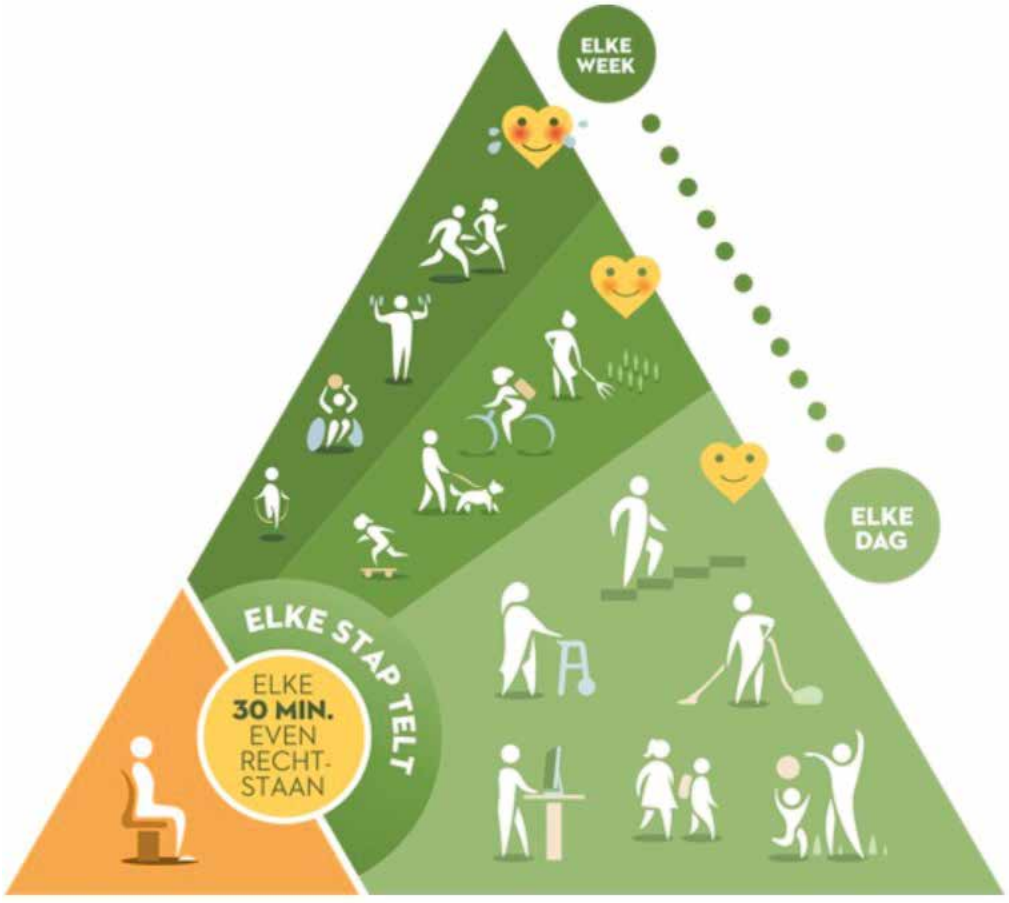
B J P
Belgian Journal of Paediatrics
Publication of the Belgian Society of Paediatrics

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

2019 - Volume 21 - number 2 - June



Article

An Update: Epilepsy in Tuberous Sclerosis Complex

Side effects of 4-component meningococcal B vaccine (Bexsero®): a systematic review

Nutrition and hydration in sporting children

Atypical severe combined immunodeficiency (SCID): case report and literature review

Made in Belgium

Is Autosomal Dominant Polycystic Kidney Disease a pediatric disorder? From AdultDPKD to ADPediatricKD

The structural and functional impact of CFTR dysfunction on the lung

Case Report

Heterozygous variant in the aggrecan gene leading to poor pubertal growth and short adult stature: a case report and review of the literature

Paediatric Cochrane Corner

Probiotics probably reduce antibiotic-associated diarrhoea in children

Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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

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

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

Bexsero : premier vaccin contre le méningocoque de sérogroupe B.

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

BEXSERO

Vaccin méningococcique groupe B (ADNr, composant, adsorbé)

RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament ▼Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique « Effets Indésirables » pour les modalités de déclaration des effets indésirables. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue prérempliVaccin 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]
Nourrissons de 3 à 5 mois	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	Besoin non établi [d]
Adolescents (à partir de 11 ans)et adultes*	Deux doses de 0,5 ml chacune	1 mois minimum	Besoin non établi [d]

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée 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 avec 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. 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. **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 avec 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 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 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 EUROSTATION II Place Victor Horta, 40/40 B-1060 Bruxelles Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/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** 06/2018(v05) **MODE DE DELIVRANCE** Sur prescription médicale.

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

BE/BEX/0011/16a(1) – July 2018 - E.R.: GlaxoSmithKline Pharmaceuticals s.a., av Pascal 2-4-6, 1300 Wavre

Editorial Board

- **Editorial** 53
- **President's Address** 54
- **Article**

  An Update: Epilepsy in Tuberous Sclerosis Complex
  J. De Ridder, L. Lagae 58

  Side effects of 4-component meningococcal B vaccine (Bexsero®): a systematic review
  A. S. Lemoine, J. Toelen, M. Raes 63

  Nutrition and hydration in sporting children
  S. Van Biervliet 68

  Atypical severe combined immunodeficiency (SCID): case report and literature review
  J. Vandersnickt, I. De La Fuente Garcia, G. Bucciol, L. Moens, R. Pérez de Diego, I. Meyts 72
- **Made in Belgium**

  Is Autosomal Dominant Polycystic Kidney Disease a pediatric disorder? From AdultDPKD to ADPediatricKD
  S. De Rechter 77

  The structural and functional impact of CFTR dysfunction on the lung
  B. Bosch 82
- **Case Report**

  Heterozygous variant in the aggrecan gene leading to poor pubertal growth and short adult stature: a case report and review of the literature
  K. Stabenow, K. Van De Maele, T. de Ravel, C. Bert, J. De Schepper 86
- **Paediatric Cochrane Corner**

  Probiotics probably reduce antibiotic-associated diarrhoea in children
  T. Bekkering, A. C. Vanhove, F. Cools 88
- **Editorial Policy** 89

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

In this summer issue of the BJP 2019/2, the editorial board wishes to warmly congratulate Prof. Gunnar Buyse (UZLeuven, KUL) and his team for the excellent organization of the annual BVK/SBP recent congress. A record number of members and professionals involved in our Belgian paediatric world attended the diverse sessions of the meeting held in the EGG. The compound is conveniently located in close neighborhood of Brussels South station, the main train station allowing easy connections from all cardinal points of our country. We are happy to announce that the next 2020 annual congress will be held in the same EGG compound, under the responsibility of Prof Pierre Smeesters (HUDERF, ULB).

Another helpful news concerns our editorial board, enlarged with new younger collaborators (see the list) and honored by the election of Marc Raes, our co-chief editor, as president of the BVK/SBP.

Besides two case reports "Atypical severe combined immunodeficiency (SCID): case report and literature review " by Jan Vandersnickt and "Variant in the aggrecan gene leading to poor pubertal growth and short adult stature: a case report and review of the literature" by Katharina Stabenow, we publish the article "Side effects of Bexsero: a systematic review" by An-Sophie Lemoine. This article is particularly useful to objectively and scientifically correct erroneous "fake news" widely broadcasted by the anti-vaccine lobby and wrongly reported by ignorant media looking to make the "buzz" without real knowledge of the dangerous consequences. Because the recent epidemy of evitable diseases such as measles and polio in our civilized societies is definitely not acceptable, paediatricians should firmly fight against these ideologically wrong attitudes.

As usual we publish summaries of doctoral theses under the section MIB (made in Belgium). In this issue you can read "The structural and functional impact of CFTR dysfunction on the lung" by Barbara Bosch and "Is autosomal dominant polycystic kidney disease a paediatric disorder?" by Stéphanie De Rechter.

The largely controversial subject about treatment of acute diarrhoea is discussed under the recently inaugurated section the Paediatric Cochrane Corner in "Probiotics probably reduce antibiotic-associated diarrhoea in children". This section will be continued on a regular quarterly basis and, furhermore we would like to revive two other sections: "Metabolic diseases campaign" interrupted following the decease of our estimated colleague Linda De Meirleir and also "Surgeon's corner" with the aim to instruct paediatricians about critical surgical conditions. We also want to highlight our section: "Focus on Symptoms". Suggestions about subjects/symptoms are welcome.

Last but not least, the article by Stephanie Van Biervliet "Nutrition and hydration in sporting children" derives from a presentation at the last annual congress. It is our purpose to ask the invited speakers of the BVK/SBP congress to publish this sort of contribution in the summer edition of the BJP in order to offer its reading to those unable to attend the annual congress of some of its sessions.

On behalf of the editorial board we wish you a fruitful reading and pleasant summer holidays.

Samy Cadranel and Marc Raes.

Uw vragen of commentaar
Vos questions ou commentaires

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

Comité de rédaction - Redactieraad
M. Raes - S. Cadranel

Gasthuisberg - Kindergeneeskunde

Herestraat 49 - 3000 Leuven
E-mail BJ-Ped@hotmail.com

President's Address

FLASH :

Visit our BVK/SBP Website

Go to the website of the BVK/SBP : www.bvk-sbp.be

- Choose your language : NL / FR
- Login : "leden"/"membres"

Toolbar : e.g.

- Agenda: Congresses/ E-learning
- Publicaties/publications:
  - Richtlijnen/directives (BAPCOC, vaccinations,...)
  - CEBAM (EBM)
    (voorbehouden voor leden van de BVK / réservé aux members de la SBP)
  - Journal Club
- BJP (Belgian Journal of Paediatrics)
  (voorbehouden voor leden van de BVK / réservé aux members de la SBP)
- BPCRN (Belgian Pediatric Clinical Research Network)
- Congres : congress overview - 2018 - 2019 (foto) - Awards & Prizes
- Dossiers: e.g. meningitis
- Partners/Parternaires
- Info: e.g. subspecialiteiten / sousspécialités - vacatures
- Zoeken/Chercher.

Come and visit us. You will not be disappointed!

Marc Raes
President BVK - SBP

INNOVATIONS FOR BETTER HEALTH IN PEDIATRICS

Pierre Smeesters, MD PhD
Congress President, HUDERF UKZKF

Marc Raes, MD PhD
President BVK/SBP

BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

Save The Date

Aalst Breda Course of Pediatric Dermatology

Sixth edition

Friday 20 September 2019
Congress Center De Montil

Invitation

Dear colleague,

Both dermatologists and pediatricians encounter children with skin problems on a daily basis. The aim of this course is to provide the participants with detailed up-to-date knowledge of common skin conditions and clinical clues to arrive at the diagnosis of rarer and more serious conditions.

This year again the lectures will be delivered by leading experts in respective fields, chosen to inspire as well as educate.

In order to facilitate interactions, the number of participants is limited. Registration forms will be treated on a strictly first come first served basis. Participation is not guaranteed until full payment of the registration fee is received.
Thanks to our main sponsors (Eucerin, Nestlé & Pierre Fabre) and several co-sponsors the registration fee for dermatologists and pediatricians can be kept down to the symbolic amount of 40 €. The course is free to trainees and members of the ESPD and ISPD.

We look forward to welcoming you to our symposium.

Dr. D. Van Gysel, Aalst
Dr. A. Hulsmann, Breda

Program

08:45h **Registration and coffee**

09:25h **Welcoming**

09:30h - 11:00h

- **Skin conditions that imitate child abuse**
  Dr. K. Gholam (London)
- **Benign and malignant tumors**
  Prof. Dr. Z. Szalai (Budapest)
- **Urticarial disorders**
  Prof. Dr. S. Pasmans (Rotterdam)

11:00h **Coffee break**

11:30h - 13:00h

- **Clinical cases from Italy**
  Dr. M. Cutrone (Venice)
- **Clinical cases from Germany**
  Dr. B. Kunz (Hamburg)
- **Clinical cases from Greece**
  Prof. Dr. T. Kakourou (Athens)

13:00h **Lunch**

14:15h - 16:15h

- **Emergencies**
  Prof. Dr. C. Bodemer (Paris)
- **The skin microbiome**
  Prof. Dr. R. Grimalt (Barcelona)
- **What's new in atopic dermatitis**
  Prof. Dr. A. Paller (Chicago)

16:15h **Test yourself in Pediatric Dermatology**
Dr. A. Hulsmann (Breda) & Dr. D. Van Gysel (Aalst)

17:00h **Closing**

www.olvz.be

President' s address

On behalf of the co-founders, I am pleased to announce that the *BPDA*, the *Belgian Pediatric Dermatology Association*, has been created on last December, 15 and has been introduced into the BSP by the President-in-Office of the *BSP,* Prof. Anne Malfroot, during the last BSP congress on March, 22, 2019.

We are very happy that the General Assembly approved the incorporation of the *BPDA* inside the *BSP*. In doing so, our newly recognized subspecialty can jump onto the big train of Belgian Pediatrics as the latest car.

I would like to thank my friend Dirk Van Gysel, who had been convinced of our shared goal since the beginning and has built the BPDA' s foundations with me.

Thanks to the other board members and the founding members for their enthusiasm and commitment.

Thanks also to Prof. Anne Malfroot and the BSP board for their kind support and Natacha for her secretariat coming help.

In a guest editors' address from 2014, Dirk and I were reporting in the BJP : « A survey designed by the Society for Pediatric Dermatology in the United States provided evidence to support the importance of early exposure to the field [of Pediatric Dermatology]… ».

Our statutes have been written in this way, … intentionally open to all pediatricians.

Actually, the first condition for effective membership is « … having an interest for Pediatric Dermatology… ».

So the BPDA intention is to gather enthusiastic pediatricians wishing to actively improve their knowledge in pediatric dermatology around trained, confirmed dermatopediatricians to drive the association.

Teaching activities, training courses, symposia had already started for some years and are further being scheduled in Belgium and abroad.

The active membership of Dirk inside the board of the ESPD, European Society for Pediatric Dermatology and the ISPD, International Society of Pediatric Dermatology will surely provide a useful link with the global community of pediatric dermatologists.

Despite some difficulties, we also want to continue to persuade Belgian dermatologists that Pediatric Dermatology needs specific skills and that pediatricians and dermatologists have to put their own knowledge and experience together.

Ready to join us? Conditions and applications for membership are starting within a few months at the time of the BSP membership renewal.

Should you need some information now, please, don't hesitate to contact us by emailing bpda_dermato@hotmail.com.

We are looking forward to welcoming you aboard!

Best regards,

Vincent.

Vincent Bernier	Dirk Van Gysel	Justine Pêtre	Hannelore De Maeseneer
President	Vice-President	Secretary	Treasurer

DEXERYL

BEHANDELT DE DROGE HUID VAN HET HELE GEZIN

VOORDELIGE PRIJS
VOOR LANGDURIG GEBRUIK

HYDRATATIE & HERSTEL

ZEER DROGE HUID MET NEIGING TOT ATOPIE

200 ml
P.P. 6,50€*
CNK 3461-829

500 ml
P.P. 13,00€*
CNK 3461-845

VOCHT-INBRENGENDE CRÈME VOOR DE BEHANDELING VAN ALLE VORMEN VAN DROGE HUID

CE

250 ml
P.P. 7,00€*
CNK 1551-258

500 ml
P.P. 13,50€*
CNK 2717-775

HYGIËNE
DERMOCOSMETICUM

+

BEHANDELING
MEDISCH HULPMIDDEL

20170427 – 12/17

*Aanbevolen richtprijs

Pierre Fabre DERMATOLOGIE | SKIN EXPERTISE IN OUR DNA

An Update: Epilepsy in Tuberous Sclerosis Complex

Jessie De Ridder, Lieven Lagae

jessie.deridder@uzleuven.be

Abstract

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant disease affecting approximately 1 person in 5800. Neurological manifestations, including epilepsy and TSC-associated neuropsychiatric disorders (TAND) are common and are responsible for a major burden of disease. TSC represents one of the most common genetic causes of epilepsy. 80 to 90% of the TSC patients are affected by epilepsy. The majority of the patients develop seizures during the first year of life. Early seizure onset is associated with an increased risk of cognitive impairment and neuropsychiatric problems. Prenatal or early postnatal diagnosis of the disease gives the opportunity to monitor infants with serial video electroencephalograms (EEGs) and can be of help to identify children at risk of developing epilepsy. This creates the possibility to intervene in the process of epileptogenesis, increasing the opportunity of seizure freedom and reducing the risk of an epileptic encephalopathy.

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder affecting multiple organ systems. The birth incidence of the disorder is approximately 1 in 5800 individuals. [1] The disease was first described in depth in 1880 by Desire-Magloire Bourneville. The name is derived from the Latin word "tuber" which means 'root-shaped growths' and the Greek word "skleros", which means 'hard'. [2]

The disease is caused by a loss of function mutation in the tumour-suppressor genes *TSC1* or *TSC2*. [2] These mutations lead to overactivation of the mammalian target of rapamycin (mTOR) complex [1]. The mTOR complex is a key regulator of cell proliferation, cell growth, protein and lipid synthesis and autophagy. Overactivation of the mTOR complex results in disorganized cellular overgrowth, abnormal differentiation, and the formation of hamartomatous lesions in various organs.[3]

In 85-90% of the patients with a clinical diagnosis or suspicion of TSC a pathogenic mutation will be identified based on conventional molecular diagnostic assessment in the *TSC1* (on chromosome9q34) or in *TSC2* (on chromosome 16p13) gene. [4] In the majority (85%) of the 10-15% of the patients with no identified mutation, next generation DNA sequencing can identify intronic or mosaic mutations or variants in promotor regions in the *TSC1* or *TSC2* genes using blood and saliva DNA samples and biopsies of cutaneous tumours. [5, 6] It's therefore unlikely that a third TSC gene exists. [5] Approximately one-third of the *TSC1* or *TSC2* mutations are inherited and two-thirds of the TSC patients carry de novo germline mutations, some of which are mosaic.[2, 6, 7]

The clinical manifestations of TSC are partly due to benign malformations of the brain, skin, eyes, heart, lungs and kidney. The clinical features of TSC can vary widely between individuals and even between members of the same family [2, 6]. These manifestations have an age-related expression and therefore become manifest at different timepoints in the lifespan. [4, 8] Structural brain malformations in TSC are tubers, subependymal nodules, subependymal giant cell astrocytoma (SEGA) and cerebral white matter radial migration lines. Neurological manifestations, including epilepsy and TSC-associated neuropsychiatric disorder (TAND) are common, affecting approximately 90% of the patients with TSC. [2, 9, 10] TAND is an umbrella term, including autism spectrum disorder (ASD), intellectual disability, behavioural, psychiatric, academic, and psychosocial difficulties seen in association with TSC.[9-11] In children epilepsy and neuropsychiatric manifestations represent the most disabling problems of the disease.

TAND is common and is highly underdiagnosed and undertreated. [12] Approximately 45% of the TSC patients have intellectual disability, defined as an intelligence quotient (IQ) below 70. [13, 14] In a retrospective study of 44 infants with TSC only 20% have a normal or borderline cognitive level at the age of 3.5 years. [15] 30 to 40% of the children with TSC are diagnosed with ASD. [15, 16]

Early diagnosis of TSC before seizure onset is feasible and facilitates genetic counselling, therapeutic interventions and disease monitoring. [6, 17, 18] Prenatal diagnosis is possible due to the visualisation of cardiac rhabdomyoma's on foetal ultrasound, tubers on prenatal magnetic resonance imaging (MRI) and prenatal genetic testing. [4, 18] Early postnatal diagnosis can be a challenge due to the wide phenotypic variation. A diagnosis in every infant with suspicion of TSC should be made early by performing careful skin examination with Wood's lamp, brain MRI, echocardiography and genetic testing. [19]

In this short update, we want to highlight new insights in the pathogenesis of TSC related epilepsy, since they have important clinical implications.

Epileptogenesis

Epileptogenesis refers to a chronic process that can be triggered by genetic or acquired factors and which triggers a cascade of molecular and cellular changes that leads to the development of dysfunctional brain network capable of generating spontaneous seizures. [20, 21]

In patients with TSC, epileptogenesis can be a rapid process partly due to the structural abnormalities with a well-known genetic basis. [22] Experimental studies and post mortem examination of stillborn prematures have shown that as a consequence of the TSC genes mutation, mTOR overactivation already during embryonic brain development results in anomalies of cellular morphology, altered synaptogenesis, an imbalance between excitation and inhibition, alterations of migration and orientation of neural cells, and connectivity abnormalities. These alterations likely provide a neuroanatomical substrate for the early appearance of seizures. [23-25] Foetal autopsy also provides evidence for prenatal activation of important inflammatory pathways in developing brain malformations. These immune-inflammatory alterations can be responsible for the dynamic changes occurring over time in TSC brain malformations, including calcification and cystic changes, which may also contribute to epileptogenesis and TAND in TSC patients. [24]

At the neurotransmitter level, deficiency of gamma-aminobutyric acid (GABA)-ergic interneurons, abnormally GABA excitation shifting to inhibition, disruption of GABA-ergic interneuron migration, and/or alterations in GABA-A receptors may account for the early onset and severity of seizures and for the generalisation of focal seizures [15, 26, 27]. Reduced GABA function may cause epileptic synchronization and hereby facilitating the spread of epileptic events [15].

There still exists some controversy in the literature about the contribution of the localisation of the emergence of epileptiform discharges: the tuber or the perituberal rim. [19] A significant relation is found between the number of large tubers and EEG foci in 34 children with TSC who are prospectively followed by MRI and EEG. This study suggests that cortical tubers are epileptogenic and that their expression might be influenced by regional cortical maturation. [28] Another study using intracranial EEG recording shows that focal seizures and interictal epileptiform discharges in TSC arise in the centre of epileptogenic tubers and propagate to the tuber rim, perituberal cortex and other epileptogenic tubers. [29]

In addition, also the white matter is aberrant in TSC. White matter migration lines are described in 20% of the TSC patients. [12] White matter abnormalities, using diffusion tensor imaging, are more pronounced is TSC patients with persistent seizures. The alterations are more evident in areas of great importance for global cognitive maturation, executive functions, and language functions. [28]

EEG, a biomarker of epileptogenesis in TSC?

A biomarker is a characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. [21] The possibility of an early diagnosis of TSC prenatally and in the early postnatal period, provides an opportunity to study epileptogenesis in TSC. [29] Identification of biomarkers of epileptogenesis could help to identify possibilities for counteracting the effects of epileptogenesis, including prevention, seizure modification, and cure. [20, 22] As EEG changes possibly reflect the ongoing epileptogenesis, close EEG surveillance could enable the identification of children at risk of developing epilepsy.

In a small prospective study 5 infants with TSC are followed with EEG every 4 to 6 weeks. EEG abnormalities precede the onset of focal motor seizures in all patients by an interval of 1 to 8 days. [30] In a larger prospective cohort of 28 infants with TSC, all children with epileptiform discharges subsequently develop epilepsy, leading to a positive predictive value of 100%. The negative predictive value of the absence of epileptiform activity on the EEG and no development of epilepsy is 64%. [29] Hypsarrhythmia is not reported prior to the onset of focal seizures or epileptic spasms. [29, 30] In 74% epileptiform discharges precede the onset of clinical seizures by an average interval of 2.8 months. This study demonstrates the importance of close EEG surveillance in infants in TSC and suggests that there might be a critical window of time between the emergence of epileptiform discharges and clinical seizure onset. This provides an opportunity to investigate if antiepileptogenic treatment might delay or prevent the onset of clinical seizures. [29] Serial EEGs can therefore help in predicting which TSC infants are at higher risk of developing epilepsy, but the use of EEG as a reliable biomarker has to be validated. [22]

European experts recommend close EEG surveillance in infants with TSC: every 4 weeks in the first 6 months of life and then every 6 to 8 weeks. [31]

Epilepsy course in TSC

Neurological manifestations are a major burden of disease in patients TSC, and epilepsy is common, affecting 80-90% of the patients [12, 14, 32-34].

The first seizure occurs often during the first year of life. [33-35] In a retrospective study of 421 TSC patients, 6% of the patients present in the first 4 weeks of life with epilepsy.[34] Almost 2/3 of 237 retrospectively studied TSC patients with epilepsy develop seizures before the age of 1 year, 46% already develop seizures before the age of 6 months and 6.5% within the first 4 weeks of life.[33] Another multicentre prospective study in which 130 infants with TSC are enrolled reports a seizure onset within 6 months in 39% of the patients and within 12 months in 57%. [35]

Most TSC patients with epilepsy develop multiple seizure types in their infancy and childhood [19, 33]. Seizure semeiology varies between and within patients. The epilepsy can start with almost any seizure type including tonic, atonic, tonic-clonic seizures and epileptic spasms. [33] Epileptic spasms and focal seizures are the 2 most common seizure types during the first year of life.

