinetics of Ciprofloxacin in Pediatric Patients. J Clin Pharmacol [Internet]. 2003 Jul;43(7):698–710. Available from: http://doi.wiley.com/10.1177/0091270003254802
13. Payen S, Serreau R, Munck A, Aujard Y, Aigrain Y, Bressolle F, et al. Population pharmacokinetics of ciprofloxacin in pediatric and adolescent patients with acute infections. Antimicrob Agents Chemother. 2003;47(10):3170–8.
14. Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, Hughes D, et al. Selection of resistant bacteria at very low antibiotic concentrations. PLoS Pathog. 2011;7(7):1–9.
15. Guillot E, Sermet I, Ferroni A, Chhun S, Pons G, Zahar J-R, et al. Suboptimal ciprofloxacin dosing as a potential cause of decreased Pseudomonas aeruginosa susceptibility in children with cystic fibrosis. Pharmacotherapy [Internet]. 2010;30(12):1252–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21114393
16. Balbas-Martinez V, Michelet R, Edginton AN, Meesters K, Trocóniz IF, Vermeulen A. Physiologically-Based Pharmacokinetic model for Ciprofloxacin in healthy children and extrapolation to children with complicated Urinary Tract Infection. Poster Present PAGE 27 [Internet]. 2018;128(July 2018):2009. Available from: PAGE 27 (2018) Abstr 8676 [www.page-meeting.org/?abstract=8676]
17. Khalil F, Läer S. Physiologically Based Pharmacokinetic Modeling: Methodology, Applications, and Limitations with a Focus on Its Role in Pediatric Drug Development. J Biomed Biotechnol [Internet]. 2011;2011:1–13. Available from: http://www.hindawi.com/journals/bmri/2011/907461/
18. Kshirsagar N, Swaminathan S, Jog P, Dalwai S, Mathur R, Shekhar C, et al. Regulatory and Ethical Issues in Pediatric Clinical Research: Recommendations From a Panel Discussion. J Clin Pharmacol. 2017;57(8):943–6.
19. Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label Medication Prescribing Patterns in Pediatrics: An Update. Hosp Pediatr. 2019;9(3):186–93.

In collaboration with Cebam, Cochrane Belgium
(http://belgium.cochrane.org)

Alarm interventions for nocturnal enuresis: possibly effective but uncertainty as to best treatment remains

Anne-Catherine Vanhove [1, 2], Trudy Bekkering [1], Filip Cools [1]

[1] Cochrane Belgium, Belgian Centre for Evidence-Based Medicine (Cebam)
[2] Centre for Evidence-Based Practice (CEBaP) of the Belgian Red Cross-Flanders

Question

Is alarm training an effective treatment for nocturnal enuresis in children?

Context

Nocturnal enuresis (bedwetting) is common in childhood and affects up to 20% of five-year-olds. It is defined as involuntary loss of urine at night at an age when a child could reasonably be expected to be dry (usually 5 years of age). It is thought that bedwetting occurs if there is a defective arousal response to the sensation of a full bladder, a lack of inhibition of bladder emptying during sleep, a low capacity or overactive bladder or excessive nocturnal urine production. Although bedwetting usually resolves spontaneously, it can affect children's quality of life and self-esteem.

Treatments for bedwetting include alarms, behavioural interventions and drugs. This Cochrane review assessed the effectiveness of alarm treatments. In alarm treatments, urine coming into contact with a sensor will trigger an alarm waking up the child. The sensor is either located in a pad placed on the bed under the child or is placed in the child's underwear in case of a body-worn alarm. The alarm will wake the children each time they wet the bed and eventually they learn to wake up in response to a distending bladder or they learn to contract their urethral sphincter to avoid bedwetting.

Criteria for study selection

The Cochrane review included studies using enuresis alarms for treating bedwetting in children between 5 and 16 years old. The alarms were either used as monotherapy or in combination with other interventions and compared to no treatment or other treatments. The main outcomes of interest were the mean number of wet nights per week and the proportion of children achieving 14 consecutive dry nights at the end of treatment.

