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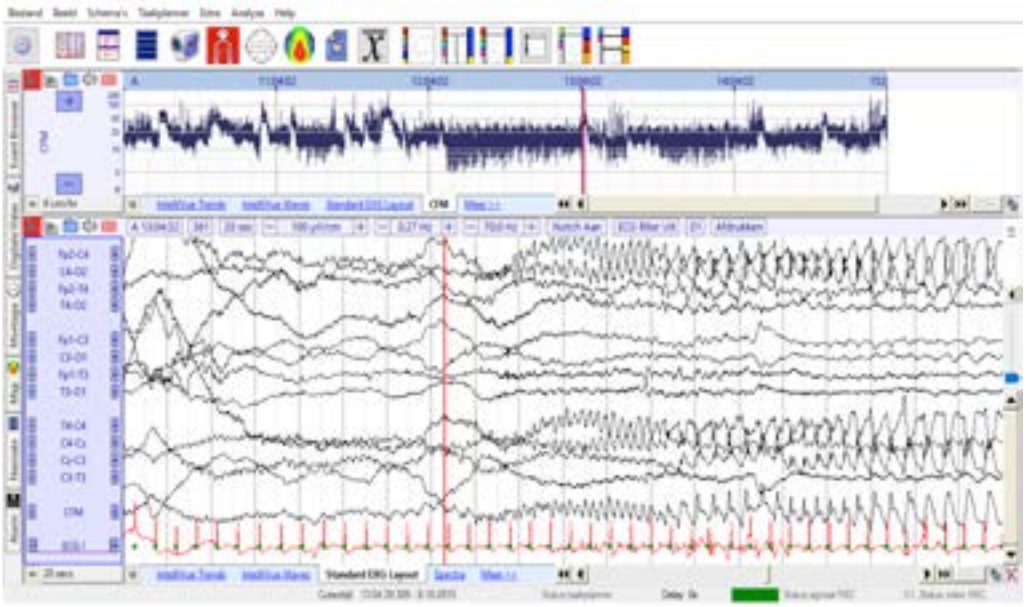



Belgische Vereniging voor Kindergeneeskunde
Société Belge de Pédiatrie

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# 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.

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GOLD - 2019
SPA SOUTIENT
LA SOCIÉTÉ BELGE DE PÉDIATRIE

SPA
NATURAL SINCE 1583
A la vie

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## LA SBP REMERCIE SES PARTENAIRES POUR LEUR SOUTIEN

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# Editorial

Viruses are as old as life itself. In “wild” nature they live in symbiosis with their environment and are part of the ecosystem. During the last few centuries mankind actively influenced and dysregulated this natural balance. Rainforests are invaded and changed in agricultural land, wild animal species are killed or illegally traded, bovine animals are farmed in artificial conditions. Bush-meat from exotic animals is distributed and consumed all over the world. Viruses are “jumping” from one living species to another and threaten vulnerable hosts that are not adapted to them. Modern lifestyle and industrial (r)evolution also influence and inappropriately accelerate ancient “natural” climate changes. Urbanization is distancing us from our natural habitat. Globalization disrupts “natural” borders.

Are we responsible for more and more viruses becoming our enemy? Shouldn’t we stop thinking that we can control nature? Will cognitive dissonance bring us (back) to a more positive balance between man and nature? Although people usually resist change, it’s a tremendous challenge and opportunity for the coming years and decennia not only to respect but specially to integrate nature in the further necessary redrawing of our societies and of the whole of our planet.

Nowadays, COVID-19 controls our entire life and the whole world. Emergency plans are worked out and constantly adapted to the continuously changing situation.

Health care could be totally different once this pandemic hopefully gets controlled.

Although we all are overwhelmed with mails, Newsletters, guidelines and all kind of information how to handle the ongoing COVID-19 pandemic, we decided to send you this issue of the Belgian Journal of Paediatrics. Perhaps you can temporary clear your mind reading non-corona related issues.

Unfortunately, we have to start with sad news.

On January 5th 2020 professor Dirk Matthys (17th Jan 1951 – 5th Jan 2020) died. He was President of the BVK/SBP and medical head of the pediatric department University Hospital Gent.

In the tribute in this issue he is described as a man of “dialogue”.

On March 1st 2020 professor Isi Dab (28th October 1938 – 1st March 2020) passed away. He was paediatric pulmonologist at the paediatric department University Hospital Brussel. Referring to the In Memoriam by Prof Anne Malfroot and Prof Yvan Vandenplas he is described as "a man of integrity and contrasts” “

On behalf of the editorial board and the whole paediatric community we present to their families our deepest condolences.

This issue features original articles, case reports and Paediatric Cochrane corner.

You can also read the report of the last BVK/SBP board meeting on February 20th 2020.