Focal seizures are the first seizure type in 95.2% of the TSC patients. [34] In a retrospective study of 237 TSC patients with epilepsy, focal seizures are reported as the most common seizure type (87%), followed by epileptic spasms (45%). [33] The TOSCA study, the largest clinical case series with 2093 included TSC patients, reports that focal seizures are the most prevalent seizure type, followed by epileptic spams. [12]

Epileptic spasms are reported as the most common seizure type in a prospective cohort of 134 children with TSC followed until the age of 36 months. [14] In a retrospective study of 44 infants, 55% present with epileptic spasms, 32% with focal seizures, 11% with the combination of epileptic spasms and focal seizures and in 2% with a tonic clonic seizure. [15] In a prospective study of 28 TSC infants 68% develop seizures during the observation period and this study identifies epileptic spasm as the most common seizure type (56%), followed by focal seizures (42%). Seizures with generalized onset are rare. [29] A longitudinally study of 11 infants reports that 55% developed epileptic spasms and 45 % develop other seizure types. [36]

Discrepancies between the reported prevalences of focal seizures and epileptic spasms as most frequent seizure type may be due to different age spans studied in different cohorts and to the observation that short-lasting subtle focal seizures may be missed or misinterpreted by caregivers. Undiagnosed and untreated focal seizures may evolve into epileptic spasms. [19]

Two-third of the epilepsy patients in a retrospective series develop refractory epilepsy [12, 33]. Refractory epilepsy is significantly more frequently reported in patients with a history of epileptic spasms compared to patients with epilepsy without a history of epileptic spasms (75% vs 40%, p-value <0.0001). [33] 27% of the patients with seizures develop a Lennox-Gastaut-like phenotype. This phenotype is significantly more frequently observed in children with a history of epileptic spasms. [33]

Epilepsy and TAND

In TSC the cause of the cognitive impairment and ASD is multifactorial: the underlying TSC mutation, a history of seizures and epilepsy characteristics, such as the age at seizure onset, a history of epileptic spasms and refractory epilepsy are contributing factors. [15, 37]

A retrospective single centre study in 107 TSC patients with available neuropsychiatric testing shows that 57% of the patients have a normal IQ. [38] Refractory epilepsy and a mutation in the *TSC2* gene are predictors of a lower IQ. [38, 39]

A prospective, multicentre study evaluates 130 children with TSC longitudinally between the age of 0 and 36 months with standardized cognitive, behavioural and ASD-specific assessments. The neurodevelopmental assessment in children with a history of seizures are worse compared to the development in children without seizures. A history of epileptic spasms before the age of 12 months and a higher seizure frequency correlates with a poorer neurodevelopmental outcome and higher ASD risk. Only complete seizure control results in a better outcome with improved language and communication scores. In a multivariate logistic model predicting developmental delay with age at clinical seizure onset, a history of epileptic spasms and seizure frequency as covariates reveals that the age at seizure onset is the most important factor predicting developmental outcome. [14] Other trials also identify a younger age at seizure onset as a major contributor to a poor cognitive outcome. [15, 37, 40]

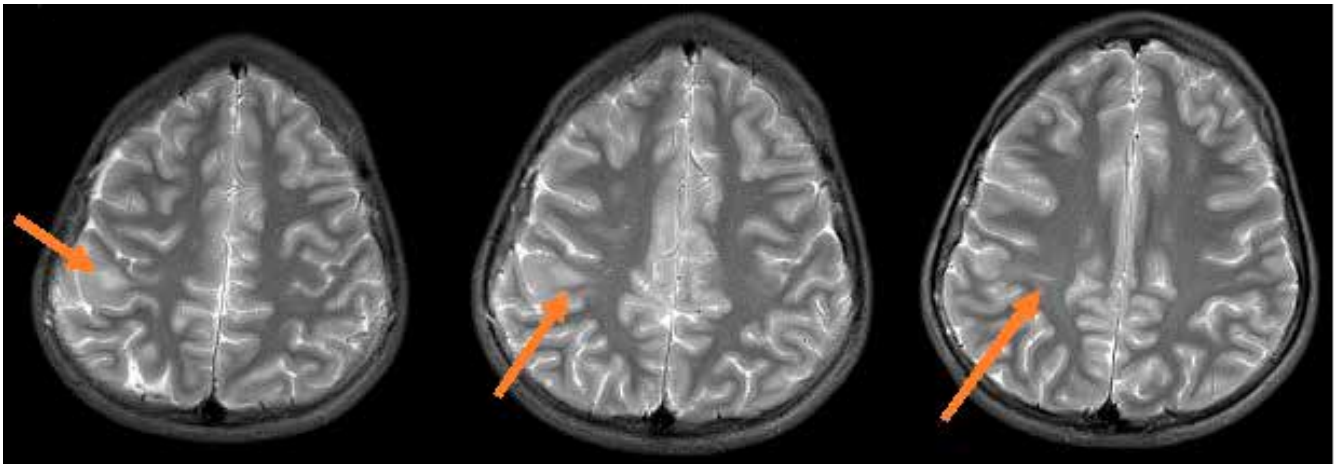
A history of epilepsy and epileptic spasm is associated with a reduction in IQ. [13] An epidemiological study in 41 TSC patients demonstrates that a history of epileptic spasms is strongly associated with a lower IQ: the mean IQ score drops from 93 in TSC patients without epileptic spasms to 72 in patients with spasms (p-value 0.0005). [41] The risk of a cognitive impairment increases significantly with prolonged duration of epileptic spasms, prolonged time from treatment initiation until the cessation of spasms, and poor control of subsequent seizures. [36, 42]

Not only cognitive impairment and ASD, also behavioural problems are an important burden of disease in TSC patients. Self-injurious behaviour occurs in 10% of the TSC patients and is significantly associated with a *TSC2* mutation, a history of seizures, a history of epileptic spasms, mental retardation and ASD. [43]

Treatment of epilepsy in TSC

Early target interventions of epilepsy increase the probability of reaching seizure-freedom and might protect neurodevelopment. [22] Possible treatment options are: anti-epileptic drugs, mTOR inhibitors, epilepsy surgery, ketogenic diet and vagus nerve stimulation (VNS).

Figure: Magnetic resonance imaging in a 13-year old boy with TSC. The arrow shows a tuber in the right parietal lobe with transmantle sign.



Vigabatrin is a structural analogue of GABA and it irreversibly inhibits the major degradative enzyme for GABA, GABA-transaminase which leads to increased brain levels of GABA. By increasing the synaptic concentration of GABA, vigabatrin could stop and prevent diffusion of the epileptiform activity. [44, 45] Vigabatrin is the first line treatment in infants and children with TSC for both epileptic spasms and/ or focal seizures. [31] A retrospective study of 71 children aged 0 – 18 years shows that vigabatrin is the most effective antiepileptic drug. 46 The importance of early start with vigabatrin soon after seizure onset is demonstrated by a study in infants with TSC showing that the start of treatment with vigabatrin within one week after seizure onset is accompanied by improved seizure control compared with later treatment after 3 weeks. (p-value <0.01) [15] A normal or borderline cognitive development is more frequently observed in children with early treatment compared to late treatment (39% vs 0%, p-value < 0.004). Moreover, severe or profound intellectual disability is more frequently observed in children with later introduction of treatment (57% vs 9%, p-value <0.01) [15] However, irreversible visual field defects are associated with the use of vigabatrin. The risk depends on the dose and duration of administration. [44] However the balance between the advantages on seizure control and the associated positive effects on neurocognitive outcome against the disadvantages are still in support of this treatment option.

As second-line drugs for the treatment of focal seizures, GABA-ergic drugs other than vigabatrin (e.g. carbamazepine, oxcarbazepine and topiramate) are used. [22, 46] For the second-line treatment of epileptic spasms, the combination of vigabatrin and prednisolone or ACTH is recommended. [22]

A hypothesis is proposed that preventive antiepileptic treatment with vigabatrin of infants with TSC after the appearance of EEG abnormalities, but before the onset of seizures might improve the epilepsy and neurodevelopmental outcome at the age of 2 years. In a prospective open label study 31 infants with TSC receive vigabatrin after the onset of seizures in the standard of care group and 14 infants start with vigabatrin when multifocal spikes were first seen on the EEG in the preventive group. At the age of 24 months there are significantly more patients in the preventive treatment group with seizure freedom (93% vs 35%; p- value 0.004) and less children with drug resistant epilepsy (7% vs 42%; p-value 0.021). Mental retardation is only observed in children with epilepsy and it is significantly more frequent in the standard of care treatment group compared to the preventive group. (48% vs 14%; p-value 0.031; mean IQ score 68.7 vs 92.3; p-value < 0.05) [47] The benefits of preventive vigabatrin need to be confirmed by other trials: EPISTOP (NCT02098759) in Europa and PREVeNT (NCT02849457) in the United States. If these trials confirm these findings, then antiepileptic treatment before the start of clinical seizures, and after the first epileptic abnormalities on EEG, will become the new standard treatment option in infants with TSC.

Two mTOR inhibitors, everolimus and sirolimus, which were originally developed as immunosuppressants and anticancer drugs, are also applied to treat TSC manifestations. They inhibit the mTOR pathway by reduction of the phosphorylation of downstream mTOR effectors. Everolimus has a better pharmokinetic profile than sirolimus. The mTOR inhibitors are effective in treating subependymal giant cell astrocytoma (SEGA) and renal angiomyolipomata. [11, 48, 49] Moreover, other TSC-associated manifestations, like skin manifestations, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyoma, and epilepsy can also benefit from everolimus treatment. [49, 50] The effect of everolimus is prospectively studied in 20 TSC patients older then 2 years with refractory epilepsy. 60% of the patients experience a seizure reduction of ≥ 50%. [51] Another prospective trial studies 15 children less then 18 years with refractory focal seizures, tonic-clonic seizures or drop-attacks and finds that 80% has a seizure frequency reduction of ≥ 50%. Moreover 58% are seizure-free at a median follow-up of 22 months. [48] In the EXIST 3 trial everolimus is used as an adjunctive treatment in children older then 2 years of age with refractory epilepsy. This study shows a median seizure reduction of 30-50% depending on the age group and studied dose. The seizure reduction sustains after one year of treatment. [52] The efficacy and safety profile of everolimus need to be studied in children younger then 2 years of age. The use of mTOR inhibitors in TSC can be considered as 'precision' medicine, as they interfere directly with the pathophysiology in TSC and are not a merely symptomatic treatment for seizures.

Another treatment option is epilepsy surgery. In the case of failure of two appropriate anti-epileptic drugs, pre-surgical evaluation should be planned. [31, 53] EEG, MRI, functional MRI, positron emission tomography (PET) and single photon emission computed tomography (SPECT) with subtracted ictal SPECT co-registered to MRI (SISCOM) are non-invasive techniques that can help with the identification of the epileptogenic zone. [53] The presence of epileptic spasms is not a contra-indication of epilepsy surgery. [53] Commonly used techniques are tuber resections, lobectomies or a combination of both. [54] Although underused, resective surgery offers excellent long-term chance of seizure-freedom. [53] The follow-up of 66 TSC patients with TSC and epilepsy surgery shows that 74.5% were seizure-free after 1 year, 58.8% after 5 years and 47.8% after 10 years. Epilepsy surgery is significantly associated with improvements in performance IQ, full-scale IQ, and quality of life, especially in postoperative seizure-free patients. [54]

Ketogenic diet can be beneficial in children with refractory epilepsy. The diet is used in 12 children with medically refractory epilepsy. Three months after initiation, a seizure reduction of ≥ 50% is reported in 83.3%. 58.3% of the caregivers report an improvement of cognition and behaviour. Additional studies should explore the mechanism and therapeutic value of the ketogenic diet in TSC. [55]

VNS can be a treatment option in TSC children with refractory epilepsy who are not able to undergo resective surgery. [19] In a small study of 11 patients, 82% experiences a seizure frequency reduction of at least 67%. [56] In another retrospective trial 50% out of 16 TSC patients experiences a ≥ 50% reduction in seizure burden after VNS implantation. [57]

Conclusion

Early diagnosis of an infant with clinical suspicion of TSC now becomes even more important as early interventions might result in a better overall outcome. 80 to 90 % of the TSC patients develop epilepsy, most commonly in the first months of life. Early seizure onset is associated with an increased risk of a developmental delay and neuropsychiatric problems. Education of caregivers with the aim of early recognition of subtle focal seizures and epileptic spasms is of importance to avoid treatment delay. Serial video EEGs could identify children at risk of developing epilepsy and enable the initiation of anti-epileptic treatment soon after seizure onset which might result in an improved developmental outcome. Since preventive treatment with vigabatrin before seizure onset possibly intervenes in the process of epileptogenesis, this could be a succesful new treatment option when it is validated in the ongoing international trials. The use of mTOR inhibitors could also be a new treatment approach in the future when efficacy and safety are better demonstrated in the youngest patients.

REFERENCES:

1. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125-7.
2. Henske EP, Jozwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:16035.
3. Borkowska J, Schwartz RA, Kotulska K, Jozwiak S. Tuberous sclerosis complex: tumors and tumorigenesis. Int J Dermatol. 2011;50(1):13-20.
4. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657-68.
5. Tyburczy ME, Dies KA, Glass J, Camposano S, Chekaluk Y, Thorner AR, et al. Mosaic and Intronic Mutations in TSC1/TSC2 Explain the Majority of TSC Patients with No Mutation Identified by Conventional Testing. PLoS Genet. 2015;11(11):e1005637.
6. Nellist M, Brouwer RW, Kockx CE, van Veghel-Plandsoen M, Withagen-Hermans C, Prins-Bakker L, et al. Targeted Next Generation Sequencing reveals previously unidentified TSC1 and TSC2 mutations. BMC Med Genet. 2015;16(1):10.
7. Caban C, Khan N, Hasbani DM, Crino PB. Genetics of tuberous sclerosis complex: implications for clinical practice. Appl Clin Genet. 2017;10:1-8.
8. Peron A, Northrup H, Vries PJ, Wilde L, Vries MC, Moavero R, et al. A clinical update on tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). Am J Med Genet C Semin Med Genet. 2018;178(3):309.
9. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015;14(7):733-45.
10. de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn D, Ess KC, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. Pediatr Neurol. 2015;52(1):25-35.
11. Gipson TT, Johnston MV. New insights into the pathogenesis and prevention of tuberous sclerosis-associated neuropsychiatric disorders (TAND). F1000Res. 2017;6.
12. Kingswood JC, d'Augeres GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. TuberOus SClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. Orphanet J Rare Dis. 2017;12(1):2.
13. Joinson C, Ocallaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med. 2003;33(2):335-44.
14. Capal JK, Bernardino-Cuesta B, Horn PS, Murray D, Byars AW, Bing NM, et al. Influence of seizures on early development in tuberous sclerosis complex. Epilepsy & Behav. 2017;70(Pt A):245-52.
15. Cusmai R, Moavero R, Bombardieri R, Vigevano F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. Epilepsy Behav. 2011;22(4):735-9.

16. Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. Neurology. 2011;76(11):981-7.
17. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus G. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243-54.
18. Slowinska M, Jozwiak S, Peron A, Borkowska J, Chmielewski D, Sadowski K, et al. Early diagnosis of tuberous sclerosis complex: a race against time. How to make the diagnosis before seizures? Orphanet J Rare Dis. 2018;13(1):25.
19. Canevini MP, Kotulska-Jozwiak K, Curatolo P, La Briola F, Peron A, Slowinska M, et al. Current concepts on epilepsy management in tuberous sclerosis complex. Am J Med Genet C Semin Med Genet. 2018;178(3):299-308.
20. Pitkanen A, Engel J, Jr. Past and present definitions of epileptogenesis and its biomarkers. Neurotherapeutics. 2014;11(2):231-41.
21. Pitkanen A, Ekolle Ndode-Ekane X, Lapinlampi N, Puhakka N. Epilepsy biomarkers - Toward etiology and pathology specificity. Neurobiol Dis. 2019;123:42-58.
22. Curatolo P, Nabbout R, Lagae L, Aronica E, Ferreira JC, Feucht M, et al. Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations. Eur J Paediatr Neurol. 2018;22(5):738-48.
23. Curatolo P, Aronica E, Jansen A, Jansen F, Kotulska K, Lagae L, et al. Early onset epileptic encephalopathy or genetically determined encephalopathy with early onset epilepsy? Lessons learned from TSC. Eur J Paediatr Neurol. 2016;20(2):203-11.
24. Prabowo AS, Anink JJ, Lammens M, Nellist M, van den Ouweland AM, Adle-Biassette H, et al. Fetal brain lesions in tuberous sclerosis complex: TORC1 activation and inflammation. Brain Pathol. 2013;23(1):45-59.
25. Muhlebner A, Iyer AM, van Scheppingen J, Anink JJ, Jansen FE, Veersema TJ, et al. Specific pattern of maturation and differentiation in the formation of cortical tubers in tuberous sclerosis omplex (TSC): evidence from layer-specific marker expression. J Neurodev Disord. 2016;8:9.
26. Valencia I, Legido A, Yelin K, Khurana D, Kothare SV, Katsetos CD. Anomalous inhibitory circuits in cortical tubers of human tuberous sclerosis complex associated with refractory epilepsy: aberrant expression of parvalbumin and calbindin-D28k in dysplastic cortex. J Child Neurol. 2006;21(12):1058-63.
27. Wang Y, Greenwood JS, Calcagnotto ME, Kirsch HE, Barbaro NM, Baraban SC. Neocortical hyperexcitability in a human case of tuberous sclerosis complex and mice lacking neuronal expression of TSC1. Ann Neurol. 2007;61(2):139-52.
28. Moavero R, Napolitano A, Cusmai R, Vigevano F, Figa-Talamanca L, Calbi G, et al. White matter disruption is associated with persistent seizures in tuberous sclerosis complex. Epilepsy Behav. 2016;60:63-7.
29. Wu JY, Peters JM, Goyal M, Krueger D, Sahin M, Northrup H, et al. Clinical Electroencephalographic Biomarker for Impending Epilepsy in Asymptomatic Tuberous Sclerosis Complex Infants. Pediatr Neurol. 2016;54:29-34.
30. Domanska-Pakiela D, Kaczorowska M, Jurkiewicz E, Kotulska K, Dunin-Wasowicz D, Jozwiak S. EEG abnormalities preceding the epilepsy onset in tuberous sclerosis complex patients - a prospective study of 5 patients. Eur J Paediatr Neurol. 2014;18(4):458-68.
31. Curatolo P, Jozwiak S, Nabbout R. Management of epilepsy associated with tuberous sclerosis complex (TSC): clinical recommendations. Eur J Paediatr Neurol. 2012;16(6):582-6.
32. Holmes GL, Stafstrom CE. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia. 2007;48(4):617-30.
33. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010;51(7):1236-41.
34. Kotulska K, Jurkiewicz E, Domanska-Pakiela D, Grajkowska W, Mandera M, Borkowska J, et al. Epilepsy in newborns with tuberous sclerosis complex. Eur J Paediatr Neurol. 2014;18(6):714-21.
35. Davis PE, Filip-Dhima R, Sideridis G, Peters JM, Au KS, Northrup H, et al. Presentation and Diagnosis of Tuberous Sclerosis Complex in Infants. Pediatrics. 2017;140(6).
36. Humphrey A, MacLean C, Ploubidis GB, Granader Y, Clifford M, Haslop M, et al. Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis. Epilepsia. 2014;55(1):108-16.
37. Jansen FE, Vincken KL, Algra A, Anbeek P, Braams O, Nellist M, et al. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. Neurology. 2008;70(12):916-23.
38. Winterkorn BE, Pulsifer BM, Thiele AE. Cognitive prognosis of patients with tuberous sclerosis complex. Neurology. 2007;68(1):62-4.
39. Benova B, Petrak B, Kyncl M, Jezdik P, Maulisova A, Jahodova A, et al. Early predictors of clinical and mental outcome in tuberous sclerosis complex: A prospective study. Eur J Paediatr Neurol. 2018;22(4):632-41.
40. Kaczorowska M, Jurkiewicz E, Domanska-Pakiela D, Syczewska M, Lojszczyk B, Chmielewski D, et al. Cerebral tuber count and its impact on mental outcome of patients with tuberous sclerosis complex. Epilepsia. 2011;52(1):22-7.
41. O'Callaghan FJ, Harris T, Joinson C, Bolton P, Noakes M, Presdee D, et al. The relation of infantile spasms, tubers, and intelligence in tuberous sclerosis complex. Arch Dis Child. 2004;89(6):530-3.
42. Goh JS, Kwiatkowski JD, Dorer AD, Thiele AE. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. Neurology. 2005;65(2):235-8.
43. Staley BA, Montenegro MA, Major P, Muzykewicz DA, Halpern EF, Kopp CM, et al. Self-injurious behavior and tuberous sclerosis complex: frequency and possible associations in a population of 257 patients. Epilepsy Behav. 2008;13(4):650-3.
44. James Willmore L, Abelson MB, Ben-Menachem E, Pellock JM, Donald Shields W. Vigabatrin: 2008 Update. Epilepsia. 2009;50(2):163-73.
45. Lortie A, Plouin P, Chiron C, Delalande O, Dulac O. Characteristics of epilepsy in focal cortical dysplasia in infancy (vol 51, pg 133, 2002). Epilepsy Res. 2003;53(1-2):163-5.
46. Overwater IE, Bindels-de Heus K, Rietman AB, Ten Hoopen LW, Vergouwe Y, Moll HA, et al. Epilepsy in children with tuberous sclerosis complex: Chance of remission and response to antiepileptic drugs. Epilepsia. 2015;56(8):1239-45.
47. Jozwiak S, Kotulska K, Domanska-Pakiela D, Lojszczyk B, Syczewska M, Chmielewski D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol. 2011;15(5):424-31.
48. Samueli S, Abraham K, Dressler A, Groppel G, Muhlebner-Fahrngruber A, Scholl T, et al. Efficacy and safety of Everolimus in children with TSC - associated epilepsy - Pilot data from an open single-center prospective study. Orphanet J Rare Dis. 2016;11(1):145.
49. Curatolo P, Bjornvold M, Dill PE, Ferreira JC, Feucht M, Hertzberg C, et al. The Role of mTOR Inhibitors in the Treatment of Patients with Tuberous Sclerosis Complex: Evidence-based and Expert Opinions. Drugs. 2016;76(5):551-65.
50. Moavero R, Coniglio A, Garaci F, Curatolo P. Is mTOR inhibition a systemic treatment for tuberous sclerosis? Ital J Pediatr. 2013;39(1):57.
51. Krueger DA, Wilfong AA, Holland-Bouley K, Anderson AE, Agricola K, Tudor C, et al. Everolimus treatment of refractory epilepsy in tuberous sclerosis complex. Ann Neurol. 2013;74(5):679-87.
52. Curatolo P, Franz DN, Lawson JA, Yapici Z, Ikeda H, Polster T, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. Lancet Child Adolesc Health. 2018;2(7):495-504.
53. Ostrowsky-Coste K, Neal A, Guenot M, Ryvlin P, Bouvard S, Bourdillon P, et al. Resective surgery in tuberous Sclerosis complex, from Penfield to 2018: A critical review. Rev Neurol (Paris). 2019;175(3):163-82.
54. Liang S, Zhang J, Yang Z, Zhang S, Cui Z, Cui J, et al. Long-term outcomes of epilepsy surgery in tuberous sclerosis complex. J Neurol. 2017;264(6):1146-54.
55. Park S, Lee EJ, Eom S, Kang HC, Lee JS, Kim HD. Ketogenic Diet for the Management of Epilepsy Associated with Tuberous Sclerosis Complex in Children. J Epilepsy Res. 2017;7(1):45-9.
56. Elliott RE, Carlson C, Kalhorn SP, Moshel YA, Weiner HL, Devinsky O, et al. Refractory epilepsy in tuberous sclerosis: vagus nerve stimulation with or without subsequent resective surgery. Epilepsy Behav. 2009;16(3):454-60.
57. Major P, Thiele EA. Vagus nerve stimulation for intractable epilepsy in tuberous sclerosis complex. Epilepsy Behav. 2008;13(2):357-60.

Mustela®

baby - child

I want zero redness

MUSTELA CARES

80% of babies | Reduction of irritations and redness

From the 1st day of use[1]

Certified B Corporation

OFFICIAL PARTNER BRONZE - 2019

MUSTELA SUPPORTS THE BELGIAN SOCIETY OF PAEDIATRICS

98% INGREDIENTS OF NATURAL ORIGIN

1. Use test conducted under dermatologic and pediatric control on 69 children, including babies under 3 months (self-assessment)

✓ FROM BIRTH ON DERMATOLOGIST TESTED | MADE IN FRANCE | ✓ INGREDIENT SAFETY POLICY

EXPANSCIENCE® LABORATOIRES

Side effects of 4-component meningococcal B vaccine (Bexsero®): a systematic review

An-Sophie Lemoine[1*], Jaan Toelen[2,3], Marc Raes[4]

[1] Department of Medicine, KU Leuven, Leuven, Belgium
[2] Department of Development and Regeneration, Cluster Organ Systems, KU Leuven, Leuven, Belgium.
[3] Department of Pediatrics, UZ Leuven, Leuven, Belgium.
[4] Department of Pediatrics, Jessa Hospital, Hasselt, Belgium.

ansophie.lemoine@student.kuleuven.be

Abstract

Background *Neiserria meningitis* is a bacterium that causes an invasive meningococcal disease (IMD), which can result in severe disability or death within hours. The bacterium has 12 serogroups of which A, B, C, W, X and Y are responsible for most of the infections. Vaccines are available for the serogroups A, C, W and Y, leaving serogroup B as an important cause of IMD worldwide. Serogroup B infection has a case fatality rate estimated at 5.4% for all ages. Bexsero® (4CMenB) has been developed as a multicomponent meningococcal serogroup B recombinant protein-based vaccine. Today, it is licensed in 41 countries worldwide. Unfortunately, Bexsero® is associated with an increased occurrence of adverse effects.

Methods This systematic review reports the adverse effects of Bexsero® in children aged 0-18 years. The intervention in the studies consisted of the administration 4CMenB versus placebo or other immunizations.