Summary of the results

The review identified 74 trials with 5983 children in total. The duration of the alarm training ranged between 2 weeks and 6 months. Most trials included a follow-up period after the end of treatment. Only a few studies used a body-worn alarm. The alarm was most often an audio stimulus but vibration and electric shock were used too. Studies varied also in the different alarm stimuli (loudness, delayed triggering etc), in whether parents were also woken up, the reward systems, etc. The alarm was compared to no treatment or waitlist (18), a non-functioning alarm (1), placebo drugs or active drug treatment (24), behavioural interventions (10) or another version of the alarm treatment (13).

Alarm training as monotherapy

Compared to no treatment, alarms may reduce the number of wet nights with 2.68 fewer wet nights a week (95% * CI: 4.59 fewer to 0.76 fewer; 4 studies, 127 participants, low-certainty evidence). It may increase the proportion of children achieving 14 consecutive dry nights by the end of treatment (control: 133 per 1000 vs alarm: 958 per 1000 (95 CI 186-1000); 18 studies, 827 children, low-certainty evidence) and more children may remain dry post-treatment (control: 18 per 1000 vs alarm: 177 per 1000 (95% CI 87-361); 10 studies, 366 children, low-certainty evidence). Compared to placebo drugs, alarms may increase the number of children that are dry at the end of treatment (2 studies, 181 participants, low-certainty evidence). Whether it also increases the number of dry nights a week remains uncertain (1 study, very low-certainty evidence).

Code-word alarms (in which children hear a pre-recorded personalised message when woken up that they are encouraged to remember in the morning) probably have little or no effect compared to control alarms on the number of dry nights or on the number of children becoming or remaining dry and there was insufficient evidence regarding adverse events to draw any conclusions (1 study, 353 children, moderate-certainty evidence). We are uncertain about the effects of the other types of alarms compared to each other (very low-certainty evidence).

The evidence suggests that alarm training compared to behavioural interventions (waking, bladder training,…) or to desmopressin results in little or no difference in the number of wet nights a week and in the number of children that are dry at the end of treatment or at follow-up (low-certainty to moderate-certainty evidence). However, alarm treatment probably reduces the number of children with adverse events compared to desmopressin (desmopressin: 212 per 1000 vs alarm: 81 per 1000 (95% CI: 42-150); 5 studies, 565 children, moderate-certainty evidence).

We are uncertain of the effects of alarm treatment compared to tricyclics, cognitive behavioural therapy, psychotherapy, hypnotherapy and restricted diet (very low-certainty evidence).

Alarm training as adjuvant therapy

Alarm plus desmopressin compared to desmopressin alone may reduce the number of wet nights a week and increase the number of children successfully dry at the end of treatment and remaining dry at follow up (low-certainty evidence). Alarm plus dry-bed training versus dry-bed training alone may increase the number of children who become dry but there may be little to no difference in the number that remain dry (low-certainty evidence).

Conclusion

Alarm therapy seems to be effective to treat bedwetting, but it remains uncertain whether it is more effective than other active interventions. Adding alarm treatment to treatment with desmopressin or dry-bed training may be more effective than desmopressin or dry-bed training alone.

Implications for practice

As parents are often reluctant to start medication due to the potential risk of side effects, alarm therapy continues to be an important option to treat nocturnal enuresis.

REFERENCE:

Caldwell PHY, Codarini M, Stewart F, Hahn D, Sureshkumar P. Alarm interventions for nocturnal enuresis in children. Cochrane Database of Systematic Reviews 2020, Issue 5. Art. No.: CD002911.

DOI: 10.1002/14651858.CD002911.pub3.Access the full text of these reviews via the Cebam Digital Library for Health (www.cebam.be/nl/cdlh or www.cebam.be/fr/cdlh)

*** CI:** confidence interval

Het nieuw **gamma BIO-gecertificeerd**

Olijfolie en Aloë Vera uit biologische landbouw

99%[2] ingrediënten van natuurlijke oorsprong

Vegan gecertificeerd gamma[3] Zonder parfum

beschikbaar vanaf midden juni 2020 in uw apotheek

Vanaf **de geboorte**[1] en **voor heel de familie**

1 Ook voor baby's die de neonatologie hebben verlaten. 2 Gemiddeld. 3 Zonder ingrediënten van dierlijke oorsprong.

The 'Voronov Plot' in COVID19 children

Pasquale Striano[1,2]

[1] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy
[2] Pediatric Neurology and Muscular Diseases Unit, IRCCS 'G. Gaslini' Institute, Genoa, Italy

strianop@gmail.com

Figure. Excerpt from the comic book 'The Voronov Plot' (Cinebook Ltd, September 2010).