The core content of this BJP issue is devoted to the theme *“Epilepsy in childhood”*, coordinated by Berten Ceulemans (UZA) and Alec Aeby (HUDERF). We wish to thank our guest editors for their very dedicated commitment to coordinate the topics and all the authors of these constrictive contributions. When you start reading, you won’t be able to stop!

Last but not least we want to remember that due to the COVID-19 outbreak we took the decision to postpone the 48th BVK/SBP annual congress *“Innovations for better health in Paediatrics”*, organized by the paediatric department of ULB (prof Pierre Smeesters),to **22- 23th October 2020**. All registrations will be automatically transferred to the new dates. More practical information will be sent in a later stage.

On behalf of the entire editorial board,

We wish all of you the very best in this frightening and apocalyptic period.

Out of the Darkness comes the Light.

Stay healthy, help and support each other

Samy Cadranel and Marc Raes

**Uw vragen of commentaar**
**Vos questions ou commentaires**

BELGISCHE VERENIGING
VOOR KINDERGENEESKUNDE
SOCIÉTÉ BELGE DE PÉDIATRIE

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# In Memoriam

## DIRK MATTHYS
## (17.01.1951 - 05.01.2020)

Dirk Matthys est décédé le 5 janvier 2020, à l'âge de 68 ans. Dirk était un pédiatre "de cœur et d'âme". Ayant commencé ses études en 1974 à la clinique pédiatrique de l'Hôpital Universitaire de Gand, il a travaillé pendant plusieurs années comme pédiatre à l'hôpital Maria Middelares à Gand pour revenir à l'Hôpital Universitaire en tant que cardiologue pédiatrique et, finalement, devenir le chef de service de la Pédiatrie de l'Hôpital Universitaire de Gand. En octobre 1995, il a été nommé maître de conférence à l'Université de Gand à temps partiel et promu, en octobre 1999, maître de conférence principal à temps plein.

Par la suite il a été promu professeur en 2004 et, en 2010, professeur ordinaire en pédiatrie.

Dirk a grandement contribué à développer la médecine pédiatrique de l'Hôpital Universitaire de Gand en un service spécialisé offrant des soins de haute qualité. Il était vice-président du Conseil médical de l'Hôpital Universitaire de Gand et, de 2008 à 2014, directeur éducatif à la Faculté de médecine et des sciences de la santé. Il a également assumé la responsabilité du comité d'éthique médicale. Après sa retraite en octobre 2016, il est resté actif en tant que président de ce comité, fonction qu'il a continué à occuper avec beaucoup de dévouement et de savoir-faire.

En plus de son travail à l'Hôpital Universitaire de Gand et à l'Université de Gand, Dirk a joué un rôle très actif au sein de la Société Belge de Pédiatrie, notamment en tant que président. Il croyait sincèrement que la SBP/BVK était le forum idéal où pédiatres académiques et non académiques, flamands, wallons et bruxellois, médecins généralistes et spécialistes pouvaient dialoguer afin d'élargir et améliorer la base scientifique de notre profession.

Les collègues s'en souviendront comme un homme aimable, d'une grande honnêteté, doué d'une véritable volonté d'écoute et soucieux de l'intérêt public, privilégiant le dialogue.

Dirk n'était pas seulement une personnalité remarquable en tant que pédiatre, il était aussi entièrement dévoué à sa famille avec, en outre, de vastes intérêts et un esprit ouvert. Grand connaisseur et grand amateur d'art moderne, de littérature et de musique classique, il pouvait tout aussi bien profiter d'une de ses plus grandes passions, le football !

Pour ceux qui ont pris la peine de mieux le connaître, après un contact peut-être réservé dans un premier temps, Dirk se révélait un homme agréable et érudit, attentif, doué d'une grande empathie. Pour ceux qui le voulaient bien, il était le mentor idéal. Et pour ceux qui ont eu cette chance, c'était un ami loyal et chaleureux.

Dirk était un homme de grande qualité, qui nous manquera, à tous, beaucoup ...

Op 5 januari 2020 is Dirk Matthys op de leeftijd van 68 jaar overleden.

Dirk was kinderarts met hart en ziel. Hij begon zijn opleiding in 1974 in de kinderkliniek van het UZ Gent en werkte vervolgens enige jaren als kinderarts in Maria Middelares in Gent. Nadien verhuisde hij opnieuw naar het UZ als kindercardioloog om uiteindelijk diensthoofd van de kindergeneeskunde van het UZ Gent te worden. In oktober 1995 werd hij aangesteld als deeltijds docent aan UGent om in oktober 1999 benoemd te worden als voltijds hoofddocent in de kindergeneeskunde. Vervolgens promoveerde hij in 2004 tot hoogleraar en in 2010 tot gewoon hoogleraar.