Results Fourteen studies describe the occurrence of AEs within infants, 3 in children and 3 in adolescents. The most frequent local reaction is erythema in infants (median 59%) and pain in children and adolescent (median 92.5% and 40%). The most frequent systemic reaction is irritability in infants and children (median 68% and 40%) and myalgia in adolescents (median 47.5%). Median incidence of fever is 48% in infants and 10.5% in children. There are only few serious AEs. No deaths occurred.

Conclusion Bexsero® is proven to be effective with an acceptable tolerability profile without major safety concerns. Common side effects should be communicated with the patients or their parents.

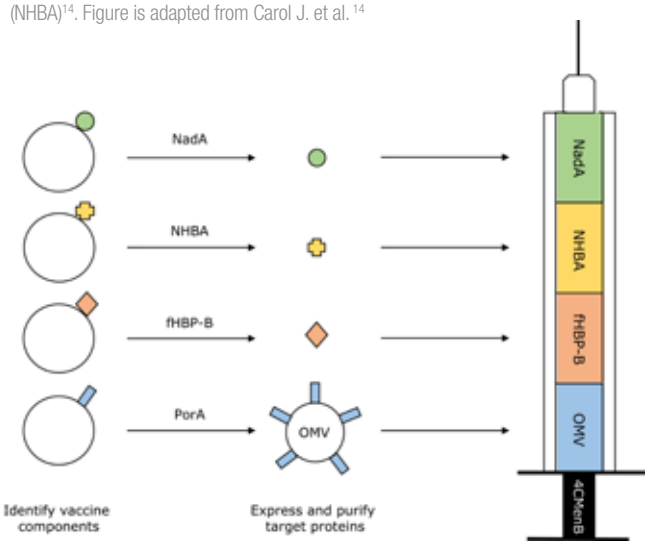
Introduction

Neisseria meningitides is a gram-negative bacterium that causes an invasive meningococcal disease (IMD), which can result in severe disability or death within hours. IMD comprises bacteremia (35-40%), meningitis (50%) and purpura fulminans (10-15%)[1]. The bacterium has 12 serogroups, of which A, B, C, W, X and Y are responsible for the majority of the infections. The transmission and contamination of the bacterium takes place through aerosol[2]. Asymptomatic carriage can occur and is most common in adolescents[3]. Everyone can be infected, but infants, children and adolescents are more prone[4]. There is an increased risk in people with asplenia or complement deficiencies[5]. Patients recovering from IMD may have 10-20% chance of suffering sequellae such as seizures, hearing impairment, amputations and visual or cognitive dysfunction[1].

Its incidence has changed over the last years and depends on residency[6]. Meningococcal B is now the dominant serogroup in Australia, New Zealand, Northern Africa, Europe and the United States[7]. Every year, 1.2 million cases are described with a fatality rate of 10-40%[8]. The case fatality rate for serogroup B disease is estimated at 5.4% for all ages[1]. More specific for Belgium, in the first trimester of 2017, 31 cases were diagnosed in a reference center of which 19 were caused by serogroup B. Children under the age of 5 represent 11 of these cases and another 6 were adolescents between the age of 15 and 19[9].

Because of the significant morbidity and mortality, IMD ensures a major global health problem with a clinical and financial burden. Vaccination has been proven the best strategy for prevention[5,8]. Vaccines are already available for the serogroups A, C, W and Y, thereby leaving serogroup B as an important cause of IMD worldwide[10]. The vaccine development against this serogroup B proved challenging. This as a result of the poor immunogenic potential of the capsular polysaccharide because of its similarity to human neural tissue polysaccharides[11,12]. Bexsero® (4CMenB) is a multicomponent meningococcal serogroup B recombinant protein-based vaccine. It consists of outer membrane vesicles (OMV) from the New Zealand epidemic strain NZ98/254 expressing porin A (PorA) protein, factor H-binding protein (fHbp), Neiserrial adhesion A (NadA) and Neiserria heparin-binding antigen (NHBA), as illustrated in Figure 1[7,13,14]. At present, the vaccine is licensed in 41 countries worldwide, more specifically in Australia, Canada, the United States, Europe and some countries in South America[15,16]. However, the only country that includes the vaccine in the infant national immunization schedule is the UK7. From 1 October 2018, 4CMenB had been offered as part of an ongoing program for infants up to the age of 12 months in the state of South-Australia[17]. The general introduction of Bexsero® will be an important step towards repressing this invasive meningococcal disease.

Figure 1: Molecular structure of 4CMenB (Bexsero®). The vaccine consist of NadA, outer membrane vesicles (OMV) from the New Zealand epidemic strain NZ98/254 expressing porin A (PorA) protein, factor H-binding protein (fHbp), N. meningitides purified antigens Neiserrial adhesion A (NadA) and Neiserria heparin-binding antigen (NHBA)[14]. Figure is adapted from Carol J. et al. [14]



Although current clinical trials report an acceptable safety profile, Bexsero® has been proven to increase the occurrence of adverse effects[18]. At present, parents as well as medical doctors may have some concerns towards the administration of the vaccine and its potential side effects. Most trials only looked into safety and reactogenicity as co-primary objectives, but did not report a complete overview[12]. Therefore, in this systematic review we present an overview of the most common adverse effects and their incidence to guide physicians in their counseling of parents and patients.

Materials and Methods

We formulated the research question for this literature review based on the PICO (population, intervention, comparison and outcome) guidelines[19]. The selected population includes children (aged 0-18 years). The intervention consisted of the administration of the meningitis B vaccine (4CMenB), the control condition was either placebo or other immunizations. The outcomes were defined as safety and adverse effects of the 4CMenB vaccination. The research articles that were included in the systematic review had to document the adverse effects or safety of the 4CMenB vaccine (Bexsero®). Only human clinical studies were included. Expert opinions, single cases, case series reports, reviews and clinically irrelevant papers were excluded.

The Embase and Pubmed databases were accessed in November 2018. This resulted in 201 articles. All the resulting titles were manually screened. Subsequently, the references of all retained papers were examined for relevant studies. In total, 19 articles were included in the data extraction in accordance to the inclusion and exclusion criteria. The risk of bias was assessed in all included studies according to the Cochrane Risk of Bias Tool[20].

All data reporting the frequency of adverse events were filtered. Then normality was checked for each adverse event using the Shapiro-Wilk test. When the data were normal distributed, they were described through average and standard deviation. When they were not normally distributed, median and interquartile range (IR) was used, as shown in Table 1-3. Statistical analysis was performed using the SPSS® version 25,0 (IBM Corp., Armonk, NY, USA).

Results

Infants

A total of 14 studies described adverse effects in infants, five phase 2 randomized controlled trials, six phase 3, two retrospective studies and one prospective study over a time period of 10 years. Figure 2A provides an overview of all studies on a chronological basis.

The phase 2 studies focused on the composition on the vaccine and its effects. There was no clear conclusion with regard to side effects comparing recombinant meningococcal serogroup B vaccine (rMenB) with rMenB plus different concentrations of OMV[21,22]. The phase 3 studies used the current composition of Bexsero®: N. meningitides purified antigens NadA, fHbp and NHBA; OMV from N. meningitides strain PorA and aluminium hydroxide; sodium chloride, sucrose; histidine and water in a volume of 5ml7. Five studies combined 4CMenB with routine vaccines[6,7,11–13,23,24] (see Table S2).

The vaccine was administered intramuscularly in the thigh or in the deltoid area of the non-dominant arm. The studies did not distinguish between injections in the arm or in the leg.

Most studies observed safety and reactogenicity as a secondary outcome. Infants were observed after each vaccination for 30 minutes. Parents recorded predefined local and systemic reactions for 7 days on a diary card, as well as unanticipated adverse events (AEs). Throughout the complete duration of the study, any other

Figure 2: Selection procedurel.

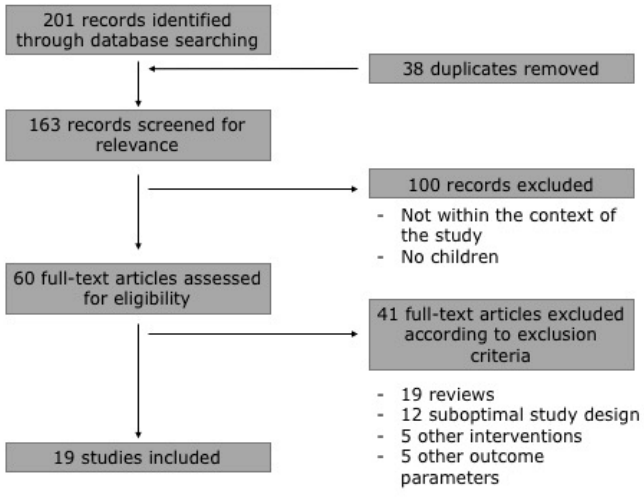


Table 1: Adverse events in infants. Frequency of adverse events after the primary dose of 4CmenB in infants[6,7,25,11–13,15,21–24]. The data are presented as median with interquartile range. The systemic reactions are ranged according to frequency.

		Median (IR)
Local reaction	Tenderness	58% (53-63)
	Erythema	59% (45-70)
	Induration	44% (40-55)
	Swelling	29% (23-38.5)
Systemic reaction	Irritability	68% (59-75)
	Sleepiness	63% (39-66)
	Unusual crying	56% (28-65)
	Fever	48% (33.75-54)
	Change in eating habits	35% (26-50)
	Diarrhea	19% (17-31)
	Vomiting	13% (7-15)
	Rash	5% (4-12)

Table 2: Adverse events in children. Frequency of adverse events after the primary dose of 4CmenB in children[8,15,26]. The data are presented as median with interquartile range. The systemic reactions are ranged according to frequency.

		Median (IR)
Local reaction	Pain	92.5% (82.75-97)
	Erythema	52.5% (50.5-83.75)
	Induration	35% (28.25-44)
	Swelling	39% (37.25-41.5)
Systemic reaction	Irritability	40% (35-44)
	Change in eating habits	30% (27-32)
	Myalgia	28.5% (27-30)
	Sleepiness	28% (23-32)
	Malaise	22% (15-29)
	Chills	20% (8-32)
	Arthralgia	16.5% (14-19.75)
	Headache	15% (5.5-29)
	Fever	10.5% (8.5-14)
	Nausea	9.5% (9-10)
	Vomiting	8% (5-9)
	Diarrhea	8% (6-8)
	Rash	5.5% (3.25-7.75)

Table 3: Adverse events in adolescents. Frequency of adverse events after the primary dose of 4CmenB in adolescents[30–32]. The data are presented as median with interquartile range. The systemic reactions are ranged according to frequency.

		Median (IR)
Local reaction	Pain	92% (87-96.25)
	Erythema	45.5% (38.5-50.25)
	Induration	29.5% (26-37.5)
	Swelling	30% (26.25-36)
Systemic reaction	Myalgia	47.5% (29.25-57.5)
	Malaise	40.5% (29-52)
	Fatigue	35% (23.5-35.5)
	Headache	34% (26-40.5)
	Nausea	17.5% (11.75-18.75)
	Arthralgia	14.5% (9-22.5)
	Rash	4% (3.5-4)
	Fever	3% (2.5-3.5)

unsolicited AEs were recorded, along with medically attended AEs and AEs responsible for early termination from the trial. The severity of AEs and its possible causal relationship to the study vaccine was defined by the investigator. Local reactions were described as injection site tenderness, erythema, induration and swelling. Systemic reactions were described as change in eating habits, fever, sleepiness, vomiting, diarrhea, irritability, unusual crying and urticarial or other rash[6,7,11–13,15,21–25]. Fever was defined as axillar temperature ≥ 38°C[7,11,13,22–26] or rectal temperature ≥ 38.5°C[12,21] or ≥ 38°C[6]. The median frequency of the most common AEs after the first dose of 4CmenB is summarized in Table 1. Erythema and tenderness are the most frequent local reactions, whereas irritability and sleepiness are the most frequent systemic reactions within infants. In the studies there was limited reporting of possible related serious AEs, all of which resolved completely. In only one study fatal outcome occurred, namely 2 reports of sudden unexplained death and 3 reports of death, all within 3 days after receiving 4CMenB and their routine vaccination. It was not possible to proof causality with 4CMenB[6,7,11–13,15,21–25,27].

The retrospective trials studied the medical care attendance rate for the side effects. Nainai et al. found that there was an increase in the mean annual incidence of 12 to 38 presentations of possible AE following immunization (AEFI) at primary care and emergency department. This was measured over a period of 3 years after the introduction of the 4CmenB vaccination. This increase is most significant after the immunization at 2 and 4 months[28]. While Hartcourt et al. focused more on the care attendance of fever in particular. They found an increase in de all-cause fever consultation after 4CmenB vaccination in comparison with the preceding years, 1.6-fold higher in 7-10 week old infants and 1.5-fold higher in 15-18 week old infants[29].

Children

One phase 2 and two phase 3 trials studied children (Figure 2B). The administration of the vaccine was done in the deltoid area of the non-dominant arm. The observation of AEs occurred in the same manner as with the infants. Fever was defined as axillar temperature ≥38°C. An estimation of the average frequency of the adverse events after first dose of the 4CmenB vaccine is summarized in Table 2. They studied different local and systemic reactions compared to those in infants. As local reaction tenderness was replaced by pain. When looking at the prevalence of AEs in children, there is a downward trend in the prevalence of systemic reactions. Additionally systemic reactions as myalgia, arthralgia, headache, nausea, chills and malaise were observed. it is clear that older children are better capable of expressing themselves, so they may mention more reactions such as local pain or myalgia [11,26]. Pain was the most recurrent of the reported local reactions. As seen in infants, irritability is the most frequent systemic reaction. No serious AEs or deaths occurred[8,15,26].

Adolescents

One phase 2b/3 and two phase 3 studies took place with 4CmenB vaccination at adolescent age (Figure 2C). The vaccine was administered in the deltoid muscle of the non-dominant arm. The observation of AEs was similar to the one in the infant and children studies. Fever was defined as axillar temperature ≥38°C. An estimation of the median frequency of AEs after first dose of the 4CmenB vaccine is summarized in Table 3. Pain at the injection site, was the most reported local reaction[31,32]. Several of the systemic reactions observed in the previous studies are not described here, an additional systemic reaction is fatigue[30–32]. The most frequent systemic reactions are myalgia and malaise. Studies confirm the significant reduction in the occurrence of fever with increasing age, only 3% of the adolescents experiences post-vaccination fever[32]. Santolaya et al. reported 2 serious AEs possible related to the vaccine: 2 cases of juvenile arthritis respectively 170 and 198 days after vaccination[32]. No other serious AEs possible related to the vaccine were reported. No deaths occurred[30–32].

Discussion

In this systematic review, we provide a thorough overview of the side effects of Bexsero®. Striking is that 94-97% of the participants experienced at least 1 AEs[8]. The local and systemic reactions following vaccination are the most prominent after the first administration, but they do not increase with subsequent vaccinations[6,15,25]. Four of the included studies emphasize the rise in frequency of AEs when 4CMenB is given concomitant with routine vaccinations[7,13,23,24].

Most notable in infants is the high frequency of fever as a systemic reaction. The high temperature was mostly detected 6 hours after the vaccination and decreased after 2-3 days. Although fever ≥40°C was rare (≥2%), 0.8% of infants between the age of 1 to 6 months attended the emergency department for AEs following immunization, mostly with fever (80%) and irritability (71%)[6,24,33]. Infants presenting with fever have a high risk of a serious bacterial infection (SBI), and this distinction between post-vaccination fever and SBI is sometimes hard to make. More than 60% of the infants underwent at least one investigation (e.g. venipuncture, lumbar puncture or urine sample) in congruity with the national or local guidelines for fever in infants. In cases where the fever is only secondary to the immunization, this may lead to overshooting and to invasive testing [17,33]. A similar trend was seen after the introduction of the pneumococcal conjugate vaccine, but with 4CmenB the admission rate was significantly higher[34]. It is important to note that diagnosed fevers were not only vaccine-related and seasonal variation should be taken into account. Visits to physicians also result in extra work absence of the parents and medical expenses[12]. It is possible that these numbers will decline when doctors and parents are better informed due to increased experience with the vaccine.

The prophylactic use of paracetamol can help minimize the presentation of patients at primary care or the accident and emergency department[33]. The optimal time to administer paracetamol is immediately before the vaccination, followed by 2 doses at a 4-6 hours interval. After the administration of paracetamol, a diminution in frequency and severity of all local reactions has been demonstrated. However, the fundamental goal is a reduction in the incidence of fever and to increase the comfort of the infant. Paracetamol has the biggest impact on fever ≥39°C[12]. Paracetamol has a good safety profile when given at the right pediatric dosage[35]. An important advantage is that there is no significant impact on the immune response to 4CmenB or the routine vaccines[12]. However, there is still insufficient data to prove that the use of prophylactic paracetamol can decrease hospitalizations[34].

Compared to the well-known vaccine against meningococcal serogroup C in infants, administration of 4CmenB results in more side effects. For example, Safadi et al. reports a 17% difference in frequency of tenderness at the injection site between patients receiving 4CmenB + conjugate meningococcal serogroup C vaccine (MenC) (group 1) and MenC alone (group 2)[6]. As for the systemic reactions, fever was reported 39-48% in group 1 and 10-20% in group 2 after each vaccination[6]. Vesikari et al. makes the comparison between routine vaccination plus 4CmenB or MenC. They also confirmed a 33% higher frequency of tenderness and a 31.6% increase in fever when 4CmenB was administered instead of MenC[24]. Even despite the use of paracetamol 4CMenB keeps resulting in a higher frequency of side effects than MenC[12]. When compared to a conjugate vaccine in which the capsular polysaccharides from Neisseria meningitidis serogroups A, C, W, and Y are conjugated to the diphtheria toxin mutant CRM197 (MenACWY-CRM), 4CMenB (or the combination of 4CMenB with MenACWY-CRM) gives a higher frequency of local reactions and fever[25].

It is important that parents are given correct information about effectiveness of Bexsero®, but also about the possibility of AEs. The vaccine is proven to be effective in 82.9% of all meningococcal serogroup B cases after introduction in the national vaccination program in the UK. Resulting in a 50% reduction of the incidence rate ratio of MenB cases after only 10 months [36]. 4CMenB approximately protects against 88% of the MenB strains, a number that may be different in Belgium depending on the prevalence of circulating strains[33]. There are no major safety concerns described until now[27]. Marshall et al. interviewed 3055 individuals between the age of 15 and 97 years for opinions about whether or not to vaccinate[18]. They reported that 82.5% of the parents agreed to a meningococcal B vaccination for their children, 12.2% was unsure about their decision. The strongest independent factor influencing their decision was the recommendation of a general practitioner. 97.7% Of the parents would administer a vaccine if the general practitioner (GP) recommended it[18]. So again it is important that parents are well informed, as it also plays a role in their medical attention seeking behavior (which will influence the number of visits at the primary care and accident and emergency departments)[24,28,29,33].

There are some limitations of this systematic review. As previously mentioned, the studies use different schedules which can influence the frequency of AEs and the opinion of parents about whether or not to vaccinate. Some of the described trials are open-label, which might have caused bias of reporting the local and systemic reactions. Knowing that their child receives Bexsero® might have resulted in parents expecting more AEs and therefore being more vigilant. In some studies the parents scored the severity of the reactions themselves. It is uncertain if every parent or legal guardian had the same level of objectivity when reporting the AEs[15].

Conclusion

A new multicomponent recombinant protein-based meningococcal B vaccine is released, 4CmenB (Bexsero®), currently licensed in 39 countries. It provides effective prevention against IMD caused by meningococcal serogroup B. Bexsero® had an increased reactogenicity, especially when co-administered with routine vaccination. The most important side effects are tenderness at the injection site and fever.

Current recommendations are the use of prophylactic paracetamol to mitigate these reactions. However, there are little to no serious AEs, with most reactions resolving within 2 days. We can conclude that Bexsero® has an acceptable tolerability profile with no major safety concerns. It is very important that doctors and parent are fully informed, resulting in a well-considered choice to vaccinate their children. There is still need for further research about the effects on nasopharyngeal carriage and herd-immunity.

Conflict of interest

We declare no competing interest. This article was writing as part of a master thesis proposed to achieve the degree of master in medicine by An-Sophie Lemoine.

Financial disclosure

We declare no financial disclosure.

Funding

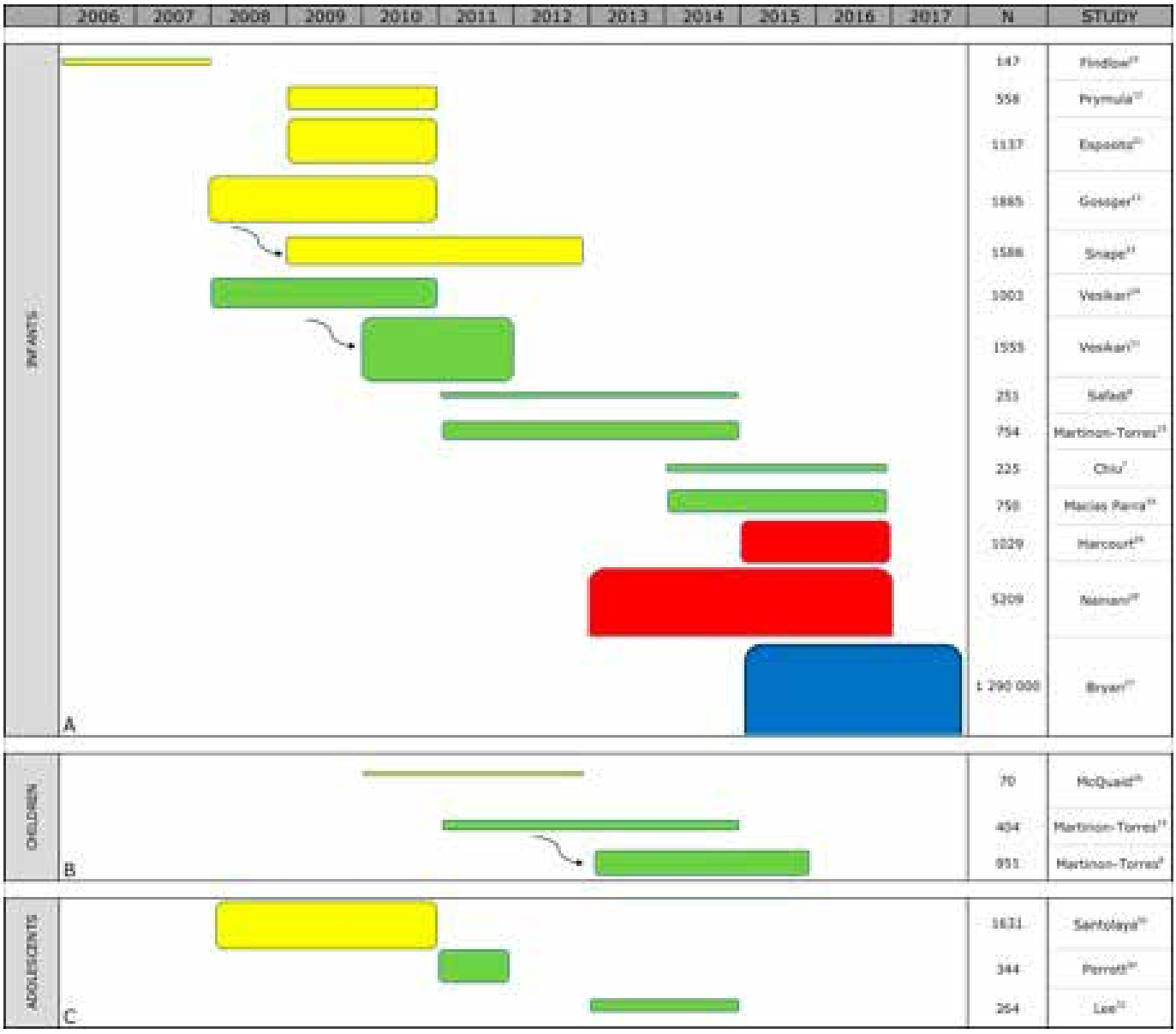
There were nog financial resources used to write this review.

Acknowledgement

I would like to thank Prof. MD. Jaan Toelen and MD. Marc Raes for the support to realize this thesis.

I would also like to thank Phd. Lieselotte Lemoine for helping with the statistics of this review and commenting the draft manuscript.

Figure 4: Study overview. The colors indicate the study design. Yellow: phase 2; green: phase 3; red: retrospective; blue: prospective. The size of the oval indicates the number of participants, with a ratio of 3cm2:500 participants. The length shows the time span. The arrow implies that the study was extended.