Since 31 December 2019 and as of 3 June 2020, over than 6.2 millions cases of coronavirus disease 2019 (COVID-19) have been reported, including 376 000 deaths, affecting 213 countries around the world and 2 international conveyances [1]. Although an emerging inflammatory syndrome has been associated with COVID-19 affected children 2, this population remains minimally affected by SARS-CoV-2 infection overall. In the largest pediatric series including 2143 Chinese children [3], only 112 (5.6%) of the patients had severe disease (defined as hypoxia) and about 0.6% developed multiorgan failure or acute respiratory distress syndrome (ARDS).

The deaths worldwide in children can be easily counted in stark contrast to the 4% global mortality rate in adults. However, the reasons for this relative resistance of children remains obscure and several mechanisms have been suggested [4], including a more active immune response (secondary to live-vaccines and frequent viral infections), healthier respiratory tracts, fewer underlying comorbidities, and a difference in the distribution or maturation of viral receptors.

In the 14th book of the 'Blake and Mortimer' comic series, released in 2000, the infamous Dr Voronov, head of a clinic of the KGB, discovers a mutant pathogen ("bacteria Z") that causes death within 24 hours by simple contact and uses it as a biological weapon against the West. While that the death of personalities around the world keep coming, the lead character of the story, Prof. Philippe Mortimer realizes that young rats turn out to be healthy carriers because of the thymus allows them to resist the pathogen (Figure).

Following the Occam's razor principle, this vignette does offer the simplest explanation for children's resistance to COVID19. The thymus gland aids in the production of T cells, which are crucial for the immune system. It is the largest and most active in children and begins to shrink and fade away in adolescence. Therefore, children have strong innate immune response whereas adults show suppressed adaptive immunity and dysfunctional over-active innate immune response in severe infections, which is not seen in children. In recent years, thymus-stimulatory, -regenerative and -protective strategies have been developed to enhance and repair thymus function, including the use of growth and differentiation factors or the transfer of T cell progenitors [5]. Understanding this basis of this low-impact of the infection in children might provide vital information about protection from COVID-19 either in children and adults.

Disclosures. PS is the only contributor to the paper and he declares no competing interest; he has exclusive licence on the paper content. Patient and Public Involvement statement is not applicable for this manuscript.

REFERENCES:

1. ECDC [Internet]. Solna, Sweden [cited 2020 June 3]. Available from: www.ecdc.europa.eu
2. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020 (Jun 6);395(10239):1771-1778. Online ahead of print.
3. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. (Chinese Pediatric Novel Coronavirus Study Team). SARS-CoV-2 Infection in Children. N Engl J Med. 2020 (Apr 23);382(17):1663-1665.
4. Lyu J, Miao T, Dong J, Cao R, Chen Q. Reflection on Lower Rates of COVID-19 in Children: Does Childhood Immunizations Offer Unexpected Protection? Med Hypotheses 2020 (May 15);109842. doi: 10.1016/j.mehy.2020.109842. Online ahead of print.
5. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020 (Jun); 53(3):371-372. Online ahead of print.

Editorial Policy

Aims and scope

The *Belgian Journal of Paediatrics (BJP)* is the Official Journal of the Belgian Society of Paediatrics.

The *Belgian Journal of Paediatrics* publishes peer reviewed original articles, review articles, short communications and case reports on all aspects of paediatrics. In addition, all official reports of the Belgian Academy of Paediatrics are published in the BJP.

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

The Journal is published quarterly. The printed version is sent to all Belgian paediatricians and paediatricians in training, the electronic version is only accessible to the members of the Belgian Society of Paediatrics.