REFERENCES:

1. Hoge Gezondheidsraad. Vaccinatie van kinderen, adolescenten en personen met verhoogd risico tegen meningokokken van groep B. 2017;nr 9125.
2. Findlow J, Bai X, Findlow H, Newton E, Kaczmarski E, Miller E, et al. Safety and immunogenicity of a four-component meningococcal group B vaccine (4CMenB) and a quadrivalent meningococcal group ACWY conjugate vaccine administered concomitantly in healthy laboratory workers. Vaccine [Internet]. 2015 Jun 26 [cited 2018 Apr 2];33(29):3322–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26025807
3. Read RC, Baxter D, Chadwick DR, Faust SN, Finn A, Gordon SB, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. Lancet [Internet]. 2014 Dec 13 [cited 2018 Aug 15];384(9960):2123–31. Available from: https://www.sciencedirect.com/science/article/pii/S0140673614608424
4. Kimura A, Toneatto D, Kleinschmidt A, Wang H, Dull P. Immunogenicity and Safety of a Multicomponent Meningococcal Serogroup B Vaccine and a Quadrivalent Meningococcal CRM 197 Conjugate Vaccine against Serogroups A, C, W-135, and Y in Adults Who Are at Increased Risk for Occupational Exposure to Meningococcal Isolates. Clin Vaccine Immunol [Internet]. 2011 Mar [cited 2018 Mar 24];18(3):483–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21177912
5. Crum-Cianflone N, Sullivan E. Meningococcal Vaccinations. Infect Dis Ther [Internet]. 2016 Jun 16;5(2):89–112. Available from: http://link.springer.com/10.1007/s40121-016-0107-0
6. P. Safadi MA, Martinon-Torres F, Weckx LY, Moreira ED, da Fonseca Lima EJ, Mensi I, et al. Immunogenicity and safety of concomitant administration of meningococcal serogroup B (4CMenB) and serogroup C (MenC-CRM) vaccines in infants: A phase 3b, randomized controlled trial. Vaccine [Internet]. 2017 Apr 11 [cited 2018 Apr 2];35(16):2052–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28318767
7. Chiu N-C, Huang L-M, Willemsen A, Bhusal C, Arora AK, Mojares ZR, et al. Safety and immunogenicity of a meningococcal B recombinant vaccine when administered with routine vaccines to healthy infants in Taiwan: A phase 3, open-label, randomized study. Hum Vaccin Immunother [Internet]. 2018 Jan 16 [cited 2018 Apr 2];1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29337653
8. Martinón-Torres F, Carmona Martinez A, Simkó R, Infante Marquez P, Arimany J-L, Gimenez-Sanchez F, et al. Antibody persistence and booster responses 24–36 months after different 4CMenB vaccination schedules in infants and children: A randomised trial. J Infect [Internet]. 2018 Mar [cited 2018 Apr 2];76(3):258–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29253560
9. Wetenschappelijk Instituut Volksgezondheid. Infoblad meningokokkeninfecties. 2017.
10. Snape MD, Medini D, Halperin SA, DeTora L, Drori J, Moxon ER. The challenge of post-implementation surveillance for novel meningococcal vaccines. Vaccine [Internet]. 2012 May 30 [cited 2018 Mar 24];30 Suppl 2:B67-72. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0264410X11020871
11. Vesikari T, Prymula R, Merrall E, Kohl I, Toneatto D, Dull PM. Meningococcal serogroup B vaccine (4CMenB): Booster dose in previously vaccinated infants and primary vaccination in toddlers and two-year-old children. Vaccine [Internet]. 2015 Jul 31 [cited 2018 Apr 2];33(32):3850–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26141011
12. Prymula R, Esposito S, Zuccotti GV, Xie F, Toneatto D, Kohl I, et al. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I). Hum Vaccin Immunother [Internet]. 2014 Jul 7 [cited 2018 Feb 25];10(7):1993–2004. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25424809
13. Gossger N, Snape MD, Yu L-M, Finn A, Bona G, Esposito S, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA [Internet]. 2012 Feb 8 [cited 2018 Mar 24];307(6):573–82. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.85
14. Baker CJ. Prevention of Meningococcal Infection in the United States: Current Recommendations and Future Considerations. J Adolesc Heal [Internet]. 2016 [cited 2018 Dec 10];59:S29–37. Available from: http://dx.doi.org/10.1016/j.jadohealth.2016.03.040
15. Martinón-Torres F, Safadi MAP, Martinez AC, Marquez PI, Torres JCT, Weckx LY, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: Immunogenicity and safety results from a randomised open-label phase 3b trial. Vaccine [Internet]. 2017 Jun 16 [cited 2018 Mar 24];35(28):3548–57. Available from: https://www-sciencedirect-com.kuleuven.ezproxy.kuleuven.be/science/article/pii/S0264410X1730631X?via%3Dihub
16. Toneatto D, Pizza M, Masignani V, Rappuoli R. Emerging experience with meningococcal serogroup B protein vaccines. Expert Rev Vaccines [Internet]. 2017 May 4 [cited 2018 Dec 16];16(5):433–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28375029
17. Campbell G, Bland RM, Hendry SJ. Fever after meningococcal B immunisation: A case series. J Paediatr Child Health [Internet]. 2018 Nov 28 [cited 2018 Dec 17]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30488608
18. Marshall H, Clarke M, Sullivan T. Parental and community acceptance of the benefits and risks associated with meningococcal B vaccines. Vaccine [Internet]. 2014 Jan 9 [cited 2018 Mar 24];32(3):338–44. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0264410X13015636
19. Coleman J. Subject Guides: Systematic Reviews: Using PICO or PICo. [cited 2018 Dec 10]; Available from: https://libguides.murdoch.edu.au/systematic/PICO
20. Assessing Risk of Bias in Included Studies | Cochrane Bias [Internet]. [cited 2018 Jun 24]. Available from: http://methods.cochrane.org/bias/assessing-risk-bias-included-studies
21. Esposito S, Prymula R, Zuccotti GV, Xie F, Barone M, Dull PM, et al. A phase II randomized controlled trial of a multicomponent meningococcal serogroup B vaccine, 4CMenB, in infants (II). Hum Vaccin Immunother [Internet]. 2014 Jul 7 [cited 2018 Feb 25];10(7):2005–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25424810
22. Findlow J, Borrow R, Snape MD, Dawson T, Holland A, John TM, et al. Multicenter, Open- Label, Randomized Phase II Controlled Trial of an Investigational Recombinant Meningococcal Serogroup B Vaccine With and Without Outer Membrane Vesicles, Administered in Infancy. Clin Infect Dis [Internet]. 2010 Nov 15 [cited 2018 Mar 24];51(10):1127–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20954968
23. Snape MD, Voysey M, Finn A, Bona G, Esposito S, Principi N, et al. Persistence of Bactericidal Antibodies After Infant Serogroup B Meningococcal Immunization and Booster Dose Response at 12, 18 or 24 Months of Age. Pediatr Infect Dis J [Internet]. 2016 Apr [cited 2018 Feb 25];35(4):e113–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26756390
24. Vesikari T, Esposito S, Prymula R, Ypma E, Kohl I, Toneatto D, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet [Internet]. 2013 Mar 9 [cited 2018 Mar 24];381(9869):825–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23324563
25. Macias Parra M, Gentile A, Vazquez Narvaez JA, Capdevila A, Minguez A, Carrascal M, et al. Immunogenicity and safety of the 4CMenB and MenACWY-CRM meningococcal vaccines administered concomitantly in infants: A phase 3b, randomized controlled trial. Vaccine [Internet]. 2018 Nov 29 [cited 2018 Dec 2];36(50):7609–17. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0264410X18314932
26. McQuaid F, Snape MD, John TM, Kelly S, Robinson H, Yu L-M, et al. Persistence of specific bactericidal antibodies at 5 years of age after vaccination against serogroup B meningococcus in infancy and at 40 months. Can Med Assoc J [Internet]. 2015 Apr 21 [cited 2018 Feb 25];187(7):E215–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25802309
27. Bryan P, Seabroke S, Wong J, Donegan K, Webb E, Goldsmith C, et al. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. Lancet Child Adolesc Heal [Internet]. 2018 Jun [cited 2018 Nov 19];2(6):395–403. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30169281
28. Nainani V, Galal U, Buttery J, Snape MD. An increase in accident and emergency presentations for adverse events following immunisation after introduction of the group B meningococcal vaccine: an observational study. Arch Dis Child [Internet]. 2017 Oct 9 [cited 2018 Mar 24];102(10):958–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28794096
29. Harcourt S, Morbey RA, Bates C, Carter H, Ladhani SN, de Lusignan S, et al. Estimating primary care attendance rates for fever in infants after meningococcal B vaccination in England using national syndromic surveillance data. Vaccine [Internet]. 2018 Jan 25 [cited 2018 Apr 2];36(4):565–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29246475
30. Perrett KP, McVernon J, Richmond PC, Marshall H, Nissen M, August A, et al. Immune responses to a recombinant, four-component, meningococcal serogroup B vaccine (4CMenB) in adolescents: A phase III, randomized, multicentre, lot-to-lot consistency study. Vaccine [Internet]. 2015 Sep 22 [cited 2018 Feb 25];33(39):5217–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26232542
31. Lee HJ, Choe YJ, Hong Y-J, Kim K-H, Park SE, Kim Y-K, et al. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine in healthy adolescents in Korea—A randomised trial. Vaccine [Internet]. 2016 Feb 24 [cited 2018 Apr 2];34(9):1180–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26826544
32. Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Muñoz A, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet [Internet]. 2012 Feb 18 [cited 2018 Feb 26];379(9816):617–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22260988
33. Kapur S, Bourke T, Maney J-A, Moriarty P. Emergency department attendance following 4-component meningococcal B vaccination in infants. Arch Dis Child [Internet]. 2017 Oct [cited 2018 Feb 25];102(10):899–902. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28637642
34. Murdoch H, Wallace L, Bishop J, Robertson C, Claire Cameron J. Risk of hospitalisation with fever following MenB vaccination: self-controlled case series analysis. Arch Dis Child [Internet]. 2017 Oct 20 [cited 2018 Feb 25];102(10):894–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28931535
35. Section on Clinical Pharmacology and Therapeutics JE, Committee on Drugs HC, Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics [Internet]. 2011 Mar 1 [cited 2018 Oct 12];127(3):580–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21357332
36. Parikh SR, Andrews NJ, Beebeejaun K, Campbell H, Ribeiro S, Ward C, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet (London, England) [Internet]. 2016 Dec 3 [cited 2018 Oct 10];388(10061):2775–82. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673616319213

Nutrition and hydration in sporting children

Stephanie Van Biervliet

Paediatric gastro-enterology and nutrition. Ghent university hospital

Stephanie.vanbiervliet@ugent.be

Abstract

Despite the overall decreased physical activity in children, the proportion engaging in elite sports increases. The activity level can be very demanding putting them at risk for the development of relative energy deficit-in sports. Good guidance of elite youth athletes is necessary. This review summarises the current advises for youth athletes concerning nutrition and hydration. A normal balanced healthy diet taking into account the extra-energy needs for exercise should be sufficient. The micronutrients at risk for deficiency are iron, calcium and vitamin D. Supplements have not proven their benefit and are potentially hazardous for the growing child. Correct hydration during sports is important and parents should be thought how to monitor. Paediatricians have an important role in advising sporting children.

Introduction

Due to their beneficial effect on the body, physical activity and sports became an integral part of health care and medicine[1]. It has a positive influence on aerobic fitness, general health and leads to a stronger hart and bones as well as a better blood pressure and glycaemic control. Furthermore it will improve social contact and mood[2]. In the preventive medicine it has its own visualisation through the movement triangle (fig. 1)[3].

In children sports are promoted in view of prevention since healthy habits learned as a child will more readily be continued through adulthood[4]. Furthermore, it is an important element in the treatment of overweight and obesity in children, but it also improves outcomes of chronic diseases as diabetes and cystic fibrosis amongst others[5,6].

Sport intensity can vary tremendously between recreational sport and elite athletes. Advices will need to be adapted accordingly.

Physical activity in adults shifted from daily activity towards leisure[7]. This evolution resulted in the fact that only 1/3 of the adult population complies with the world health organisation (WHO) guidelines[8,9]. In children physical activity shifted from child-driven recreational free play for pleasure towards adult-driven highly structured deliberate practice devoted to sport-specific skill development[10].

Despite the increased attention for physical activity, the global activity decreased. A Belgian study demonstrated a decreasing caloric intake between 1983 and 2002 in adolescent soccer players[11]. The number and duration of trainings and competitions didn't change. Also the body mass index (BMI) remained identical, therefore the only explanation for this observation is a decreased physical activity outside the soccer practice[11]. If this is the case in highly devoted soccer players this will probably also be the case in the general population.

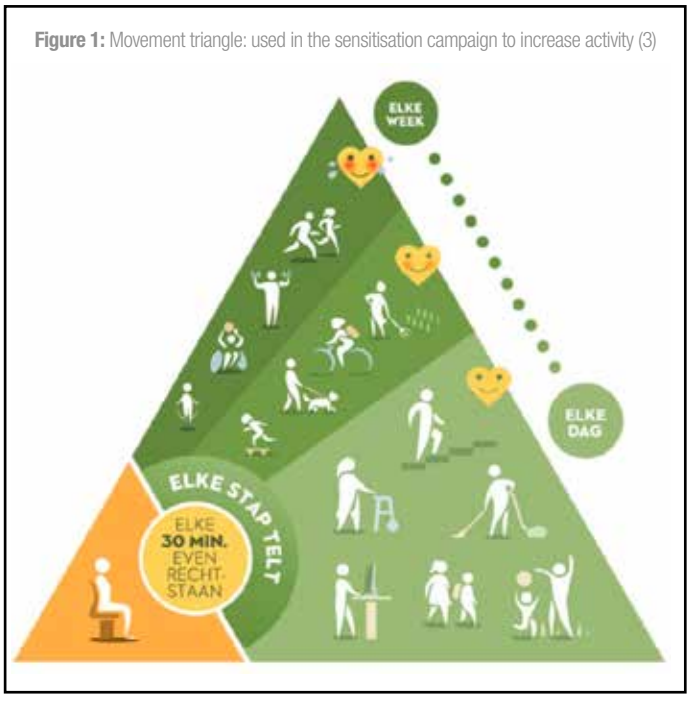


Figure 1: Movement triangle: used in the sensitisation campaign to increase activity (3)

The type of sport performed by the child will mainly be influenced by the preferences of parents whereas intensity lies within the hands of trainers[12]. The risk for injury will increase with early specialisation, an active time above 16 hours a week and competition on (inter-) national level. Periods of rapid growth are especially injury sensitive[13].

Nutrition in sporting children

When guiding youth athletes it is important to be aware of the "relative energy deficit in sports" syndrome (RED-S syndrome)[14]. This entity defined by the international Olympic committee, describes the deleterious effect of an energy imbalance on the body[14] (fig 2). It reaches further than the well-known female athlete triad. It is applicable in both male and female athletes and will negatively influence performance on several levels[15].

Nutrition in athletes is no static entity and must adapt to training and competition intensity, which also fluctuate through time[16].

The purpose of training nutrition is to develop metabolic efficiency whereas competition nutrition provides the adequate energy stores to fuel the demands of the competition and support cognitive function.

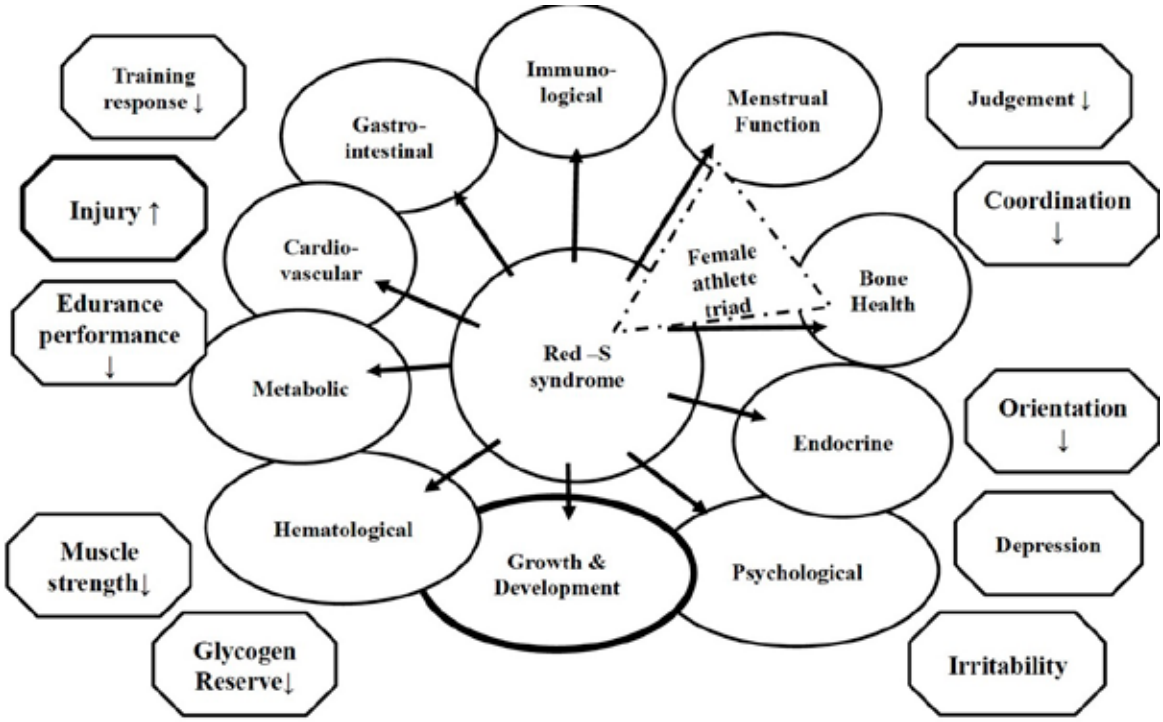
In paediatrics energy needs vary with age and sex[17] (Table 1). These needs will have to be supplemented with the energy needed for the physical activity. The supplementary energy will differ according to age, sex and type of activity. A 30 kg girl will need about 300 kCal for 60 minutes of soccer play whereas a 60 kg boy playing 60 minutes of ice hockey will need almost 1000 kCal[18].

Nutrition of elite athletes should consist of a normal balanced healthy diet including all macronutrients (45-55 energy% carbohydrates, 10-30 energy% protein, 25-35 energy% Fat). Carbohydrates are essential as energy for the exercise but should consist of complex carbohydrates (grains, fruits, vegetables, diary). Proteins are important to build and repair muscle. They are ideally retrieved from lean meat, poultry, fish, dairy, legumes, beans, nuts. Finally, fat is essential, due to its caloric density, to meet caloric needs[16]. Saturated fatty acids and trans-fatty acids should, however, be limited. Therefor, it is advised to give them fresh cooked meals using oils, fish and lean meat. Although supplements are frequently used, they should not be given to children since they didn't prove to improve performance and are potentially dangerous[18].

Table 1: Caloric needs according to age to ensure proper growth according to Purcell (16)

Years	Male	Female
4-6	1800 KCal	1800 KCal
7-10	2000 KCal	2000 KCal
11-14	2500 KCal	2200 KCal
15-18	3000 KCal	2200 KCal

Figure 2: Spoke and wheel figure dapted from Montjoy et al (14). Influences of RED-S on human body (circle) and exercise performance (octagon).



The micronutrients needing extra attention are iron, calcium and vitamin D. Iron needs are higher in adolescents and there might be an insufficient intake associated with increased losses in urine, stools and menses. Therefore, vegetarians, long distance runners and female athletes are at risk for iron deficiency[16]. Dietary iron can be obtained from meat, legumes and whole grains. Calcium and vitamin D are essential tot get an adequate bone accretion during puberty. The daily calcium intake should be questioned since daily calcium intake decreased over the years[11]. Recommended daily allowances (1000 mg 4-8 year-old; 1300 mg during puberty) weren't reached by 50% of soccer players[11]. Finally, indoor athletes and athletes in Northern latitudes are at risk for vitamin D deficiency.

Some diseases, as cystic fibrosis, have higher caloric needs and have an increased risk for RED-S syndrome. Therefor, adapted dietary advice will be needed if these patients want to perform competition sports.

Hydration in sporting children

A good hydration is important in athletes since dehydration leads to decreased performance, concentration and heath regulation[19]. When advising children in their hydration habits, climate circumstances as well as intensity and duration of physical activity needs to be taken into account. Thirst is the physiologic drive for fluid intake but will replace only 50-66% of fluid losses during physical activity, also called voluntary hypohydration[20].

It has, however, also been demonstrated that almost 75% of child athletes will start their physical activity in a hypohydrated state[21]. When athletes start dehydrated they have an increased risk for the development of pseudonephritis[22]. This leads to proteinuria, haematuria and granular casts in the urine after activity.

An educational intervention, teaching athletes to use a urine colour chart not only decreased dehydration at the start of exercise but also improved performance[23]. It can therefore be useful to teach parents and child-athletes to check urinary colour before the exercise. The purpose is to start with light or straw-coloured urine[24].

The weight loss during exercise can give the athlete an idea of how much should be compensated. It is important to measure the weight losses since overhydrating has also its' risks. Activity related hyponatremia is a risk, which exists when there is a mismatch between fluid intake and sodium body reserve[24].

In most cases it will be sufficient to give the child ample opportunity to sip drink water during activity. Parents and trainers should stimulate the children to drink regularly small amounts. The use of sport drinks might only be useful when intense physical activity is maintained for more than 60-90 minutes[24]. The high caloric density of sport drinks is a concern when used inadequately. The intake of sport drinks in children increased dramatically over the years. This intake is mainly influenced by the health believes of the caregivers[25].

Some clinical conditions will need more medical attention when advices concerning hydration are given. Conditions leading to increased salt losses such as patients after total colectomy, ileostomy or cystic fibrosis patients are at risk for important salt and fluid losses during physical activity[26]. Therefore these patients need specific advice regarding salt and fluid intake during exercise[27]. Furthermore, children with obesity display a decreased urinary concentration capacity when facing physical activity induced dehydration[28]. They should be instructed to drink regularly.

After exercise, refuelling should start within 30 minutes. Energy, salt and fluid reserves should be replenished. Chocolate milk has demonstrated to induce more fluid retention compared to water and sports drinks[29]. Furthermore, the nutrient profile of chocolate milk is an excellent post-exercise supplement for replenishing muscle glycogen and building muscle protein[30,31]. Finally, the calcium content of the drink is important as there is a trend for decreasing calcium intake amongst youth athletes good and childhood is a crucial period for bone accretion[11]. Chocolate milk is therefor a low-cost, readily available post-recovery drink for youth athletes.

In young athletes, meal planning is as important as in adults. One should work with main balanced meals and snacks and should build up towards the exercise as well as provide recovery foods[16].

Conclusion

A good guidance of youth athletes but also children with chronic disease is advocated. Alertness for the RED-S syndrome should be high. Finally, children are no small adults and should be protected against potential dangerous supplements, which haven't proven to improve performance.

REFERENCES:

1. Rush E, Coppinger T. Improving health through diet and exercise in children. Eur J Clin Nutr. 2018; 72(9): 1251-4.
2. Marker AM, Steele RG, Noser AE. Physical activity and health-related quality of life in children and adolescents: A systematic review and meta-analysis. Health Psychol. 2018; 37(10): 893-903.
3. https://www.gezondleven.be/themas/beweging-sedentair-gedrag/bewegingsdriehoek.
4. Arpino B, Gumà J, Julià A. Early-life conditions and health at older ages: The mediating role of educational attainment, family and employment trajectories. PLoS One. 2018; 13(4): e0195320.
5. Cuda SE, Censani M. Pediatric Obesity Algorithm: A Practical Approach to Obesity Diagnosis and Management. Front Pediatr. 2019; 6: 431.
6. Coleman N, Nemeth BA, LeBlanc CMA. Increasing Wellness Through Physical Activity in Children With Chronic Disease and Disability. Curr Sports Med Rep. 2018; 17(12): 425-32.

7. Loyen A, Clarke-Cornwell AM, Anderssen SA, Hagströmer M, Sardinha LB, Sundquist K, et al. Sedentary time and physical activity surveillance through accelerometer pooling in four European countries. Sports Med. 2017; 47(7): 1421-35.

8. Borodulin K, Harald K, Jousilahti P, Laatikainen T, Männistö S, Vartainen E. Time trends in physical activity from 1982 to 2012 in Finland. Scan J Med Sci Sports. 2016; 26(1): 93-100.

9. World Health Organization. Global recommendations on physical activity for health. 2010; World Health Organization, Geneva. https://www.who.int/dietphysicalactivity/factsheet_recommendations/en/

10. Maffulli N. The growing child in sport. Br Med Bull. 1992; 48(3): 561-8.

11. Van Biervliet S, Van Biervliet JP, De Neve J, Watteyne R, D'Hooghe M. Nutritional intake evolution in adolescent sporting boys over the last two decades. Acta Clin Belg. 2011; 66(4): 280-2.

12. Baxter-Jones AD, Maffulli N; TOYA Study Group. Parental influence on sport participation in elite young athletes. J Sports Med Phys Fitness. 2003; 43(2): 250-5.

13. Jayanthi N, Pinkham C, Dugas L, Patrick B, Labella C. Sports specialization in young athletes: evidence-based recommendations. Sports Health. 2013; 5(3): 251-7.

14. Mountjoy M1, Sundgot-Borgen J, Burke L, Carter S, Constantini N, Lebrun C, et al. The IOC consensus statement: beyond the Female Athlete Triad--Relative Energy Deficiency in Sport (RED-S). Br J Sports Med. 2014(7); 48: 491-7.

15. Statuta SM, Asif IM, Drezner JA. Relative energy deficiency in sport (RED-S). Br J Sports Med. 2017; 51(21): 1570-1.

16. Purcell LK, Canadian paediatric society, paediatric sports and exercise medicine section. Sport nutrition for young athletes. Paediatr Child Health 2013(4); 18: 200-2.

17. Litt A. Fuel for young athletes: essential foods and fluids for future champions. Windsor, human kinetics 2004.

18. McDowell JA. Supplement use by young athletes. J sport scie med 2007; 6(3): 337-42.

19. Rowland T. Fluid replacement requirements for child athletes. Sports Med 2011; 41(4): 279-88.

20. Bar-Or O, Dotan R, Inbar O, Rotshtein A, Zonder H. Voluntary hypohydration in 10- to 12-year-old boys. J Appl Physiol Respir Environ Exerc Physiol. 1980; 48(1): 104-8.

21. Arnaoutis G1, Kavouras SA, Angelopoulou A, Skoulariki C, Bismpikou S, Mourtakos S, Sidossis LS. J Strength Cond Res. Fluid Balance During Training in Elite Young Athletes of Different Sports. 2015; 29(12): 3447-52.