Editors

Editors-in-Chief: S. Cadranel, M. Raes
Associate editors: C. Barrea, C. Chantrain, S. Derechter, N. Francotte, A. Rochtus, A. Vuckovic, M. Wojciechowski
Editorial office: N. Meignen, UZ Leuven, Herestraat 49, 3000 Leuven
Publisher: Vivactis,Gustave Demey Avenue 57, B-1160 Auderghem, Belgium.
Owner: Belgische Vereniging voor Kindergeneeskunde – Société Belge de Pédiatrie

Editorial Policy (version 5, June 2020)

Editorial principles

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

Invited Editors: Invited Editors are appointed by the Editors to coordinate the compilation of a special chapter of the Journal dedicated to a particular subject. They choose the topics of the chapter, they contact the authors with expertise in the field and watch for the deadlines for review. In addition, they write an editorial letter for the special chapter.

Manuscript submission: Guidelines for preparing and submitting manuscripts are described in the section 'Instructions for authors'. No publication fee is charged. The editors will ensure the confidentiality of the author's work.

Authorship criteria: Authors should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" available at www.icmje.org. Only persons that have substantially contributed to all of the following are considered as authors: conception and design, acquisition, analysis and interpretation of data; drafting the article or revising it critically; final approval of the version published. The first and, if different, the corresponding author should declare on the title page that these criteria have been satisfied. Persons who have contributed to the study or manuscript but who do not fulfil the criteria for authorship have to be listed under a heading 'acknowledgments'. Financial and material support should also be acknowledged. Any change in authors after initial submission must be approved by all authors and must be explained to the Editor. The Editor may contact any of the authors and / or contributors to verify whether they agree to any change. The authors are fully responsible for the propositions and statements in their article. Although the Editors try to recognize and reject misconduct to the best of their ability, neither the Editorial Board of the Belgian Journal of Paediatrics, nor the Executive Board of the Belgian Paediatric Society are responsible for malpractice by authors.

Misconduct: Reviewers of the manuscripts and readers of the journal are encouraged to report malpractice. Whenever misconduct is effectively established, the Editors will notify the author's institution and inform the readers of the Journal.

Copyright: By accepting publication in the Belgian Journal of Paediatrics authors automatically transfer copyright to the journal.

Ethical standards: Human subjects research requires ethics committee approval. This should be documented in the 'methods' section of the paper. No information possibly identifying patients should be included in the paper, unless the information is essential for scientific purposes and a written informed consent for publication was obtained. This should be added as a separate page to the manuscript. Even when consent was given, identifying details should be omitted if not essential. Special attention should be given to patient's images, names, initials, hospital numbers. The registration number and the site of registry of clinical trials should be provided on the title page. When reporting experiments on animals, authors should indicate whether the institutional rules and/or national legislation for the care and use of laboratory animals was respected.

Negative studies: The Belgian Journal of Paediatrics agrees with the International Committee of Medical Journal Editors statement regarding the obligation to publish negative studies.

Duplicate or prior publication: Only original manuscripts that have not been published before (except in the form of an abstract or as part of a published lecture or a thesis) can be accepted.
Reproduction of material from other sources: any written or illustrative material that has been or will be published elsewhere must be duly acknowledged and accompanied by the written consent of the copyright holder.

Publication embargo: Every submission accepted for publication in the Belgian Journal of Paediatrics is under embargo until it is published. This means that until then it may not be disclosed to third parties. However, an abstract presentation of data contained in a manuscript at a scientific meeting is acceptable, as is publication of abstracts in print and online conference proceedings, but authors should not distribute copies of the original manuscript.

Peer review: All received papers will be peer reviewed by at least 2 external reviewers, solicited by the Editors and not belonging to the same institution as the authors. Following the review process, a decision will be made to reject, accept as such or with minor or major revisions. In case of controversy or strong disagreement regarding the merits of the work, an additional review may be solicited or one of the journal's editors might give an evaluation. The reviewers' names will be blinded to the authors. Manuscripts will be submitted again to the reviewers after revision by the authors. The editors are responsible for the final decision to accept or reject a manuscript. Authors will be notified about the decision and, if the manuscript is accepted, the timing of publication. Roles and responsibilities of peer reviewers are described in the section 'Instructions for peer reviewers'.