22. Van Biervliet S, Van Biervliet JP, Watteyne K, Langlois M, Bernard D, Vande Walle J. Pseudonephritis is associated with high urinary osmolality and high specific gravity in adolescent soccer players. Pediatr Exerc Sci. 2013; 25(3): 360-9.

23. Kavouras SA, Arnaoutis G, Makrillos M, Garagouni C, Nikolaou E, Chira O, et al. Educational intervention on water intake improves hydration status and enhances exercise performance in athletic youth. Scand J Med Sci Sports. 2012; 22(5): 684-9.

24. Bergeron MF. Hydration in the Pediatric Athlete - How to Guide Your Patients. Cur Sports Med Reports 2015; 14(4): 288-93.

25. Zytnick D, Park S, Onufrak SJ. Child and caregiver attitudes about sports drinks and weekly sports drink intake among US youth. Am J Health promotion 2016; 30: e110-9.

26. Bar-Or O, Blimkie CJ, Hay JA, MacDougall JD, Ward DS, Wilson WM. Voluntary dehydration and heat intolerance in cystic fibrosis. Lancet 1992; 339(8795): 696-9.

27. Lewis D, Blow A, Tye J, Hew-Butler T. Considering exercise-associated hyponatriemia as a continuum. BMJ case rep 2018; pii: bcr-2017-222916.

28. Baert J, Van Biervliet S, Van Biervliet JP, Vande Walle J, Bentin F, De Graeve L, Vandenbossche D, De Guchtenaere A. Influence of physical activity on hydration state in children with obesity before and after a weight loss program. Acta Clin Belg. 2018; 20: 1-6.

29. Shirreffs SM, Watson P, Maughan RJ. Milk as an effective post-exercise rehydration drink. Br J Nutr. 2007; 98(1): 173-80.

30. Thomas K, Morris P, Stevenson E. Improved endurance capacity following chocolate milk consumption compared with 2 commercially available sport drinks. Appl Physiol Nutr Metab 2009, 34 (1), 78-82.

31. Born KA, Dooley EE, Cheshire PA, McGill LE, Cosgrove JM, Ivy JL, Bartholomew JB. Chocolate Milk versus carbohydrate supplements in adolescent athletes: a field based study. J Int Soc Sports Nutr. 2019; 16(1): 6.

Jong geleerd
is oud gedaan

Het natuurlijke mineraalwater **SPA REINE** wordt jarenlang door de natuur gefilterd **op een plek die strikt wordt beschermd tegen elke vorm van vervuiling, wat een uitzonderlijke zuiverheid oplevert.**
Door zijn zeer lage mineraalgehalte is het bij uitstek geschikt voor de bereiding van babyvoeding.

OFFICIËLE PARTNER
GOLD - 2019
SPA STEUNT DE BELGISCHE VERENIGING VOOR KINDERGENEESKUNDE

SPA
NATURAL SINCE 1583
Op het leven

Atypical severe combined immunodeficiency (SCID): case report and literature review

Jan Vandersnickt[1], Isabel De La Fuente Garcia[2], Giorgia Bucciol[3], Leen Moens[4], Rebeca Pérez de Diego[5], Isabelle Meyts[6]

[1] Department of Paediatric Immunology, University Hospital Leuven, Leuven, Belgium.
[2] Centre Hospitalier de Luxembourg (CHL), Luxembourg.
[3] Department of Paediatric Immunology, University Hospital Leuven, Leuven, Belgium.
[4] Research team of Paediatric Immunology, University Hospital Leuven, Leuven, Belgium.
[5] Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health research, La Paz Hospital, Madrid 28046, Spain.
Interdepartmental Group of Immunodeficiencies, Madrid, Spain.
[6] Head of Department of Paediatric Immunology, University Hospital Leuven, Leuven, Belgium.

isabelle.meyts@uzleuven.be

Key words

Atypical severe combined immunodeficiency, autoimmune pancreatitis, severe flu, RAG1 deficiency

Abstract

Severe combined immunodeficiency (SCID) is one of the most severe forms of primary immunodeficiency characterized by the disturbed development of functional T- and B-cells. The clinical heterogenicity of the disorder is the result of mutations in various genes. Next to typical SCID, Omenn syndrome and Reticular Dysgenesis, leaky or atypical SCID is described as a separate entity.

Hypomorphic mutations in SCID-associated genes allow residual protein function and partial T lymphocyte development, which causes severe infections to persist until after the neonatal period.

Here we describe a novel compound *RAG1* mutation in a patient with a late presentation of severe infectious disease with common pathogens and autoimmunity. We performed an extensive literature review specifically on atypical SCID and to our knowledge, this is the first description of an autoimmune pancreatitis in this context.

Subsequently, we will indicate an important diagnostic pitfall: despite a normal number of CD3+ T-cells and a normal lymphocyte count, our patient presents with a SCID phenotype because of a low percentage of naive T-cells and a skewed T-cell receptor pattern.

More in general we stress that the unusual evolution of infections with common pathogens and the development of extensive infections after routine vaccination with live vaccines (varicella zoster virus, mumps measles rubella) should prompt the pediatrician to an exhaustive immunological screening for SCID. The absence of the thymus on a plain radiograph remains a diagnostic hallmark that should not be overlooked.

Introduction

Severe combined immunodeficiency (SCID) is one of the most severe forms of primary immunodeficiency characterized by the disturbed development of functional T- and B-cells.[1]

A large retrospective cross-sectional study of the Primary Immune Deficiency Treatment Consortium (PIDTC) published in 2013 defined quantitative immunological parameters for the identification and qualification of SCID[2,3]. Typical SCID is characterized by a complete arrest in T- and B-cell development, with a number of CD3 T-cells below 300/µl and very low T-cell function (<10% of lower limit of normal as measured response to phytohemagglutinin (PHA)).

Atypical or leaky SCID is defined by CD3 T-cells <1000/µl before the age of 2 year, less than 30% of normal T-cell function (measured as response to PHA) and absence of maternal engraftment.

Mutations in either one of two recombination activating genes (RAG1 and RAG2) underlie severe combined immunodeficiency (SCID) in up to 30% of cases[4].

RAG1 and RAG2 play a crucial role in the assembly of antigen receptor genes by mediating V(D)J recombination, an essential process in the generation of the variable region of the B- and T cell receptors by composing different sets of variable (V), joining (J) and diversity (D) elements. A diverse antigen receptor repertoire is created by rearranging these V(D)J elements.

Partial RAG1/2 deficiency can pose a diagnostic problem as the residual RAG activity can result in a clinical picture of combined immunodeficiency with autoimmunity and granulomatous inflammation.

Other mutations in genes causing atypical SCID include adenosine deaminase (ADA), IL2RG, ILR7, JAK3 and several others.[5] The last three typically present with T-B+ leaky SCID.

We here present a patient with T-B-NK+ leaky SCID presenting with autoimmune features and acute respiratory distress syndrome (ARDS) due to H1N1 influenza A virus infection. Two heterozygous missense variants in RAG1 were found.

We aim to review the literature on atypical SCID to investigate whether the presentation with severe H1N1 infection and autoimmune pancreatitis has already been described. Moreover, our goal is to raise awareness on atypical SCID among pediatricians by indicating clinical hallmarks and diagnostic pitfalls.

Case report

A sixteen-month-old girl from European descent was referred to our hospital for an immunological work-up. She was the first child of non-consanguineous parents with a negative family history.

The neonatal period was unremarkable, followed by an appropriate weight gain and normal development.

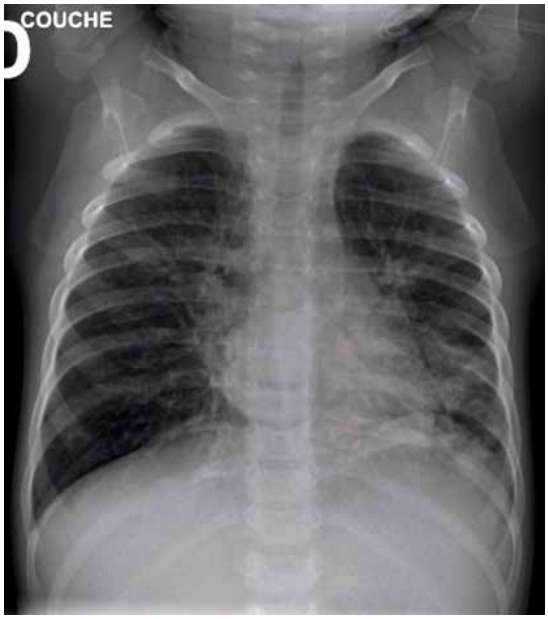
The patient had a recent history of severe respiratory infections with common pathogens, accompanied by failure to thrive.

At the age of eleven months she was hospitalized for bronchiolitis with prolonged oxygen need. Three months later the patient was admitted to the pediatric intensive care unit (PICU) for ARDS in the context of H1N1 influenza pneumonia. Respiratory insufficiency remained present despite treatment with broad spectrum antibiotics, steroids and supportive care. Two weeks after admission nasopharyngeal polymerase chain reaction was positive for Streptococcus pneumoniae, cytomegalovirus (CMV) and human herpes virus type 6 (HHV-6). A bronchoscopy confirmed CMV-pneumonia (53600 copies/ml) and also revealed Pneumocystis jiroveci (PCP) with antigenic and PCR testing on bronchoalveolar lavage: the infection was treated with trimethoprim-sulfamethoxazole for 14 days. CMV treatment with valganciclovir was correctly initiated before referral.

Next to lymphadenopathy and ARDS, chest X-ray and CT-scan revealed an only very small thymus (Pict.1-2). Moreover, significant adverse reactions following vaccination were reported: hemorrhagic varicella lesions appeared eighteen days after Varicella zoster (VZV) inoculation, only waning after starting acyclovir treatment. There also was an extensive measles rash ten days after vaccination with live measles-mumps-rubella (MMR). The patient developed a rotavirus colitis after administration of Rotarix.

An immunological work-up showed normal levels of T- and B- lymphocytes, with low naive T-cells and skewed TCR V beta repertoire (Fig.2). A markedly high level of IgG (22.4g/l, 3.0-9.8g/l) and IgM (5.9g/l, 0.2-1.6g/l) corresponded to impaired antibody response and multiple autoantibodies, leading to an autoimmune hemolytic anemia (AIHA) and autoimmune pancreatitis. We confirmed that a direct Coombs test was positive with C3d and IgG specificity.

Picture 1: Chest X-ray on admission. Notice the bilateral bronchopneumonia and absence of the thymus.



Picture 2: Chest CT-scan on admission.

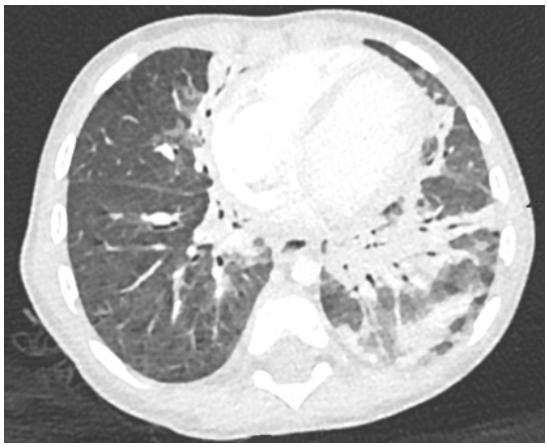


Figure 1: Sanger sequencing of the RAG1-gene in the patient and parents.

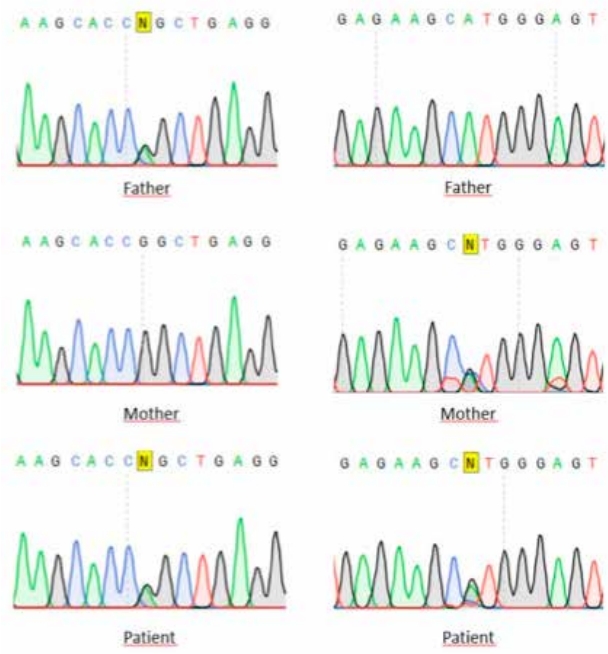


Figure 2: The patients skewed T-cell receptor pattern.

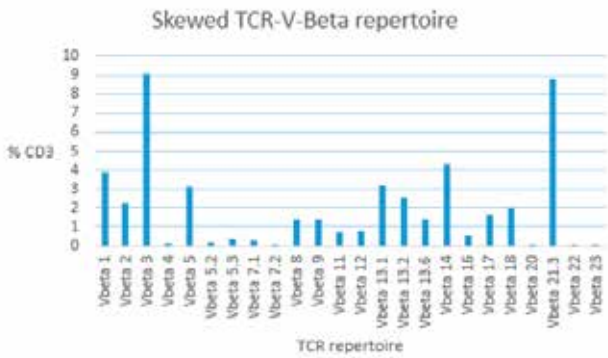
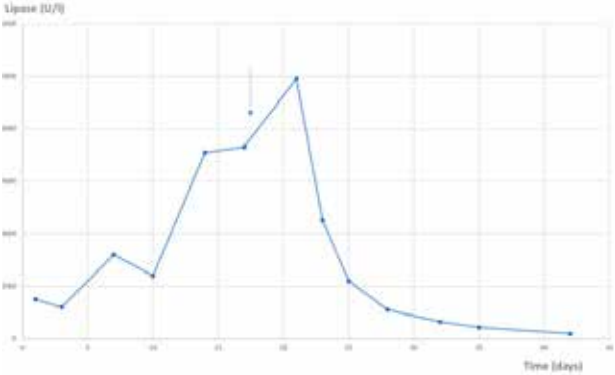


Figure 3: Lipase values in function of time after admission. The vertical arrow indicates initiation of steroids.



Pancreatic autoinflammation was successfully restrained by administration of high doses of steroids and a dose of rituximab and completely resolved upon start of conditioning (Fig.3). The patient received a haploidentical stem cell transplantation 2 months after presentation with ARDS.

Materials and methods

Genomic DNA was extracted from whole blood using QIAmp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genomic regions of RAG1 containing exons and intron-exon boundaries were amplified (primers sequences available on request). Sanger sequencing was performed on an ABI 3730 XL Genetic Analyzer (Applied Biosystems, Foster City, California) at LGC Genomics, Berlin, Germany. Sequences were analyzed using Chromas 2.6.4 (Technelysium Pty Ltd, Brisbane, Australia) and were aligned with the consensus coding sequence in nucleotide basic local alignment search tool (BLAST).[6]

Upon referral whole exome sequencing was performed for the SCID gene panel, followed by targeted sequencing of RAG1.

Informed consent was obtained from the patient's family, in accordance with the guidelines of the ethics committee.

Genetics

Whole exome sequencing (WES) and Sanger sequencing (Fig.1) confirmed the suspected diagnosis.

WES showed two heterozygous missense variants in RAG1: c.1229G>A (p.R410Q), inherited from the father, and c.1835A>G (p.H612R) inherited from the mother.

The p.R410Q mutation affects the nonamer-binding region (NBR), while p.H612R affects the heptamer-binding region (HBR) of RAG1.

Missense mutations in the NBR and in the HBR result in a significantly lower activity level of the RAG1 protein than mutations in other regions, which is consistent with the critical roles played by the NBR and HBR domains in DNA recognition and binding.[7] The mutation p.R410Q (c.1229G>A) was first described in 2001 in a RAG1 compound heterozygous patient (p.R410Q/p.R841W) diagnosed with atypical SCID.[8] VDJ recombination activity for the p.R410Q mutation is 0% of the wildtype RAG activity and the pathogenicity prediction is 90%.[9] The p.H612R (c.1835A>G) mutation is predicted to affect splicing; a patient homozygous for the c.1835A>G mutation has been reported with a typical SCID phenotype.

Moreover, a compound heterozygous mutation in RAG1, p86VfsX32 (c.256_257delAA) and p.H612R (c.1835A>G), has been documented in a patient presenting with 'common variable immunodeficiency' with a history of recurrent sinopulmonary infections, viral infections and recurrent autoimmune disease with cytopenia and vitiligo.[10]

In conclusion, there can be no doubt about the pathogenicity of the RAG1 variants found in our patient.

Discussion

We present a patient with leaky SCID syndrome due to proven pathogenic RAG1 mutations, allowing residual T and B cell development. This has recently been linked to delayed-onset combined immune deficiency with granulomas and/or autoimmunity (CID-G/AI) and abnormalities of the peripheral T and B cell repertoire.[11] Defective lymphocyte maturation leads to the production of polyreactive autoantibodies, which in our patient initiated AIHA and pancreatitis, successfully treated with high doses of steroids and rituximab.

In adults, type 1 autoimmune pancreatitis is characterized by increased serum IgG4 levels, pancreatic sclerosis by lymphoplasmacytic infiltration and steroid responsiveness.[12] Our patient showed extremely high levels of total IgG and IgM, pancreatic inflammation and sclerosis on ultrasound yet a very good response to steroids. This autoimmunity has recently been studied in a mouse model.[7] However to our knowledge, this is the first case report of autoimmune pancreatitis in the context of a leaky SCID syndrome. This is an important contribution to the constantly expanding literature on SCID.

Defective B cell maturation is not the only suggested cause of autoimmunity in primary immunodeficiencies.[13] Inappropriate survival of autoreactive T cells together with low number of regulatory T cells lacking TCR diversity may also contribute to tissue damage.[14,15]

Cytopenia is the most common autoimmune manifestation, whereas RAG diagnosis is often delayed in the setting of autoimmunity without serious infection.[16]

Next to autoimmunity, there are important observations to make on the viral infections, mainly on CMV and influenza. A recent large retrospective cohort analysis shows that elevated γδ T cells are a major feature in atypical SCID, showing elevated proportions (>15% of CD3) in 58% of cases.[17] Interestingly, γδ T cell expansion is significantly higher in all 12 cases with RAG deficiency and concomitant CMV infection, suggesting that CMV triggers the expansion, because no association with other infectious diseases are seen. This hypothesis had already been made in 2005 emphasizing the role of the genetic background and microbial environment in determining disease phenotype.[18] These 12 RAG cases also show a very high rate of 84% of autoimmune cytopenia (mainly AIHA), triggered by infection but also by cross reaction with self-antigens.

Concerning influenza, this is not the first case description of a severe H1N1 infection leading to the diagnosis of SCID.[19] It is clear that development of alternative efficient antiviral agents against influenza is needed as only few antivirals are available and mortality is proven to be higher in the presence of viral infections pre-hematopoietic cell transplant.[20]

Nevertheless, in our case the clue to the diagnosis of SCID not only came from the ARDS in the context of influenza, CMV and PCP but from the presentation of live-viral vaccine induced disease.

Live vaccine disease always is an important manifestation of an impaired T cell immune response.

Finally, we wish to stress once again the general key message that the finding of total lymphocyte counts < 3000 per microliter in any child younger than 1 year, regardless of immunoglobulin levels, should prompt follow-up and ruling out severe combined immunodeficiency. Unlike for many other disease, early diagnosis and treatment in SCID truly results in lower mortality and improved outcome.

Conclusion

We describe a patient with T-B-NK+ leaky SCID presenting with autoimmune features and ARDS due to H1N1 influenza A virus infection. A novel underlying predicted pathogenic compound heterozygous mutation in RAG1 is described.

It is the first time that autoimmune pancreatitis is described in atypical SCID.

The unusual evolution of infections with common pathogens and the development of infections after routine vaccination with live vaccines (VZV, MMR) should prompt the pediatrician to an exhaustive immunological screening for SCID, as an early diagnosis may alter the patient's clinical course.[21]

The absence of the thymus on a plain radiograph remains a diagnostic hallmark that should not be overlooked.

Be aware that a normal total lymphocyte count and CD3 number can be misleading: tests should always include naive T-cells, proliferation tests and TCR-repertoire in order not to miss the patients presenting with leaky SCID. More in general, the presentation of a child with a life-threatening infection with a common pathogen should at least alert the physician to perform some baseline immunological screening.

Acknowledgments

I thank Professor Isabelle Meyts for scientific advice and continuous teaching.

Table 1: Blood results on admission. Notice the low naïve T-cells, high antibodies and impaired response to PHA.
(CADD: combined annotation dependent depletion; MSC: mutation significance cutoffs).

Blood results			(on admission)
Hemoglobin	10.2	g/dl	11.0 - 13.5
Reticulocytes	95	109/l	20 - 100
Platelets	547	109/l	150 - 450
WBC count	8.01	109/l	
Neutrophils	28.3	%	32
Monocytes	16.2	%	5
Eosinophils	7.4	%	3
Basophils	2.0	%	<3
Lymphocytes	46.1	%	61
CD19	0.84	10^9/l	0.6 - 3.1
CD3+	1.23	10^9/l	1.4 - 8.0
CD4+ CD8-	0.34	10^9/l	0.9 - 5.5
CD4- CD8+	0.40	10^9/l	0.4 - 2.3
CD27+CD45RA+	20	% of CD3	
HLA-DR	61.7	% of CD3	
CD3+CD4-CD8-	30	%	
NK-cells	1.5	10^9/l	0.1 - 1.4
IgG	29.9	g/l	3.0 - 9.8
IgA	0.89	g/l	0.1 - 1.1
IgM	4.1	g/l	0.2 - 1.6
Anti-VZV	positive		
Anti-tetanus	0.24	UI/ml	> 0.50
PHA	33.3	10^3 cpm	
Index	139	>5.00	
Bas. medium	0.24	10^3 cpm	
c.1229G>A, p.R410Q	CADD	29.600	
	MSC	1.118	
c.1835A>G, p.H612R	CADD	23.600	
	MSC	1.118	

REFERENCES:

1. Le Deist F, Moshous D, Villa A, Al-Herz W, Roifman CM, Fisher A, Notarangelo LD. Comined T- and B-cell Immunodeficiencies. In: Rezaei N, Aghamohammadi A, Notarangelo LD, editors. Primary Immunodeficiency Diseases. Berlin Heidelberg; 2017. P. 83-182.
2. Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: The Primary Immune Deficiency Treatment Consortium experience. The Journal of allergy and clinical immunology; 2013. Vol 133.
3. Griffith LM, Cowan MJ, Notarangelo LD, Kohn DB, Puck JM, Shearer WT. et al. Primary Immune Deficiency Treatment Consortium (PIDTC) update. J Allergy Clin Immunol. 2016 Aug;138(2):375-85.
4. Dorsey MJ, Puck JM. Newborn Screening for severe combined immunodeficiency in the United States: Lessons Learned. Immunol Allergy Clin North Am. 2019 Feb;39(1):1-11.
5. Felgentreff K, Perez-Becker R, Speckmann C, Schwarz K, Kalwak K, Markelj G et al. Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency. Clin Immunol. 2011 Oct;141(1):73-82.
6. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool. J Mol Biol. 1990;215(3):403–10.
7. Lee YN, Frugoni F, Dobbs K, Walter JE, Giliani S, Gennery AR et al. A systematic analysis of recombination activity and genotype-phenotype correlation in human recombination-activating gene 1 deficiency. The Journal of allergy and clinical immunology. 2014;133(4):1099-1108.
8. Villa A, Sobacchi C, Notarangelo LD Bozzi F, Abinun M, Abrahamsen TG et al. V(D)J recombination defects in lymphocytes due to RAG mutations: severe immunodeficiency with a spectrum of clinical presentations. Blood. 2001 Jan; 97 (1):81-88.
9. Lee YN, Frugoni F, Dobbs K, Walter JE, Giliani S, Gennery AR et al. A systematic analysis of recombination activity and genotype-phenotype correlation in human recombination-activating gene 1 deficiency. The Journal of allergy and clinical immunology. 2014;133(4):1099-1108.
10. Buchbinder D, Baker R, Lee YN, Ravell J, Zhang Y, McElwee J et al. Identification of Patients with RAG-mutations previously diagnosed with Common Variable Immunodeficiency Disorders. Journal of clinical immunology. 2015;35(2):119-124.
11. Ott de Bruin LM, Bosticardo M, Barbieri A, Lin SG, Rowe JH, Poliani PL et al. Hypomorphic RAG1 mutations alter the pre-immune repertoire at early stages of lymphoid development. Blood. 2018;132(3):281-292.
12. Okazaki K, Tamiyama T, Mitsuyama T, Sumimoto K, Uchida K. Diagnosis and classification of autoimmune pancreatitis. Autoimmune Rev. 2014; 13(4-5):451-8.
13. Gennery A. Recent advances in understanding RAG deficiencies. F1000Research 2019; 8:148.
14. Avila EM, Uzel G, Hsu A, Milner JD, Turner ML, Pittaluga S et al. Highly Variable Clinical Phenotypes of Hypomorphic RAG1 Mutations. Pediatrics. 2010; Vol.126(5), 1248-1252.
15. Milner JD, Fasth A, Etzioni A. Autoimmunity in severe combined immunodeficiency (SCID): lessons from patients and experimental models. Journal of allergy and clinical immunology. 2008;28 S1: 29-33.
16. Farmer JR, Foldvari Z, Ujhazi B, De Ravin SS, Chen K, Bleesing JH et al. Outcomes and treatment strategies for autoimmunity and hyperinflammation in patients with RAG deficiency. The Journal of Allergy and Clinical Immunology: In Practice. Available online 12 March 2019; In Press, Accepted Manuscript.
17. Tometten I, Felgentreff K, Hönig M, Hauck F, Albert MH, Niehues T et al. Increased proportions of γδ T lymphocytes in atypical SCID associate with disease manifestations. Clin Immunol. 2019; 201:30-34.
18. de Villartay JP, Lim A, Al-Mousa H, Dupont S, Déchanet-Merville J, Coumau-Gatbois E et al. A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. J Clin Invest. 2005;115(11):3291-9.
19. Pichon M, Picard C, Simon B, Gaymard A, Renard C, Massenavette B et al. Clinical management and viral genomic diversity analysis of a child's influenza A(H1N1) pdm09 infection in the context of a severe combined immunodeficiency. Antiviral Research 160. 2018; 1-9.
20. Heimall J, Logan B, Cowan M, Notarangelo LD, Griffith LM, Puck JM et al. Immune reconstitution and survival of 100 SCID patient post-hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017; 21;130(25):2718-2727.
21. van der Burg M, Gennery AR. Educational paper. The expanding clinical and immunological spectrum of severe combined immunodeficiency. Eur J Pediatr. 2011;170(5):561-71.