Advertising: Advertisers are not allowed to influence or modify the content of accepted articles before publication. Advertisement of products like alcohol, tobacco or products known to be harmful for children's health are not allowed in the journal. Editors have the final authority to accept advertisements in each published issue of the Journal. Each advertisement is clearly identified as such and is not inserted in the flow of an article. The Belgian Society of Paediatrics oversees the advertising policy of the Journal. The Editors are not responsible for the advertising on linked sites of the electronic version of the journal.

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

Instructions for authors

Types of manuscripts

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

Review Articles: Review articles are broadly based and are meant to cover an important field in an authoritative way. Reviews should include an abstract of no more than 250 words and have a mean text range between 1500-4000 words, with up to 30 references.

- Systematic Review: A PRISMA style flow diagram has to be included (http://prismastatement.org/PRISMAStatement/FlowDiagram.aspx).

- Narrative Review: A narrative review gives an update on the current understanding of the pathophysiology, diagnosis and treatment of a disease. A narrative review may be illustrated by one or more case descriptions.

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

Short Communications: Short Communications are limited to an abstract of 100 words, main text of 1500 words, 1 table and/or 1 figure, and 10 references.

- **Brief communication:** Contains reports of original research. Can include any of the study types listed under Research Articles.

- **Made in Belgium:** Summary of a PhD thesis defended in Belgium. The title of the PhD thesis must be followed by a subtitle "PhD thesis presented on [date] at [university or high school], [city], Belgium. The author is the PhD student. Promotors and co-promoters are listed under the author.

- **Focus on symptoms:** A short schematic or algorithmic approach to symptoms with which a clinician is regularly confronted. For this article type, no abstract is requested.

Correspondence to the Editor: Correspondence to the Editor should be limited to 400 words and may include one table or figure, if essential, and five or fewer references. Two types of correspondence are accepted:

- Letters to the Editor addressing previously published articles.

- Personal opinion: can address any important topic in paediatric medicine, public health, research, discovery, prevention, ethics and commentaries on all aspects of paediatrics.

Reviews of books: Book reviews related to paediatrics can be submitted by authors who want to share their experience with the readers of the journal. Book reviews should not exceed 500 words. The publishers take the decision whether or not to publish.

Submission information

Manuscripts must be submitted in Word (single-spaced) and sent by e-mail to the editor at BJPed@hotmail.com.

Authors should meet the criteria for authorship according to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication" available at www.icmje.org. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and reviewers make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

Language: Manuscripts must be submitted in English. The chosen English spelling, UK or US spelling, must be used consistently throughout the article. It is recommended that authors, who are not very familiar with English, get assistance writing the article.

Title page: All submissions should be accompanied by a separate title page providing all the following information:

a) Title of the manuscript

b) Author full names and affiliations, no academic degrees. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and prior to the appropriate address.

c) Corresponding author contact information: name and address for correspondence, telephone number, e-mail address.

d) Up to five keywords in English

e) Number of words in the Abstract, Introduction, Discussion, and body of the manuscript.

f) Number of figures and tables.

g) The contribution of each author (see authorship criteria)

h) In case of clinical trial, the registration number and the site of registry should be provided

i) A statement that the manuscript has not been and will not be submitted to any other journal while it is taken into consideration by the Belgian Journal of Paediatrics

j) The authors may suggest the names and mail addresses of 2 to 4 possible peer reviewers

Information that may allow identification of patients: no information possibly identifying patients should be included in the paper, unless the information is essential for scientific purposes. A signed release from the patient or legal guardian authorizing publication should be added as a separate page to the manuscript.

Abstracts: Abstracts should not contain abbreviations or references. Abstracts for Research articles must be limited to 250 words and must be structured into subsections for: Objective, Methods, Results, Interpretation. Abstracts for Review articles are limited to 250 words and for Case reports or Short Communications to 100 words and should not include subsections.

Abbreviations: Always spell out abbreviations at first mention and place the acronym or abbreviation in parentheses immediately after. Abbreviations should be limited to terms that are both long and frequently repeated in the text. Try to avoid using more than six abbreviations in a paper, otherwise the text appears to be written in code.

Text: Organise the manuscript according to the instructions in the article type section. Sections must appear in the following order: Abstract, Introduction, Materials and Methods, Results, and Discussion, Conclusion, Acknowledgements, Author Contributions, Conflicts of Interest, References and Figure/Table Legends. Acknowledgements should include individuals who have contributed to the work (provided materials, technical assistance, etc.), but do not fulfil the criteria for authorship; all such individuals should agree to being included in this way before the manuscript is submitted. The Acknowledgements should also include sources of financial support for the work.

Data Analysis: Description of data analysis should provide the specific methods used, their rationale, the underlying assumptions, whether data met those assumptions, and how any missing data were handled

Units of measurement and laboratory values: Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI. If applicable, normal values should be given in brackets when the value is first stated.

Drugs and other products: non-proprietary names of drugs or other products should be used, unless a specific trade name is essential for discussion.

Eponyms and acronyms: Eponyms should be used in their non-possessive form (e.g. Down syndrome and not Down's syndrome). Acronyms should be avoided, if this is not possible they should be fully explained when first used.

Tables: Tables should be printable in a single page in portrait orientation. They should be typed in the same font as the rest of the paper, as text tables (rather than as figures). Tables should be numbered in order of appearance in the text. Tables and their legends should appear after the References and Figure Legends, as part of the main document of the paper. Screen captured tables are not allowed.

Figures: All figures must be submitted in JPEG format. Do not submit your figures embedded in a Microsoft Word or Adobe PDF document (i.e., as a .DOC or a .PDF file). The resolution must be at least 600 dpi. Figures should be cited in order of appearance. Each figure must have a legend. Figure legends

should appear after the References, as part of the main document of the paper.

Please do not include extra text (including keys and headings) in the artwork, spell out keys and headings in the figure legend instead. Photographs of recognizable persons should be accompanied by a signed release from the patient or legal guardian authorizing publication, as described above. Masking eyes to hide identity is not sufficient.

Patient privacy, informed consent and ethical standards: If the work involves the use of human subjects, the author should ensure that the work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. For clinical trials and clinical studies the number and place of approval by an ethical committee has to be mentioned in the methodology section, as well as the registration number and the site of registry for clinical trials. The privacy rights of human subjects must always be observed. Race / ethnicity, gender or religion should only be mentioned if relevant to the content or purpose of the article.

Animal rights: All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

References: Arrange references in order of first appearance in the text. The references must be formatted according to Vancouver style.

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

The reference list, numbered in the order of mention in the text, must appear at the end of the manuscript. [Authors]. [Title of the Article]. [Name of the Journal] [Publication date], [Volume number] [(Issue number)]: [Starting page]-[End page]. According to the Uniform Requirements the first six authors are named, followed by at al. if there's more than six. Authors are referenced as their surname followed by initials, the two separated by a comma. Names of journals are preferably abbreviated if such standard abbreviation exists. If in a journal a volume page numbering goes uninterrupted, the number of the issue may be omitted.

Examples:

Gonzalez-Aguero A, Vicente-Rodriguez G, Gomez-Cabello A, Ara I, Moreno LA, Casajus JA. A combined training intervention programme increases lean mass in youths with Down syndrome. Res Dev Disabil. 2011;32(6):2383-8.

Bervoets L, Van Noten C, Van Roosbroeck S, Hansen D, Van Hoorenbeeck K, Verheyen E, et al. Reliability and Validity of the Dutch Physical Activity Questionnaires for Children (PAQ-C) and Adolescents (PAQ-A). Arch Public Health. 2014;72(1):47.

For a chapter in a book: list [Authors].[Title (of chapter]). In: [Editors]. [Title (of book].[Place of publication]: [Publisher], [year]. [Start and end page].

Example:

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

More examples of other published and unpublished material can be found on the website of the U.S. National Library of Medicine: https://www.nlm.nih.gov/bsd/uniform_requirements.html.

Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names, or access the list at http://www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html.

Disclosure of potential conflicts of interest: The corresponding author should disclose any conflict of interest for any of the authors. The disclosure declaration must be written in a separate paragraph after the conclusion and before the references

After submission

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

All manuscripts considered for publication undergo peer review. The editors assign a least 2 external reviewers. The reviewers' names are blinded to the authors. Reviewers are requested to maintain the confidentiality of the review process: not sharing, discussing with third parties, or disclosing information from the reviewed paper.