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
- A base de coton bio
- 99% d'eau purifiée
- 0% alcool, parabène, phénoxyéthanol, colorant, parfum

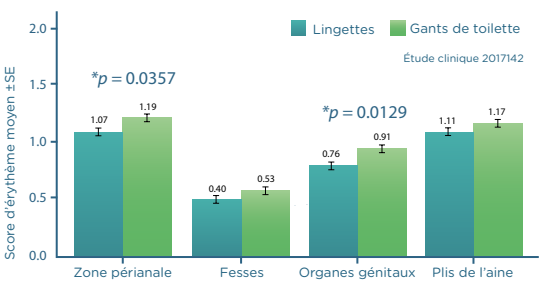
Une nouvelle étude clinique démontre que les lingettes Pampers® Aqua Pure sont au moins aussi douces qu'un gant de toilette imbibé d'eau

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

Is Autosomal Dominant Polycystic Kidney Disease a pediatric disorder? From AdultDPKD to ADPediatricKD

PhD thesis presented on 13th of December 2018 at KU Leuven, Leuven, Belgium.

Stéphanie De Rechter[1,2]

Promotors: Djalila Mekahli[1,2]

[1] Department of Pediatric Nephrology, University Hospitals Leuven, Leuven, Belgium.

[2] PKD Research Group, Department of Development and Regeneration, KU Leuven, Leuven, Leuven, Belgium.

Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects on average 1 in 1000 live births and is therefore the most common monogenic cause of end-stage kidney disease (ESKD)[1]. The disorder arises due to mutations in the *PKD* genes (*PKD1*and *PKD2*), encoding the polycystin proteins [2]. It is well known that adult patients with a PKD1 mutation are more severely affected than those with a PKD2 mutation. However, the underlying pathophysiology remains unclear [3-7]. Two other genes have recently been described to cause atypical forms of ADPKD, namely *GANAB* and *DNAJB11* [8,9,10].

ADPKD is mainly characterized by the progressive development and growth of bilateral renal cysts in all nephron segments, ultimately leading to ESKD in 50% of patients in their 6th decade [11]. Moreover, as a ciliopathy it is a systemic disorder, comprising extra-renal features such as hepatic cyst formation, cardiovascular anomalies including hypertension and intracranial arterial aneurysms, herniation and possible bone involvement (Figure 1) [11]. In adults, the only currently available targeted and disease-modifying option is the selective arginine vasopressin receptor type 2 (AVPR2) antagonist tolvaptan. The latter slows down disease progression, but comprises important adverse effects, mostly related to the increased aquaresis [12]. Currently, the safety, pharmacokinetics, tolerability and efficacy of this drug is under investigation in children and adolescents with ADPKD. Several Belgian centers are participating in this European clinical trial (NCT02964273).

As the majority of patients remains a- or oligo-symptomatic until adulthood, ADPKD is still often considered as a late-onset disease [13]. However, childhood comorbidities of ADPKD might be underdiagnosed if not actively looked for by caregivers. Lately, the awareness is growing that in some patients the clinical course of ADPKD begins early in life, although in a variable way. Indeed, the disease comprises an extensive phenotypic spectrum [14]. Moreover, children might be diagnosed with ADPKD because of various reasons, which explains the heterogeneity of the population, together with the phenotypic spectrum.

Still, guidelines on the management of both children at-risk for ADPKD due to a positive family history and those diagnosed with ADPKD are absent. Also diagnostic criteria and prognostic indicators for childhood ADPKD are lacking, while both are available for the adult patient population [15-17].

Obviously, children might be regarded as the pre-eminent targets for coming therapies. As they are in earlier disease stages, they might have a higher therapy benefit compared to patients with more extensive renal damage. Also, early detection and prevention of co-morbidities and initiating life style measures early in life might result in preserving long-term renal function. The main focus of this PhD project was to explore the current available data on childhood ADPKD, to gain knowledge on the pediatric phenotype and to expand research in this field in order to broaden the AdultDPKD with an ADPediatricKD view.

Clinicians' attitude towards family planning and timing of diagnosis [18]

Several ethical aspects in the management of ADPKD are controversial, including family planning and testing for disease presence in at-risk individuals [19]. In order to assess the opinion and current clinical practice of European caregivers, we performed an online questionnaire, validated by experts in the field. European pediatric and adult nephrologists, as well as geneticists were eligible to be included as a respondent.

A total of 410 caregivers (53% male, mean (SD) age of 48 (10) years) responded, including 216 pediatric nephrologists, 151 adult nephrologists, and 43 clinical geneticists.

All groups agreed to encourage clinical testing in asymptomatic at-risk individuals, both minors and adults. Only the geneticists would advise to perform genetic testing in asymptomatic at-risk adults ($p<0.001$). Regarding the ethical justification of prenatal genetic diagnosis, termination of pregnancy and pre-implantation genetic diagnosis (PGD) for ADPKD, we observed statistically significant disagreement. Particularly the case of PGD appeared ethically justified according to geneticists (4.48 (1.63) in a 6-point Likert response scale), whereas pediatric (3.08 (1.78); $p<0.001$) and adult nephrologists (3.66 (1.88); $p<0.05$) were less convinced.

This study suggests that most clinicians support clinical testing of at-risk individuals. However, agreement on genetic testing in asymptomatic offspring and on advise on family planning is clearly lacking. Therefore, this highlights the urgent need for a multidisciplinary consensus, to avoid that ADPKD families are being given conflicting information. A first initiative which is highly valuable here is the ADPKD Patient Route Map. The latter was launched in 2018 and is freely available online for patients (currently in English, French and German, other languages will follow, https://pkdinternational.org/adpkd-route-map)

Evaluation of disease manifestations and defining possible progression markers in childhood ADPKD

Cardiovascular phenotype [20]

Ambulatory blood pressure (BP) monitoring (ABPM) is the preferred method to diagnose hypertension in children [21, 22]. However, ABPM data in children with ADPKD remain scant (23). Therefore, we participated in the European multicentric retrospective cohort study "ADPKiDs", in which the prevalence of BP abnormalities was analyzed. Also, we analyzed ABPM vs. clinic BPM in children from the Leuven pediatric ADPKD cohort to evaluate the added value of ABPM in this patient group.

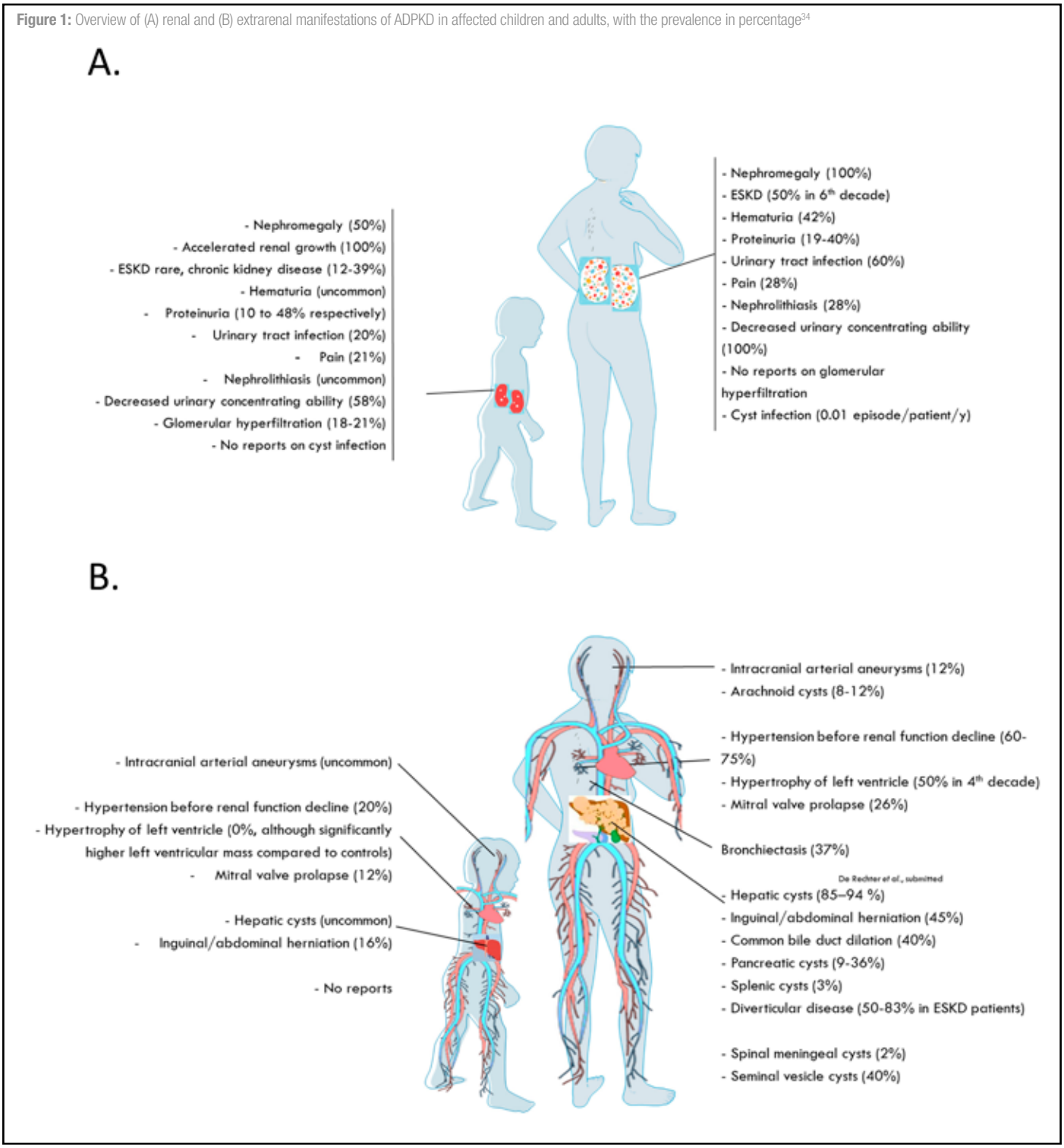
In the ADPKiDs study, 310 patients, equally distributed between genders, were included of which more than 10% were part of the Leuven cohort. One third of the study patients (35%) had either hypertension or was under treatment for hypertension. Less than half of the cohort had BP values within the optimal range (<75th percentile) without taking BP medications. In addition, half of the cohort lacked a significant BP dipping at night (52%) and nearly one-fifth (18%) had isolated nocturnal hypertension. Moreover, analysis of ABPM vs. clinic BPM in 50 patients from the Leuven cohort revealed important proportions of white-coat and masked hypertension.

Altogether, these findings support the need of routinely performing ABPM in ADPKD children and probably in children at-risk as well. However, it is still unclear whether some of these BP phenotypes, such as non-dipping, should prompt antihypertensive treatment or not.

Phosphate and bone mineral metabolism [24]

Previously, reports showed that adult ADPKD patients with preserved renal function, display hypophosphatemia, together with high levels of the phosphaturic hormone fibroblast growth factor 23 (FGF23) and low levels of soluble Klotho (sKlotho), the FGF23 co-receptor [25]. The latter explained the relative FGF23 hypo-

Figure 1: Overview of (A) renal and (B) extrarenal manifestations of ADPKD in affected children and adults, with the prevalence in percentage[34]



responsiveness in this cohort [26]. Triggered by these findings, we evaluated the phosphate and bone mineral metabolism in pediatric ADPKD, compared to what is known in adult ADPKD patients, in an observational cross-sectional multicenter study.

We included 92 children diagnosed with ADPKD (52 males, mean (SD) age: 10.2 (5.0) years) and 22 healthy controls (HC, 10 males, mean SD age: 10.3 (4.1) years).

ADPKD children had significantly lower serum phosphate levels compared to HC. A low ratio of phosphorus tubule maximum to glomerular filtration rate (TmP/GFR) was observed in 24% of patients, although not significantly different from HC. Serum FGF23 and sKlotho levels were comparable between patients and HC. Although FGF23 levels were not different from controls, they should be considered inappropriate, given the concomitant hypophosphatemia. We hypothesized that the differences in FGF23-sKlotho axis in children vs. adults might be caused by a higher skeletal and extra-skeletal FGF23 production in adults, together with the occurrence of a peripheral FGF23 resistance in the latter. This hyporesponsiveness is appears to be related to sKlotho deficiency, shown to be correlated with the total kidney volume (TKV).

In addition, we showed decreased bone alkaline phosphatase levels in ADPKD children, suggesting suppressed bone formation.

This is the first report demonstrating hypophosphatemia and suppressed bone formation in a pediatric ADPKD cohort with preserved renal function, compared to HC. Further studies are required to elucidate the underlying pathophysiology and potential clinical consequences.

Three-dimensional ultrasonography (3DUS) as an alternative to MRI for measuring kidney volume [27]

TKV, measured by magnetic resonance (MR), is a validated disease progression marker in adults with ADPKD [28-32]. In childhood however, performing MR is burdensome. Indeed, in young children (<5y), this always requires general anesthesia or sedation; and even in older children this might be necessary because of anxiety. Therefore, we need alternative imaging methods. Although two-dimensional (2D) ultrasound (US) is now used worldwide to diagnose ADPKD, US TKV measurement via both ellipsoid formula and direct method have been shown less accurate and less reproducible compared to MR based TKV measurement [33].

In this prospective monocenter study, we evaluated kidney volume (KV) in 30 ADPKD children from the Leuven cohort. We used three dimensional (3D) US, applying the ellipsoid method and manual contouring ($KV_{3DUS\text{-}ellipsoid}$, $KV_{3DUS\text{-}contour}$, respectively); manual contouring on MR (KV_{MR}) and the ellipsoid method on 2DUS (KV_{2DUS}). Correlations and differences were evaluated using Pearson's r and Wilcoxon signed-rank tests; variability in Bland-Altman plots.

We observed that all US volumetry methods resulted in significantly lower mean (SD) KV (mL), compared to MR (KV_{2DUS}: 159 (101), $KV_{3DUS\text{-}ellipsoid}$: 169 (105), $KV_{3DUS\text{-}contour}$: 185 (110) and KVMR: 206 (130); all $p<0.001$)). All US methods had a strong correlation to KVMR: 2DUS: r=0.96, $3D_{US\text{-}ellipsoid}$: r=0.89 and $3D_{US\text{-}contour}$: r=0.94. Also, we determined correction factors for converting the US measurements to MR measurements. Both before and after the application of these correction factors, Bland-Altman plots showed lower variability and absolute error for KV3DUS-contour vs. KV_{2DUS} and $KV_{3DUS\text{-}ellipsoid}$ to KV_{MR}.

We could conclude that compared to MR, US volumetry was prone to underestimation. However, KV3DUS-contour represents a valuable alternative for MR in early ADPKD. Although more time-consuming, $KV_{3DUS\text{-}contour}$ might be recommended over KV_{2DUS} for estimation and follow-up of KV in ADPKD children, given its smaller error.

Establishment of a global pediatric ADPKD registry: "ADPedKD"

Evidence-based guidelines on how to deal with children diagnosed with ADPKD or those at-risk for ADPKD are currently lacking despite the publication of KDIGO consensus, and the EAF Reports [34-38]. Also, prognostic scoring systems to stratify patients into risk categories for progression have only been established for adult patients.

There are insufficient data available on the clinical pediatric disease course. Therefore, there is a need for the development of large, well-characterized and international cohorts of pediatric ADPKD patients. We therefore initiated the global ADPedKD project (www.ADPedKD.org) to establish a large international pediatric ADPKD cohort for deep clinical characterization. This collaborative project is based on inter-operable web-based databases, comprising 7 regional and independent but uniformly organized chapters, namely Africa, Asia, Australia, Europe, North America, South America and the United Kingdom. In the database, a detailed basic data questionnaire, including genetics, is used in combination with data entry from follow-up visits, to provide both retro- and prospective longitudinal data on clinical, radiologic and laboratory findings, as well as therapeutic interventions.

The global ADPedKD initiative aims to provide evidence for the development of unified diagnostic, follow-up and treatment recommendations regarding modifiable disease factors. Moreover, this registry will serve as a platform for the development of clinical and/or biochemical markers predicting the risk of early and progressive disease.

To date, 398 patients from 30 different centers were already included in the ADPedKD database. Another 41 centers are currently in the pre-inclusion preparation phase [39].

In Belgium, all pediatric nephrology departments are participating in ADPedKD as this is now approved by all local ethical committees..

Conclusion

In this PhD project, on the eve of broadening the AdultDPKD horizon with ADPediatricKD, we explored the childhood ADPKD phenotype and the challenges concerning its management, in order to urge the need for a standardized and multidisciplinary approach, as many ambiguities still exist.

Importantly, last month, the first international consensus statement on the diagnosis and management of ADPKD in children was published [40]. The option to screen offspring should be discussed with both parents and children, when mature. Surveillance, meaning repeated screening for treatable disease manifestations without diagnostic testing, and immediate diagnostic screening should be offered as equally valid clinical approaches. However, children with a positive family history and either confirmed or unknown disease status should be monitored for hypertension by ABPM and albuminuria.

"It is easier to build strong children than to repair broken adults."

Frederick Douglas

Acknowledgements

The authors would like to thank everyone who was involved in what resulted in this thesis:

All the patients and healthy controls

Co-promotors: E. Levtchenko and H. De Smedt
PKD Research Lab & partners, KU Leuven: D. Mekahli, R. Vennekens, B. Bammens, J.P. Decuypere, P. Janssens, C. Weydert, E. Behaeghel, S. Aerschot, S. Jannes, D. Van Giel

Department of Pediatric Nephrology, UZ Leuven: staff, nurses, ASO's
Department of Nephrology, UZ Leuven: staff and study nurses
Staff of Abdominal Transplant Surgery, UZ Leuven
Department of Pediatric Nephrology Koningin Paola Kinderziekenhuis Antwerpen, Cliniques de l'Europe - Hôpital Sainte Elisabeth, UCL, UZ Brussel, HUDERF, Centre hospitalier universitaire de Charleroi, UZ Gent, Hôpital de Tivoli, CHR Liège, CHU Liège, CHC clinique de l'Espérence
Department of Radiology UZ Leuven: L. Breysem, F. De Keyzer
Laboratory of Pathophysiology, U Antwerp: P. D'Haese, G. Behets
Department of Pediatric Endocrinology, UZ Brussel: J. De Schepper
Centre de Référence des Maladies Rénales Rares, Hôpital Femme Mère Enfant, Hospices Civils de Lyon: J. Bacchetta

REFERENCES:

1. Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med. 1993;329(5):332-42.
2. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. Lancet. 2007;369(9569):1287-301.
3. Gabow PA, Johnson AM, Kaehny WD, Kimberling WJ, Lezotte DC, Duley IT, et al. Factors affecting the progression of renal disease in autosomal-dominant polycystic kidney disease. Kidney Int. 1992;41(5):1311-9.
4. Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF, Jr., et al. Volume progression in polycystic kidney disease. N Engl J Med. 2006;354(20):2122-30.
5. Hateboer N, v Dijk MA, Bogdanova N, Coto E, Saggar-Malik AK, San Millan JL, et al. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. Lancet. 1999;353(9147):103-7.
6. Johnson AM, Gabow PA. Identification of patients with autosomal dominant polycystic kidney disease at highest risk for end-stage renal disease. Journal of the American Society of Nephrology : JASN. 1997;8(10):1560-7.
7. Magistroni R, He N, Wang K, Andrew R, Johnson A, Gabow P, et al. Genotype-renal function correlation in type 2 autosomal dominant polycystic kidney disease. Journal of the American Society of Nephrology : JASN. 2003;14(5):1164-74.
8. Cornec-Le Gall E, Torres VE, Harris PC. Genetic Complexity of Autosomal Dominant Polycystic Kidney and Liver Diseases. J Am Soc Nephrol. 2017.
9. Porath B, Gainullin VG, Cornec-Le Gall E, Dillinger EK, Heyer CM, Hopp K, et al. Mutations in GANAB, Encoding the Glucosidase IIalpha Subunit, Cause Autosomal-Dominant Polycystic Kidney and Liver Disease. Am J Hum Genet. 2016;98(6):1193-207.
10. Cornec-Le Gall E, Olson RJ, Besse W, Heyer CM, Gainullin VG, Smith JM, et al. Monoallelic mutations to DNAJB11 cause atypical autosomal dominant polycystic kidney disease. American journal of human genetics. 2018;102(5):832-44.
11. Grantham JJ. Clinical practice. Autosomal dominant polycystic kidney disease. N Engl J Med. 2008;359(14):1477-85.
12. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18.
13. Reddy BV, Chapman AB. The spectrum of autosomal dominant polycystic kidney disease in children and adolescents. Pediatric nephrology (Berlin, Germany). 2017;32(1):31-42.
14. Koratala A, Malpartida FR, Kazory A. An 88-year-old patient with ADPKD: underscoring the importance of risk factor modification. Clin Case Rep. 2017;5(12):2146-7.
15. Gansevoort RT, Arici M, Benzing T, Birn H, Capasso G, Covic A, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. Nephrol Dial Transplant. 2016;31(3):337-48.
16. Ong AC, Devuyst O, Knebelmann B, Walz G. Autosomal dominant polycystic kidney disease: the changing face of clinical management. Lancet. 2015;385(9981):1993-2002.

17. Woon C, Bielinski-Bradbury A, O'Reilly K, Robinson P. A systematic review of the predictors of disease progression in patients with autosomal dominant polycystic kidney disease. BMC Nephrol. 2015;16:140.

18. De Rechter S, Kringen J, Janssens P, Liebau MC, Devriendt K, Levtchenko E, et al. Clinicians' attitude towards family planning and timing of diagnosis in autosomal dominant polycystic kidney disease. PLoS One. 2017;12(9):e0185779.

19. Genetic testing in asymptomatic minors: Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2009;17(6):720-1.

20. Massella L, Mekahli D, Paripovic D, Prikhodina L, Godefroid N, Niemirska A, et al. Prevalence of Hypertension in Children with Early-Stage ADPKD. Clin J Am Soc Nephrol. 2018.

21. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34(10):1887-920.

22. Flynn JT, Urbina EM. Pediatric ambulatory blood pressure monitoring: indications and interpretations. J Clin Hypertens (Greenwich). 2012;14(6):372-82.

23. Seeman T, Dusek J, Vondrichova H, Kyncl M, John U, Misselwitz J, et al. Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. Blood Press Monit. 2003;8(3):107-10.

24. De Rechter S, Bacchetta J, Godefroid N, Dubourg L, Cochat P, Maquet J, et al. Evidence for Bone and Mineral Metabolism Alterations in Children with Autosomal Dominant Polycystic Kidney Disease. J Clin Endocrinol Metab. 2017;102(11):42010-4217.

25. Pavik I, Jaeger P, Kistler AD, Poster D, Krauer F, Cavelti-Weder C, et al. Patients with autosomal dominant polycystic kidney disease have elevated fibroblast growth factor 23 levels and a renal leak of phosphate. Kidney Int. 2011;79(2):234-40.

26. Pavik I, Jaeger P, Ebner L, Poster D, Krauer F, Kistler AD, et al. Soluble klotho and autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012;7(2):248-57.

27. Breysem L, De Rechter S, De Keyzer F, Smet MH, Bammens B, Van Dyck M, et al. 3DUS as an alternative to MRI for measuring renal volume in children with autosomal dominant polycystic kidney disease. Pediatr Nephrol. 2018;33(5):827-35.

28. Chapman AB, Bost JE, Torres VE, Guay-Woodford L, Bae KT, Landsittel D, et al. Kidney volume and functional outcomes in autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2012;7(3):479-86.

29. Chapman AB, Guay-Woodford LM, Grantham JJ, Torres VE, Bae KT, Baumgarten DA, et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. Kidney Int. 2003;64(3):1035-45.

30. Liebau MC, Serra AL. Looking at the (w)hole: magnet resonance imaging in polycystic kidney disease. Pediatr Nephrol. 2013;28(9):1771-83.

31. Tangri N, Hougen I, Alam A, Perrone R, McFarlane P, Pei Y. Total Kidney Volume as a Biomarker of Disease Progression in Autosomal Dominant Polycystic Kidney Disease. Can J Kidney Health Dis. 2017;4:2054358117693355.