When resubmitting a manuscript after review the authors should indicate clearly their responses to the reviewers' comments. A document in which the reviewers' comments are answered point by point should be provided with the revised manuscript and include a copy of the original manuscript with track changes displaying the changes made.

After acceptance

Corresponding authors will receive electronic page proofs to check the copy-edited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents will be sent to the corresponding author by e-mail. It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content will be made. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Proofs must be checked carefully, and corrections returned within 1 week of reception.

Publication embargo: Publication embargo as described in the editorial policy section applies until effective publication of an accepted manuscript.

Corrections: Requests to publish corrections should be sent to the editorial office. Corrections are reviewed by the editors and published in the next journal issue.

Copyright: By accepting publication in the Belgian Journal of Paediatrics authors automatically transfer copyright to the journal. Authors will receive a PDF file for personal use only.

Reprints: Reprints are available for members of the Belgische Vereniging voor Kindergeneeskunde – Société Belge de Pédiatrie from the website of the society at http://bvk-sbp.be .

Instructions for peer reviewers

Review of a submitted manuscript by at least 2 external reviewers is solicited by the editors. The reviewers' names will be blinded to the authors.

Reviewers should only agree if they feel qualified to review a manuscript and are able to return the review within a reasonable time-frame of maximum 3 weeks. If they cannot review, it is helpful to make suggestions for alternative reviewers.

Reviewers must refuse to review a manuscript in case of any potentially

conflicting or competing interest.

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

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

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

Instructions for invited editors

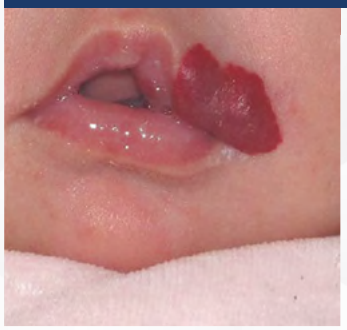
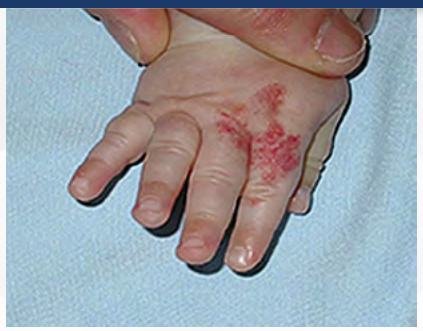
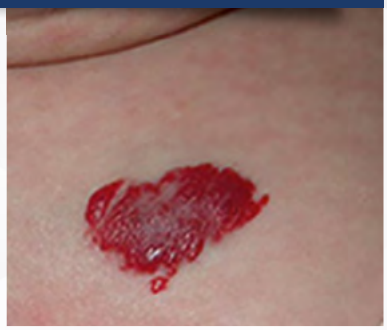
Each year, a number of issues address a special chapter dedicated to a particular subject. Two guest editors, a Dutch-speaking and a French-speaking, are responsible for the content of these chapters. A number of 6 manuscripts per chapter is expected. If more than 6 articles are needed to elaborate the topic of the chapter correctly, the editors can decide to spread the chapter over 2 issues.

The tasks of the invited editors are:

- To make choice of topics
- To invite authors
- To supervise the manuscripts in terms of content
- To watch over the deadline for publication
- To write an editorial introducing the chapter

Editorial review and solicitation of peer reviewers will be done by the editorial team of the BJP.

DOIS-JE RÉFÉRER MON PATIENT POUR CET HÉMANGIOME?

IHReS

Infantile Hemangioma Referral Score

DÉCOUVREZ UN SCORE RAPIDE ET FACILE
POUR VOUS AIDER À IDENTIFIER LES PATIENTS
QUI ONT BESOIN D'ÊTRE PRIS EN CHARGE

VERSION DIGITALE

Avec le soutien de
Pierre Fabre
Dermatologie

http://www.ihscoring.com

20200181

Pierre Fabre
DERMATOLOGIE