32. Turco D, Busutti M, Mignani R, Magistroni R, Corsi C. Comparison of Total Kidney Volume Quantification Methods in Autosomal Dominant Polycystic Disease for a Comprehensive Disease Assessment. Am J Nephrol. 2017;45(5):373-9.

33. Pei Y, Hwang YH, Conklin J, Sundsbak JL, Heyer CM, Chan W, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2015;26(3):746-53.

34. Forum EA. Translating science into policy to improve ADPKD care. 2015.

35. Harris T, Sandford R, de Coninck B, Devuyst O, Drenth JPH, Ecder T, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care: European ADPKD Forum and Multispecialist Roundtable participants. Nephrol Dial Transplant. 2017.

36. Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015;88(1):17-27.

37. De Rechter S, Breysem L, Mekahli D. Is Autosomal Dominant Polycystic Kidney Disease Becoming a Pediatric Disorder? Front Pediatr. 2017;5:272.

38. Harris T. Is It Ethical to Test Apparently "Healthy" Children for Autosomal Dominant Polycystic Kidney Disease and Risk Medicalizing Thousands? Front Pediatr. 2017;5:291.

39. De Rechter S, Bockenhauer D, Guay-Woodford LM, Liu IM, A.J., Soliman NA, Sylvestre LC, et al. ADPedKD: A Global Online Platform on the management of Children with Autosomal Dominant Polycystic Kidney Disease. Kidney Int Reports. 2019;accepted for publication.

40. Gimpel C, Bergmann C, Bockenhauer D, Breysem L, Cadnapaphornchai MA, Cetiner M, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol. 2019;May 22.

DEXERYL

TRAITER LES PEAUX SÈCHES DE TOUTE LA FAMILLE

PRIX AVANTAGEUX
POUR UNE UTILISATION PROLONGÉE

HYDRATATION & RÉPARATION

PEAUX TRÈS SÈCHES À TENDANCE ATOPIQUE

200 ml
P.P. 6,50€*
CNK 3461-829

500 ml
P.P. 13,00€*
CNK 3461-845

CRÈME ÉMOLLIENTE POUR LE TRAITEMENT DE TOUTES LES XÉROSES

CE

250 ml
P.P. 7,00€*
CNK 1551-258

500 ml
P.P. 13,50€*
CNK 2717-775

HYGIÈNE DERMO-COSMÉTIQUE + **TRAITEMENT** DISPOSITIF MÉDICAL

* Prix indicatif conseillé

20170427 – 12/17

Pierre Fabre DERMATOLOGIE | L'EXPERTISE DANS LA PEAU

The structural and functional impact of CFTR dysfunction on the lung

PhD thesis presented on June 29th, 2018 at the Catholic University of Leuven, Belgium.

Barbara Bosch, aspirant FWO[1]

Promotors: Prof. K. De Boeck

Co-promotor: Prof. J. Deprest
Prof. I. Meyts

[1] Department of Pediatrics, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

barbara.bosch@student.kuleuven.be

Cystic Fibrosis (CF) is the most common inherited life-shortening condition in the Western world.

In Belgium, around 30 patients are diagnosed with CF each year (1). The CF incidence is estimated to be 1 in 3500 live births. In Europe, 1:20 to 1:80 people are CF carrier (2). CF occurs when a patient has two deleterious mutations in the gene CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (3-5). The most common mutation in CFTR is a deletion of the amino acid phenylalanine at position 508 of the CFTR protein (dF508) (6). Today, the median age at death of patients with CF is in the early thirties (1). The current median life expectancy is much higher and around 46 years (7). Nevertheless, CF remains a life-shortening condition. CF lung disease (CFLD) is the primary cause of death in patients with CF (8). CFLD affects both the large airways (trachea and bronchi) and small airways (terminal bronchioles and alveoli). Despite the clinical importance of understanding CFLD, little is known on how CFTR deficiency alters the structure and function of the lung, specifically in early-stage, pediatric CFLD.

The structural study of early CFLD is hampered by the lack of imaging techniques that visualize the complex three-dimensional (3D) structure of the terminal bronchiole and alveolar sac. Terminal bronchioles have an average diameter of 500 µm. Lung imaging options are limited to histology and Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). Histology has micrometer spatial resolution but only provides two-dimensional information and is time-consuming. MRI or CT scanning allow 3D reconstruction but have a resolution in the millimeter range, far from the resolution needed to unravel e.g. cross-sectional area of the terminal bronchiole.

At the functional level, it remains to be elucidated why the CF carriership rate is so exceptionally high in the Caucasian population. Several people have suggested that carrying a mutation in CFTR has had an evolutionary advantage during a time that infectious diseases imposed a severe selective pressure on that the European Caucasian population (9-11), yet no epidemiological data for this hypothesis are present.

Additionally, it is unclear whether CF presents differently in other ethnicities. The diagnosis of CF is based on uniform parameters for all patients. It remains to be studied whether by applying the same diagnostic criteria to all patients, we miss CF in patients with non-Caucasian roots, especially in the Asian population.

For this thesis work, we aimed to study the structural and functional aspects of CFTR dysfunction on the CF lung.

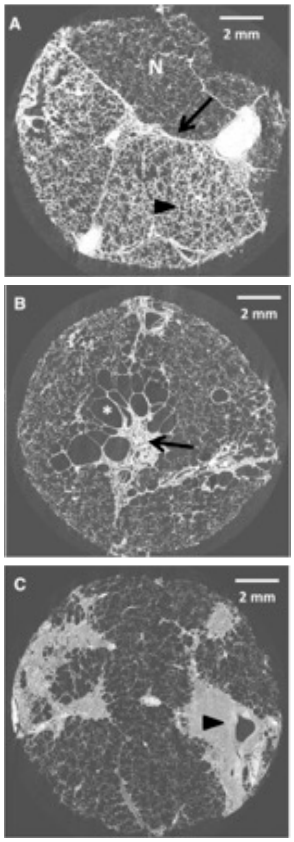
Unravelling the structural and functional impact of CFTR dysfunction and defining adequate treatment for patients with CF is key to further reduce morbidity and mortality. Specifically, fully understanding (the onset of) CFLD could have important implications in the aim to stop CF being a lethal disease.

PART I: STRUCTURAL IMPACT OF CFTR DYSFUNCTION

To overcome the limitation in imaging the small airways, we introduced micro Computed Tomography (µCT) to the study of CFLD. µCT allows 3D imaging of the respiratory airways ex vivo with a microscopic resolution (10 µm). This work was done together with the established collaborating group of the Pulmonology lab at the KULeuven, the Centre for Heart Lung Innovation at St. Paul's Hospital, Canada and Skyscan®, Belgium. They have successfully applied µCT as a novel method to the study of human lung disease (12). As the University Hospitals of Leuven is one of the largest transplant centers in Europe and performs several lung transplants on patients with CF each year (134 in the past 25 years (13)), we had access to human explanted CF lungs for our imaging research.

We thus applied µCT to 11 air-inflated CF explant lungs and 7 control lungs to measure, count and describe the abnormalities at the large and small airway level. We demonstrated that human end-stage CFLD is characterized by extensive changes of dilatation and obstruction in nearly all airway generations (14). The distal airways had less visible terminal bronchioles (2.9/mL [2.6-4.4] in CF lungs versus 5.3/mL [4.8-5.7] in control lungs; $p<0.001$). Additionally, the diameter of the terminal bronchioles that were open was reduced (0.093 mm2 [0.084-0.123] versus 0.179 mm2 [0.140-0.196]; $p<0.001$). The CFLD parenchyma was distorted in a patchy, peribronchiolar manner (Figure 1).

Figure 1: Parenchymal abnormalities visualized by µCT. (A) Normal-looking parenchyma (N) is separated by a thickened septum (arrow) from a diseased zone with increased density (arrowhead). (B) Peribronchiolar scarring (arrow) with cystic, emphysematous alveoli (asterisk). (C) Zone of scarring and atelectasis centered around a bronchiole (arrowhead) (Images from 14).



Upon this detailed study of end-stage, adult explant CF lungs, we pursued the study of early CFLD.

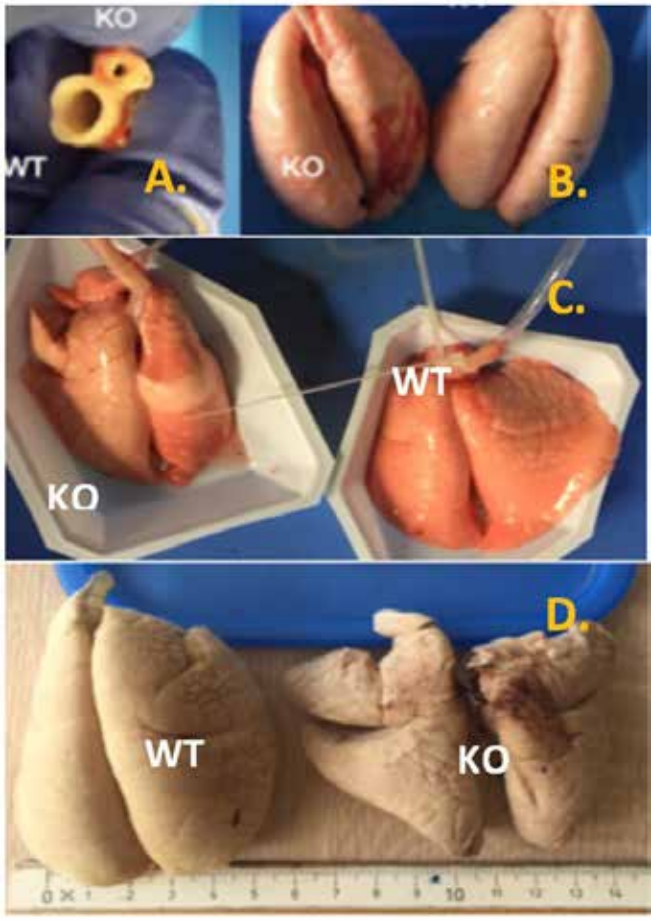
Due to the high radiation doses needed for optimal resolution, µCT is however not suited for in vivo human studies. Also, explant lungs from infants with CF are not readily available. We therefore opted to study the CF pig.

Two research groups have independently established a CF pig model that spontaneously develops lung disease (15, 16) and thereby closely resembles CF lung disease in humans. The availability of such a CF animal model allows studying CF lung disease from birth on and even prenatally. We hypothesized that applying µCT to neonatal CFTR knock-out porcine lungs would allow morphometric analysis of early CFLD.

We subsequently analyzed 9 CFTR knock-out (KO) and 9 wild-type (WT) neonatal pig lungs explanted 4-20 hours after full-term birth.

Macroscopically and qualitatively, a smaller tracheal caliber was present in all KO lungs (Figure 2A). Additionally, we noted that the inflation of KO lungs at 25 cm H2O pressure was consistently less homogenous and slower (Figure 2B) than that of WT lungs. On deflation, air trapping was noted (Figure 2C). Air-dried KO lungs had a higher density (14.4±4.0 g/cm2 versus 9.9±3.8 g/cm2 p=0.03) and their lung volume was statistically lower (15.9±7.1 cm2 (n=6) versus 23.9±7.8 cm2 (n=6); p=0.006) (Figure 2 D).

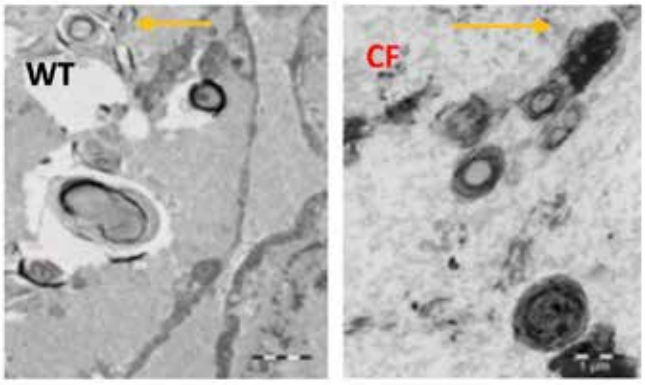
Figure 2: Macroscopic differences between the CFTR KO and WT neonatal pig lungs. A. The trachea of a KO lung is smaller than WT. B. KO lungs inflate more heterogeneously and show air trapping (C). D. Dried KO lungs are macroscopically smaller than WT.



µCT scanning of the KO pig lung at birth unveiled developmental abnormalities at the large and small airway level. CF porcine lung tissue has reduced diameters of the conducting airways compared to WT lung tissue. The number per µm3 of terminal bronchioles did not differ between KO and WT (25,6±12,9 versus 26,1±4,1 (p=0.9)). Also the mean diameter per lung was not significantly altered in neonatal CFTR KO lungs (97,9±8,1µm versus 107,9±10,7 µm (p=0.2)). Yet, the variance of small airway diameters was significantly larger in KO compared to WT animals (F = 1,347 – critical F = 1,179; p = 0,001).

We hypothesized that these structural differences could not fully explain the segmental aeration differences in our qualitative analysis and that this could potentially be explained by an abnormal surfactant function. Surfactant is produced by type II pneumocytes. Lamellar bodies are surfactant secretory organelles found in the lung. As lamellar bodies are osmiophilic they can be studied using electron microscopy (E.M.). Subsequent E.M. analysis of the same lungs used for µCT indeed identified abnormally dense lamellar bodies in the KO animals. Those lamellar bodies could be visualized in the macrophages, type II alveolar cells and extracellular spaces of all KO animals and were absent in the WT lungs (Figure 3). This finding may correspond to clinical reports of patients with early CFLD: altered surfactant composition coinciding with deficient ventilation has recently been described in children with CF (17).

Figure 3: E.M. imaging at 6000x magnification shows normally formed lamellar bodies in the WT animals and dense, potentially afunctional lamellar bodies in KO animals (arrows).



PART II: FUNCTIONAL IMPACT OF CFTR DYSFUNCTION

To address why there are so many carriers of CF, we used a novel yet more complex approach: spatial epidemiology. Many infectious diseases have been hypothesized to be causative of selection for CF carriership (9-11). Based on a mathematical model of Poolman and Galvani (9), only the European tuberculosis (TB) pandemic at the beginning of the seventeenth century could have had sufficient historical, geographically appropriate selective pressure to explain the current carriership rate of CFTR mutations in Caucasians (9). We were fortunate to have access to a multidisciplinary team of geographers and physicians with an interest in tuberculosis (TB) and CF so we could do spatial epidemiological research on the link between CF and TB. We also found a place where we could do the epidemiology at present: Brazil. Brazil is the only country in the world that figures in the 22 High Burden countries for TB and has the European Mycobacterium tuberculosis (Mtb) strain (18). Additionally, 47.73 % of the 91 million Brazilian citizens are Brasileiros blancos, Caucasians from European ancestry (19), leading to a high CF carriership rate in Brazilians. We correlated the dF508 carriership rate with the incidence of TB in Brazil. We corrected for potential confounders. These included 5 environmental factors: the per capita nominal monthly income, sanitary provisions, literacy rates, the racial composition of the population and population density. We also considered 3 comorbidities that have been described as TB risk factors: AIDS incidence rates, diabetes mellitus type 2 and smoking. We found that the carrier rate of dF508 is inversely related to the incidence of Mtb infection in Brazil, also when confounders are corrected for (20). This finding supports the theoretical model of Poolman and Galvani (9). It is also an incentive for research into genetic host factors that define resistance to Mtb.

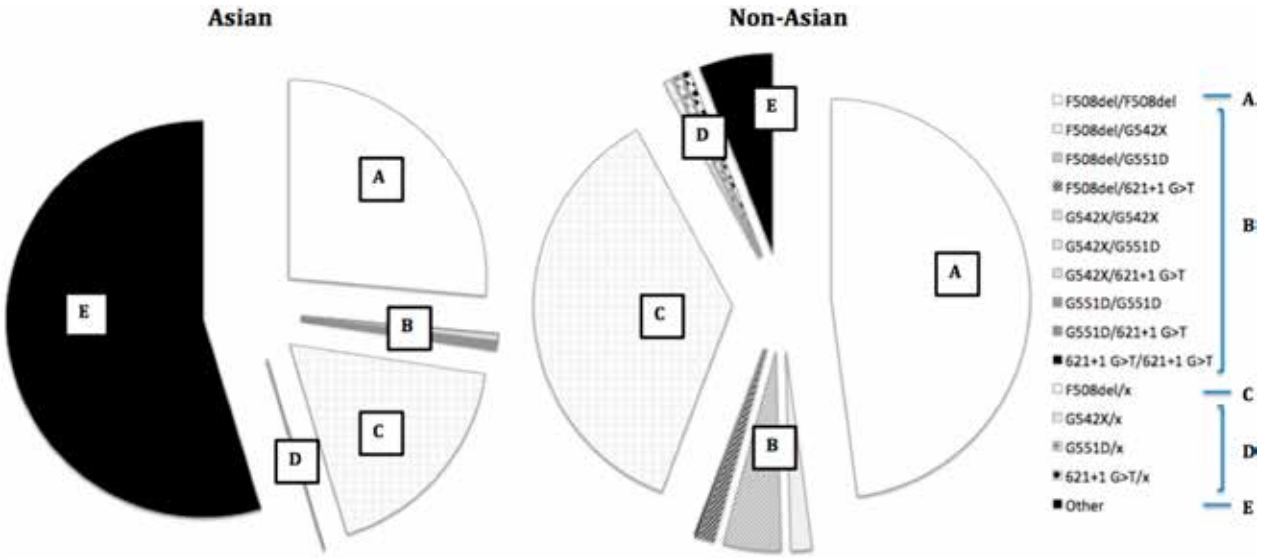
Given the strong link between CF carriership and ethnicity, we also studied whether ethnicity impacts the diagnosis of CF. Both the European CF Society and the North American CF societies base their guidelines for the diagnosis of CF on uniform parameters for all patients: 1) the clinical phenotype, a family history of CF or a positive newborn screening test plus 2) proof of CFTR dysfunction by either an elevated sweat chloride value, presence of two disease-causing CFTR mutations in cis or in a minority of cases abnormal function of CFTR protein as evidenced on nasal potential difference measurement or intestinal current

measurement (21, 22). We performed a retrospective analysis of the CFTR2 and UK CF databases for clinical phenotype, sweat chloride values and CFTR mutations. We then compared the diagnostic characteristics of Asian to matched non-Asian patients with CF (23). We found that that Asian roots impact on all three CF diagnostic pillars. Pancreatic sufficiency is more common in Asian patients with CF. Their mean sweat chloride values are lower (92±26 versus 99±22mmol/L in controls) and 14% have sweat chloride values below 60 mmol/L (versus 6% in non-Asians). Also, CFTR mutations differ from those in Caucasians: 55% of British Asian patients with CF do not have one mutation included in the routine newborn screening panel (Figure 4).

SUMMARY

This thesis work introduced micro-Computed Tomography to the study of CF lung disease. Using this technique, we showed that CFTR deficiency underlies a structural, developmental defect in the small and large airways. Our analyses suggest an altered function of the immune response and surfactant in the CF lung. It opens a path forward to understanding early lung disease in CF and other pediatric respiratory diseases and supports research into resistance genetics.

Figure 4: CFTR mutations included in the UK newborn screening panel (F508del, G542X, G551D and 621 + 1 G > T) have different frequencies in Asian (left) and non-Asian patients with CF (right). Applying the screening panel would identify most Caucasians patients with CF and only 45% of Asian patients (white and patterned): A indicates dF508 homozygotes and B compound heterozygosity with two mutations of the UK panel. C and D show the proportion of patients that has one mutation appearing in the panel (dF508 (C) or G542X, G551D and 621 + 1 G > T (D)). E marks the group of patients that has two mutations that are not included in the screening.



REFERENCES:

1. Mucovereniging. Mucoviscidose in België, anno 2016. Available on URL: http://www.muco.be/nl/mucoviscidose/mucoviscidose-belgi%C3%AB-anno-2016
2. Castellani C, Macek M Jr, Cassiman JJ, Duff A, Massie J, ten Kate LP, Barton D, et al. Benchmarks for cystic fibrosis carrier screening: a European consensus document. J Cyst Fibros. 2010 May;9(3):165-78
3. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, et al. Identification of the cystic fibrosis gene: genetic analysis. Science. 1989 Sep 8;245(4922):1073-80.
4. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989 Sep 8;245(4922):1066-73.
5. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, Rozmahel R, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science. 1989 Sep 8;245(4922):1059-65.
6. Cutting GR, Kasch LM, Rosenstein BJ, Zielenski J, Tsui LC, Antonarakis SE, Kazazian HH Jr. A cluster of cystic fibrosis mutations in the first nucleotide-binding fold of the cystic fibrosis conductance regulator protein. Nature. 1990 Jul 26;346(6282):366-9.
7. Cystic Fibrosis Foundation. Understanding changes in life expectancy – published 2017. Available on URL: https://www.cff.org/Research/Researcher-Resources/Patient-Registry/Understanding-Changes-in-Life-Expectancy/
8. Zolin A, Naehrlich L, van Rens J et al. ECFSPR Annual Report 2015 – published 2017. Available on URL: https://www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report2015_Nov2017.pdf
9. Poolman EM, Galvani AP. Evaluating candidate agents of selective pressure for cystic fibrosis. J R Soc Interface. 2007 Feb 22;4(12):91-8.
10. Rodman DM, Zamudio S. The cystic fibrosis heterozygote--advantage in surviving cholera? Med Hypotheses. 1991 Nov;36(3):253-8.
11. Quinton PM. Human genetics. What is good about cystic fibrosis? Curr Biol. 1994 Aug 1;4(8):742-3.
12. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, Wright AC, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N Engl J Med. 2011 Oct 27;365(17):1567-75.
13. Verleden GM, Dupont L, Yserbyt J, Schaevers V, Van Raemdonck D, Neyrinck A, Vos R. Recipient selection process and listing for lung transplantation. J Thorac Dis. 2017 Sep;9(9):3372-3384.
14. Boon M*, Verleden SE*, Bosch B*, Lammertyn EJ, McDonough JE, Mai C, Verschakelen J, et al. Morphometric Analysis of Explant Lungs in Cystic Fibrosis. Am J Respir Crit Care Med. 2016 Mar 1;193(5):516-26.
15. Stoltz DA, Meyerholz DK, Pezzulo AA, Ramachandran S, Rogan MP, Davis GJ, Hanfland RA, et al. Cystic fibrosis pigs develop lung disease and exhibit defective bacterial eradication at birth. Sci Transl Med. 2010 Apr 28;2(29):29ra31.
16. Klymiuk N, Mundhenk L, Kraehe K, Wuensch A, Plog S, Emrich D, Langenmayer MC, et al. Sequential targeting of CFTR by BAC vectors generates a novel pig model of cystic fibrosis. J Mol Med (Berl). 2012 May;90(5):597-608.
17. Gunasekara L, Al-Saiedy M, Green F, Pratt R, Bjornson C, Yang A, Michael Schoel W, et al. Pulmonary surfactant dysfunction in pediatric cystic fibrosis: Mechanisms and reversal with a lipid-sequestering drug. J Cyst Fibros. 2017 Sep;16(5):565-572.
18. World health Organization – stop TB. Country profile: Brazil. Available on URL: http://www.stoptb.org/assets/documents/countries/acsm/Brazil.pdf
19. IBGE; INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATISTICA. Censo demográfico 2010, IBGE, 2011.
20. Bosch L*, Bosch B*, De Boeck K, Nawrot T, Meyts I, Vanneste D, Le Bourlegat CA, et al. Cystic fibrosis carriership and tuberculosis: hints toward an evolutionary selective advantage based on data from the Brazilian territory. BMC Infect Dis. 2017 May 12;17(1):340.
21. Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, Sermet-Gaudelus I, et al. ECFS best practice guidelines: the 2018 revision. J Cyst Fibros. 2018 Mar;17(2):153-178.
22. Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, Howenstine M, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb;181S:S4-S15.e1.
23. Bosch B, Bilton D, Sosnay P, Raraigh KS, Mak DYF, Ishiguro H, Gulmans V, et al. Ethnicity impacts the cystic fibrosis diagnosis: A note of caution. J Cyst Fibros. 2017 Jul;16(4):488-491.

Publieksprijs België	86,52€

Bexsero: het eerste vaccin tegen meningokokken van serogroep B.

Het enige geïndiceerd vanaf 2 maanden.[1,2]

BEXSERO

Vaccin tegen meningokokken van groep B (rDNA, component, geadsorbeerd)

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Produktkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. ▼ Dit geneesmiddel is onderworpen aan aanvullende monitoring. Daardoor kan snel nieuwe veiligheidsinformatie worden vastgesteld. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden. Zie rubriek "Bijwerkingen" voor het rapporteren van bijwerkingen. NAAM VAN HET GENEESMIDDEL Bexsero suspensie voor injectie in voorgevulde spuit. Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) EU/1/12/812/001. Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Een dosis (0,5 ml) bevat: Recombinant ***Neisseria meningitidis*** groep B NHBAfusieeiwit [1, 2, 3] : 50 microgram Recombinant ***Neisseria meningitidis*** groep B NadAeiwit [1, 2, 3] : 50 microgram Recombinant ***Neisseria meningitidis*** groep B fHbpfusieeiwit [1, 2, 3] : 50 microgram Buitenmembraanvesikels (BMV) van ***Neisseria meningitidis*** groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat [2] : 25 microgram [1] Geproduceerd in ***E. coli***cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) THERAPEUTISCHE INDICATIES Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door ***Neisseria meningitidis*** groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. DOSERING EN WIJZE VAN TOEDIENING Dosering

Tabel 1. Samenvatting van de dosering

Leeftijd bij eerste dosis	Primaire immunisatie	Intervallen tussen primaire doses	Booster
Zuigelingen van 2 tot en met 5 maanden [a]	Drie doses, elk van 0,5 ml	Niet minder dan 1 maand	Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis [b, c]
Zuigelingen van 3 tot en met 5 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	
Zuigelingen van 6 tot en met 11 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis [c]
Kinderen van 12 tot en met 23 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis [c]
Kinderen van 2 tot en met 10 jaar	Twee doses, elk van 0,5 ml	Niet minder dan 1 maand	Noodzaak niet vastgesteld [d]
Adolescenten (11 jaar of ouder)en volwassenen*	Twee doses, elk van 0,5 ml	Niet minder dan 1 maand	Noodzaak niet vastgesteld [d]

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. CONTRAINDICATIES Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Individuen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van individuen met complement deficiëntie, asplenie of miltdisfuncties. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. BIJWERKINGEN Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38**°C**) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en ***Haemophilus influenzae*** type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon – hyporesponsieve episode Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op injectie Maagdarmstelselaandoeningen Zeer vaak: misselijkheid Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Melding van vermoedelijke bijwerkingen** Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie EUROSTATION II Victor Hortaplein, 40/40 B-1060 Brussel Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Direction de la Santé – Division de la Pharmacie et des Médicaments Villa Louvigny – Allée Marconi L-2120 Luxembourg Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië DATUM VAN DE GOEDKEURING VAN DE TEKST 06/2018(v05) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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

BE/BEX/0011/16a(1) – July 2018 - V.U.: GlaxoSmithkline Pharmaceuticals n.v., av Pascal 2-4-6, 1300 Wavre

Heterozygous variant in the aggrecan gene leading to poor pubertal growth and short adult stature: a case report and review of the literature

Katharina Stabenow[1], Karolien Van De Maele[2], Thomy de Ravel[3], Callewaert Bert[4],Jean De Schepper[2]

[1] Department of Pediatrics, UZ Brussel
[2] Department of Pediatric Endocrinology, UZ Brussel
[3] Centre for Medical Genetics, UZ Brussel
[4] Centre for Medical Genetics, Ghent University Hospitals

katharina.stabenow@uzbrussel.be

Key words

aggrecan, short stature, poor pubertal growth, advanced bone age

Abstract

Aggrecan (ACAN) is an important component of cartilage, including the growth plate. Heterozygous variants in the ACAN gene have been identified in 1.4 to 4.7% of patients with idiopathic short stature. We describe a 16 year old adolescent with short stature and poor pubertal growth due to a novel ACAN gene variant. Even though the precise pathogenic mechanisms remain to be unraveled, variants in the ACAN gene should be considered in the differential diagnosis in children with idiopathic short stature or familial short stature, especially in those with a poor or early aborted pubertal growth.

Introduction

Short stature, defined by a body height below -2 SDS, affects about 3% of the population and is the most common reason for referral to the pediatric endocrinologist[1,2]. In about 80% of the cases, short stature remains without an identified cause and is usually categorized as a familial short stature or an idiopathic short stature (ISS) [1]. Next generation sequencing (NGS) has led to the discovery of several novel genetic variants in patients with idiopathic short stature (ISS), such as in the natriuretic peptide receptor 2 (NPR2), Indian Hedgehog Signaling Molecule (IHH), and ACAN genes.

The ACAN gene codes for aggrecan, which is the most abundant non-collagenous protein in cartilage, including the growth plates. It is a proteoglycan with a 250kDa protein core with 100 chondroitin sulphate and 30 keratan sulphate chains attached between three globular domains[2].

We present the case of a 16-year old boy with idiopathic short stature due to a novel variant in the ACAN gene, stressing the need for ACAN gene screening in patients with an advanced bone maturation and aborted pubertal growth.

Case

A 16-year-old boy consulted at our pediatric endocrinology department because of a poor pubertal growth spurt. He was born after 40 weeks of gestation with a birth weight of 3.380 kg (-0.17 SDS) and a length of 49 cm (-0.82 SDS) after an uneventful gestation. He had a normal psychomotor development. He was diagnosed at the age of 10 years with allergic asthma, for which he is treated intermittently with inhalation corticosteroids. His father has a height of 165cm (-2.3 SDS curves), while the mother's height is 162 cm (-0.7 SDS). Both parents had a normal onset of pubertal development. The patient has three younger, prepubertal siblings that are currently growing normally. One of the siblings was diagnosed with oligo-articular juvenile arthritis at the age of four.

As shown in figure 1, during childhood the patient's length followed the 25th percentile, but due to poor pubertal growth spurt, his growth stopped abruptly at 14 years of age.

At physical examination, standing height was 164 cm (-1.6 SDS), sitting height 83 cm, arm span 165 cm and body weight 48 kg (-1.8SDS). Pubertal development was adult (Tanner staging: A3P5G5). Besides a high-arched palate, no other dysmorphism was seen.

Diagnostic workup showed no underlying organic dysfunction. Hormonal evaluation showed normal serum levels for IGF1, adrenal androgens and testosterone. His bone age was 18 years based on the Greulich and Pyle atlas.

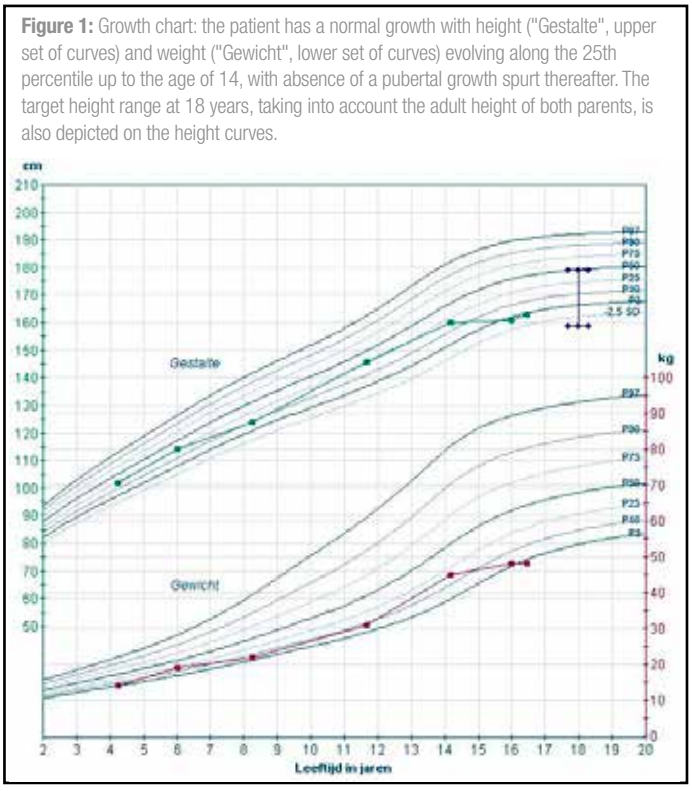


Figure 1: Growth chart: the patient has a normal growth with height ("Gestalte", upper set of curves) and weight ("Gewicht", lower set of curves) evolving along the 25th percentile up to the age of 14, with absence of a pubertal growth spurt thereafter. The target height range at 18 years, taking into account the adult height of both parents, is also depicted on the height curves.

Molecular analysis of the ACAN gene (cRNA: NM_013227.3) was performed at the Center for Medical Genetics, Ghent University Hospital, and identified a heterozygous variant: c.6856G>T,p.(Glu2286*), accounting for a premature stop codon within the chondroitin sulphate attachment domain 2. The variant is classified as a "likely pa thogenic" variant (class 4), given that the variant is absent in the controls of the Exome Sequencing Project, the 1000 Genomes Project and the Exome Aggregation consortium, and that this is a nonsense variant in a gene for which loss of function is a known pathogenic mechanism.

The results of the ACAN variant screening in the parents and sister are pending.

Discussion

Variants in the ACAN gene give rise to a phenotypic spectrum of four separate entities[3]. The first two are autosomal dominantly inherited skeletal dysplasias: familial osteochondritis dissecans (ORPHA251262) and spondylepiphyseal dysplasia, Kimberley type (ORPHA93283). The third is a severe recessive form of skeletal dysplasia called spondylepimetaphyseal dysplasia (ORPHA171866). Finally, various variants within the ACAN gene account for an autosomal dominantly inherited form of ISS. Macrocephaly with multiple epiphyseal dysplasia and distinctive facies is another separate entity with an unresolved genetic basis that could be a potential fifth member of the aggrecanopathies (OMIN607131) [3].

Idiopathic short stature due to ACAN variants are found in populations all over the world. In 2014, Nilsson et al. reported three families in the USA with heterozygous ACAN variants and short stature[4]. Another study in 2017, in which 218 Chinese children with ISS were included, identified three novel variants at the 5' end of the ACAN gene[5]. Also in 2017, Hattori et al. studied 86 Japanese children with ISS[6]. Four had a possibly damaging ACAN variants and another three children had a possibly benign ACAN variant. Hauer et al. discovered four nonsense variants and two potentially disease-causing missense variants in a study cohort including 428 families with ISS[1]. Considering these studies, the global prevalence of ACAN gene variants in patients with ISS can be estimated between 1,4% and 4,7%. This is in the same order of magnitude as the prevalence of Short stature homeobox (SHOX) (2-17%) and NPR2 (2-6%) gene variants in ISS[5].

Most patients with short stature due to a heterozygous ACAN variant have a proportional stature with an advanced bone age and an early cessation of growth with a poor pubertal growth spurt[3]. However, cases with normal or delayed bone age have been reported[1,2,5]. The severity of the growth delay is also variable. Xu et al. report an adult height of $-5.2\text{SDS} \pm 0.7$ in males and of $-3.9\text{SDS} \pm 0.9$ in females.[6] Hauer et al. on the other hand report heights between 0.9 and 5.9 SDS below the average.[1]

As aggrecan is a part of any cartilage and not only of the growth plate, variants do not solely affect growth. Minor skeletal abnormalities and mild facial dysmorphism have been described by several research teams[1,2,4]. Our patient only had a high-arched palate. Sentchordi-Montané et al. previously reported two patients with an ACAN gene variant having a high-arched palate[2]. However, more frequent findings in their case series were mid-facial hypoplasia, depressed nasal bridge, frontal bossing and brachydactyly. Hauer et al. describe barrel-shaped chest, limited supination and brachydactyly in most of their patients[1]. The three families reported by Nilsson present with midface hypoplasia and brachydactyly[4]. Nevertheless, absence of any distinct facial and skeletal features does not exclude an ACAN variant. For instance, the four patients with ACAN gene variants reported by Hattori et al. did not present any apparent dysmorphism[7].

Interestingly, some of the patients with ACAN gene variants and short stature presented with early-onset osteoarthritis and early-onset discopathy, reflecting another aspect of cartilage dysfunction due to abnormal aggrecan: some of the gene variants seem to make the cartilage less resistant to mechanical stress [4,8,9].

The exact processes leading to ISS in patients with variants in the ACAN gene remain to be clarified. Haplo-insufficiency and neomorphic mechanisms appear to play a role, depending on the localization and the type of variant[3]. Nonsense variants can give rise to both truncated proteins, and haplo-insufficiency through nonsense mediated degradation of mRNA of the mutant allele. Neomorphic mechanisms are the antagonistic, downregulating effects that mutated aggrecan could have on the wild-type aggrecan. The secretion of truncated proteins into the extracellular matrix of the cartilage may compromise its function and structure. In the case of haplo-insufficiency, the lower secretion of aggrecan may do exactly the same. Further research is needed to better understand what happens in the human cartilage in case of a heterozygous ACAN gene variant.

Therapeutic options that specifically target ACAN are still non-existent currently, but a better grasp of the pathogenic mechanisms may eventually lead to an understanding of the phenotypical diversities and possible cures. Growth hormone (GH) appears to have a beneficial role in reducing further height loss: in the cohort of Xu et al. the patients with ACAN mutations treated with GH were 5–8 cm taller than their same-sex family members who remained untreated.[6] Van der Steen et al. reports similar effects with combined growth hormone and gonadotropin-releasing hormone agonist therapy in small for gestational age children with an ACAN variant.[10] Randomized controlled trials are needed to confirm these findings.

Conclusion

Next generation sequencing has allowed for the discovery of variants within several proteins that are relevant to skeletal growth, like aggrecan. ACAN gene variants are a common cause of nonsyndromic short stature. The clinical spectrum associated with ACAN gene variants is variable and the underlying pathogenic mechanisms remain to be unraveled. Even though more research is needed in these fields, ACAN gene variants should be considered in any patient presenting with idiopathic short stature, showing a dominant inheritance pattern in the family history, normal body proportions with eventual mid facial hypoplasia and high-arched palate at physical examination, and an early aborted pubertal growth spurt in relation with an accelerated bone maturation in the second decade.

REFERENCES:

1. Hauer NN, Sticht H, Boppudi S, Büttner C, Kraus C, Trautmann U et al. Genetic screening confirms heterozygous mutations in ACAN as a major cause of idiopathic short stature. Sci Rep. 2017;7(1):12225.
2. Sentchordi-Montané L, Aza-Carmona M, Benito-Sanz S, Barreda-Bonis AC, Sánchez-Garre C, Prieto-Matos P et al. Heterozygous aggrecan variants are associated with short stature and brachydactyly: description of 16 probands and a review of literature. Clin Endocrinol (Oxf). 2018;88:820-829.
3. Gibson BG, Briggs MD. The aggrecanopathies, an evolving phenotypic spectrum of human genetic skeletal diseases. Orphanet J Rare Dis. 2016;11(1):86.
4. Nilsson O, Guo MH, Dunbar N, Popovic J, Flynn D, Jacobsen C et al. Short stature, accelerated bone maturation, and early growth cessation due to heterozygous aggrecan mutations. J Clin Endocrinol Metab.2014;99(8):E1510-8.
5. Hu X, Gui B, Su J, Li H, Li N, Yu T et al. Novel pathogenic ACAN variants in non-syndromic short stature patients. Clin Chim Acta.2017;469:126-129.
6. Xu D, Chengjun S, Zhou Z, Wu B, Yang L, Chang Z et al. Novel aggrecan variant, p. Gln2364Pro, causes severe familial nonsyndromic adult short stature and poor growth hormone response in Chinese children. BMC Medical Genetics.2018,19:79.
7. Hattori A, Katoh-Fukui Y, Nakamura A, Matsubara K, Kamimaki T, Tanaka H et al. Next generation sequencing-based mutation screening of 86 patients with idiopathic short stature. Endocr J. 2017;64(10):947-954.
8. Dateki S, Nakatomi A, Watanabe S, Shimizu H, Inoue Y, Baba H et al. Identification of a novel heterozygous mutation of the aggrecan gene in a family with idiopathic short stature and multiple intervertebral disc herniation. J Hum Genet.2017;62(7):717-721.
9. Merckx S, Moortgat S, Mouraux T, Beckers D. Small stature with osteochondritis: a clinical report of a family with ACAN mutation and review of the literature. Endocrine Abstracts.2018;57:32.
10. Van der Steen M, Pfundt R, Maas SJWH, Bakker-van Waarde WM, Odink RJ, Hokken-Koelega ACS. ACAN Gene Mutations in Short Children Born SGA and Response to Growth Hormone Treatment. J Clin Endocrinol Metab.2017;102(5):1458–1467.

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

Probiotics probably reduce antibiotic-associated diarrhoea in children

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

Clinical question

Do probiotics reduce the risk of antibiotics-associated diarrhoea in children and are they safe?

Context

Antibiotics change the microbial balance in the gut and often cause antibiotic-associated diarrhoea (AAD). Probiotics contain potentially beneficial bacteria or yeast, which may restore the natural balance of bacteria in the intestinal tract.
The review describes 33 trials including a total number of 6352 children, aged 3 days to 17 years, who received antibiotics. Studies compared probiotics with placebo, active alternative treatment i.e. diosmectite or infant formula or no treatment. All types and doses of probiotics were included. The studies used the following strains: *Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp., or Streptococcus spp.*, alone or in combination. Outcomes were incidence of diarrhoea, number and type of adverse events, duration of diarrhoea and follow-up varied from 5 days to 12 weeks.

Summary of the results

After follow-up, 8% of the probiotic group had diarrhoea compared to 19% in the control group (RR 0.45, 95% CI 0.36 to 0.56; 6352 participants; NNTB 9, 95% CI 7 to 13). High dose probiotics (≥5 billion CFUs (colony forming units) per day) were more effective than low probiotic dose (< 5 billion CFUs per day). For the high dose studies, the incidence of diarrhoea in the probiotic group was 8% compared to 23% in the control group (RR 0.37; 95% CI 0.30 to 0.46; NNTB 6, 95%CI 5 to 9, 4038 participants). For the low dose studies the incidence of diarrhoea in the probiotic group was 8% compared to 13% in the control group (RR 0.68; 95% CI 0.46 to 1.01; 2214 participants).

None of the 24 trials (4415 participants) that examined adverse events reported any serious adverse events attributable to probiotics. Adverse event rates were low. After 5 days to 4 weeks follow-up, 4% of children who took probiotics had an adverse event compared to 6% of children in the control groups (RD 0.00; 95% CI -0.01 to 0.01; 4415 participants). Common adverse events included rash, nausea, gas, flatulence, abdominal bloating, and constipation.

Eight studies recorded data on the mean duration of diarrhoea. Probiotics reduced duration of diarrhoea by almost one day (mean difference -0.91; 95% CI -1.38 to -0.44; 1263 participants).

Remarks

Quality of evidence was moderate for incidence of diarrhoea, and low for adverse events and duration of diarrhoea. Some studies had important methodological problems such as lack of blinding, inadequate randomization, high loss to follow-up and commercial sponsorships. The authors performed separate analyses to evaluate the impact of these methodological problems. For all analyses, the results remained significant. The results of the subgroup on dose were judged to be credible based on 5 criteria, including a test for subgroup differences. Studies examined mostly otherwise healthy children. Some observational studies (not included in this review) reported serious adverse events in severely debilitated or immuno-compromised children with underlying risk factors.

Conclusion:

Probiotics probably decrease AAD in children. High doses are probably most effective with a NNTB of 6, meaning that 6 children need to be treated to prevent one case of diarrhoea. Probiotics seem to be safe and may reduce the duration of diarrhoea by almost 1 day.

Implications for practice:

Probiotics probably benefit otherwise healthy children who are prescribed antibiotics. *Lactobacillus rhamnosus or Saccharomyces boulardii* at 5 to 40 billion colony forming units per day appear most appropriate.

REFERENCE:

Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub5.

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
* **NNTB:** number needed to treat to be beneficial

Editorial Policy

Aims and scope

The Belgian Journal of Paediatrics is published by the Belgian Society of Paediatrics. *The Belgian Journal of Paediatrics* publishes original articles, special reports, review articles, short communications, case reports, letters to the editor, and commentaries on all aspects of paediatrics.
The Belgian Journal of Paediatrics is published quarterly.

Editors

Publisher: Vivactis Healthcare Benelux sprl
Gustave Demeylaan 57, 1160 Brussels
Owner: Belgische Vereniging voor Kindergeneeskunde – Société Belge de Pédiatrie

Instructions for authors

Submission information

Manuscripts must be submitted in Word (single-spaced) and sent by e-mail to the editor at BJ-Ped@hotmail.com. All manuscripts considered for publication undergo peer review. In order to be eligible for peer review manuscripts must comply with the guidelines described in the instructions for authors. Manuscripts not prepared according to the instructions for authors will be returned to the author(s) without review.

A submitted manuscript must be an original contribution not previously published (except as an abstract, as part of a published lecture or a thesis, or with authorization of the publisher). 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: the preferential use of English is strongly encouraged. Papers can also be submitted in French or Dutch.

Title: should be in English. If the article is written in French or Dutch, a subtitle in the language of the article is added under the English title.

Abstracts should always be in English and limited to 250 words. Do not cite references in the abstract.

Text: Organize the manuscript into four main headings, e.g.: Introduction, Materials and Methods, Results, and Discussion, followed by a Conclusion. Define abbreviations at first mention in text and in each table and figure.

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

Abbreviations should be defined at first mention in the text and used consistently thereafter.

Units of measurement and laboratory values: measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or litre) or their decimal multiples. Temperatures should be in degrees Celsius. Blood pressures should be in millimetres of mercury. Haematologic, clinical chemistry, and other measurements can be provided in local or International System of Units (SI) with normal values between brackets.

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 should be submitted as separate files in Word or embedded Excel. Each table must have a title. Screen captured tables are not allowed.

Figures should be submitted as separate files in JPEG format. The resolution should be preferably 600 DPI. Each figure must have a legend. Legends should be typed on a separate manuscript page, directly following the reference list.

Patient privacy and informed consent: it is the author's responsibility to ensure that a patient's privacy is carefully protected and to verify that any experimental investigation with human subjects reported in the manuscript was performed according to all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated.

Permissions: Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source.

Footnotes can be used to give additional information. Footnotes should be numbered consecutively.

References: authors are responsible for the accuracy of the cited references. References must be numbered sequentially as they appear in the text. Reference numbers in the text must use superscript and put at the end of the sentence. 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. If the same citation is referenced several times, then the first reference counts. 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. The references must be formatted according to Vancouver style.

For journal articles: the first 6 authors should be listed followed by 'et al.' Then: Title. Journal year; volume (number): start and end page. 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.

Acknowledgements should be placed in a separate section after the conclusion.

Title page: a title page should accompany all submissions and provide following information:

a) Complete manuscript title

b) Authors' full names, in order first name (given name) then last name (family name), and affiliations

c) Name and address for correspondence, including fax number, telephone number, and e-mail address

d) Up to five keywords in English

e) The contribution of each author (see authorship criteria in the editorial policy)

f) The word count of the manuscript body (excluding abstract, keywords, references and figure legends), number of figures and number of tables

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

h) If the article reports a clinical trial: the registration number and the site of registry

i) Suggestion of the names and mail address of minimum 2 and up to 4 possible peer reviewers

Patient information: a written informed consent for publication of any information possibly identifying patients should be added as a separate page.

Disclosure of potential conflicts of interest: the corresponding author should disclose any conflict of interest for any of the authors. Each author should submit to the corresponding author a separate filled-in ICMJE form for disclosure of potential conflicts of interest (downloadable at http://www.icmje.org/conflicts-of-interest/), that the corresponding author must keep.

Article types

Original Articles: original articles are full-length reports of original research. Authors should aim for accuracy, clarity, and brevity. Long introductions, repetition of data among tables, figures, and the text, and unfocused discussions should be avoided. Include an abstract of no more than 250 words. Limit the number of references to 30.

Review Articles: review articles are usually solicited by the Editorial Board. However, unsolicited reviews of exceptional interest will also be considered. Reviews should be balanced and unbiased. Include an abstract of no more than 250 words. The number of references should preferably be limited to 30. Review articles include Expert Opinion papers, State of the Art articles and articles in theme numbers coordinated by guest editors.

Short Communications: brief reports on topics relevant to the Belgian Journal of Paediatrics reader and preliminary reports of original studies of relevant scientific importance. Short Communications must not exceed 1500 words (excluding the title, author names, abstract and references), 1 table and/or 1 figure, and no more than 10 references. Include an abstract of 100 words or less.

Focus on Symptoms: a short (maximum 2 A4 sheets), schematic or algorithmic approach to symptoms with which a clinician is regularly confronted. No abstract nor references are requested.

Case Reports: case reports must not exceed 1500 words (excluding the title, author names, abstract and references), and may include up to three tables and figures and no more than 10 references. Include an abstract of 100 words or less.

Letters to the Editor: letters should be brief (less than 250 words and 3 references), and will be published at the discretion of the editor.

Made in Belgium: summary of a PhD thesis in Belgium. The summary must not exceed 2000 words (excluding title, author names and references). 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.

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.

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.

Editorial policy

Editorship: the editors have full authority over the editorial content of the Journal and the timing of publication of that content.

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 are 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. Neither the editors, editorial board and publisher of the TBK-JPB nor the executive board of the Belgian Paediatric Society are responsible for mistakes or omissions

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 letter of submission.

Duplicate or prior publication: only original manuscripts can be accepted that have not been published before (except in the form of an abstract, as part of a published lecture or a thesis, or with authorization of the publisher).

Reproducing 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.

The articles published in Belgian Journal of Paediatrics can be published in other journals with authorization of the editors.

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

Peer review: all received papers will be peer reviewed by 2 reviewers designated by the editors. After review decision will be made to reject, accept as such or with minor or major revisions. The reviewers’ names will be blinded to the authors. Revised manuscripts will be submitted again to the reviewers. 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.

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.

Les bons choix
commencent tôt

L'eau minérale naturelle **SPA REINE** a été filtrée par la nature pendant plusieurs années dans un endroit rigoureusement **protégé de toute pollution, donnant à cette eau unique une pureté extrême.**
Sa faible minéralisation la rend idéale pour la préparation des repas de bébé.

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

SPA
NATURAL SINCE 1583
A la vie

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

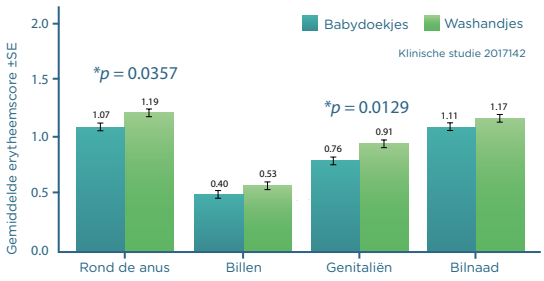
Een nieuwe klinische studie toont aan dat Pampers Aqua Pure-babydoekjes minstens even mild en zacht zijn als een washandje en water

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