Dirk hielp de kindergeneeskunde aan het UZ Gent uitbouwen tot een gespecialiseerde dienst die hoogkwalitatieve zorg biedt. Hij was ondervoorzitter van de Medische Raad van het Universitair Ziekenhuis Gent en van 2008 tot 2014 onderwijsdirecteur van de Faculteit Geneeskunde en Gezondheidswetenschappen. Hij nam verantwoordelijkheid op in de Commissie voor Medische Ethiek. Na zijn emeritaat in oktober 2016 was hij nog actief als voorzitter van deze commissie, een functie die hij tot op het laatst met heel veel inzet en kennis heeft uitgevoerd.

Naast zijn werk in het Gentse universitair ziekenhuis en aan de Gentse universiteit speelde Dirk een zeer actieve rol in De Belgische Vereniging voor Kindergeneeskunde, ook als voorzitter. Hij geloofde oprecht dat de BVK/SBP het forum was waar academische en niet- academische, Vlaamse, Waalse en Brusselse, algemene en gespecialiseerde kinderartsen met mekaar in dialoog konden treden om de wetenschappelijke basis van ons beroep te verbreden en verbeteren. De collega's leerden hem kennen als een integer man met grote luisterbereidheid, eerlijkheid en met oog voor het algemeen belang en de dialoog.

Dirk was niet alleen een markante persoonlijkheid als kinderarts, hij was ook een echte familieman met bovendien brede interesses en een open geest. Hij was een groot kenner en liefhebber van moderne kunst, literatuur en klassieke muziek, maar kon evengoed genieten van één van zijn grootste passies: voetbal!

Voor wie de moeite nam om hem na een eerste- misschien gereserveerd-contact, beter te leren kennen was Dirk een aangename en erudiete man, met een luisterend oor en grote empathie. Voor diegenen die het toelieten was hij de ideale mentor. En voor diegenen die geluk hadden was hij een warme en dierbare vriend. Dirk was een "schone" mens, die hard zal gemist worden….

**Save The Date**

# Aalst Breda Course of Pediatric Dermatology

## Seventh edition

Friday 11 September 2020
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 changes in pediatric oncology patients**
  Prof. Dr. J. Izakovic (Basel, Miami)
- **Sexually transmitted disorders**
  Prof. Dr. Z. Szalai (Budapest)
- **Skin manifestations of internal diseases**
  Prof. Dr. L. Weibel (Zurich)

**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**
  Dr. A. Alexopoulos (Athens)

**13:00h** **Lunch**

**14:15h - 15:45h**

- **Germline RASopathies**
  Prof. Dr. S. Barbarot (Nantes)
- **Dermatomyositis**
  Prof. Dr. M. Nikolic (Belgrade)
- **Autoinflammatory diseases**
  Dr. A. Torrelo (Madrid)

**15:45h** **Test yourself in Pediatric Dermatology**
Dr. A. Hulsmann (Breda) & Dr. D. Van Gysel (Aalst)

**16:30h** **Closing**

**www.olvz.be**

# ISIDOOR “ISI” DAB
# (OCTOBER 28, 1938 - MARCH 1, 2020)

Isidoor "Isi" Dab passed away on March 1 in Uccle, surrounded by his loving family.

Isi was a paediatrician with a “golden heart” particularly devoted to his patients and profoundly humanist. He graduated in medicine at the ULB and trained in paediatrics at Saint-Pierre Hospital in Brussels which, until the 1980s, housed the paediatric services of ULB and VUB simultaneously.

He then specialized in paediatric pulmonology that attracted him because it allowed him to fully exercise his mathematical and technical skills. His publications in 1976 on the specific measurement of resistance in lung function have been cited worldwide. He introduced paediatric bronchoscopy in Belgium and trained several young colleagues. In 1996 he founded the Belgische Kring voor Kinderlongartsen (BKKL) - Groupement belge de pneumologues pédiatriques (GBPP). In addition, he strongly fought for the recognition of the different subspecialties in paediatrics which, cynically, is still not yet obtained in 2020.

As a paediatric pulmonologist, he was very closely involved in the care of patients with cystic fibrosis, both clinically and scientifically. He stimulated many young people in cystic fibrosis research and supervised several doctoral theses. Thanks in part to his efforts, INAMI-RIZIV created, in 1999, the Cystic Fibrosis Reference Centers. He became the first director of the current cystic fibrosis center at UZ Brussel and spent many years in the Muco Association, as chairman and secretary of the medical committee. He was promoted to full-time teacher at VUB. He loved to teach, and especially his lessons on cystic fibrosis were contagious for students and everyone else.

Colleagues got to know him as a man of integrity, with a great sense of justice and never being afraid to give his opinion. He was a man of contrasts.

Isi Dab was a hard worker, with enormous language skills. He was very interested in culture, photography and music. He was also a good cook and an excellent father.

After becoming emeritus in October 2003, he retired completely from the academic and clinical world.

He had so many other things to do ...

Anne Malfroot Yvan Vandenplas

Fondation Mustela

# APPEL à PROJETS 2020

## PRIX DE PÉDIATRIE SOCIALE

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ASSOCIATION FLAMANDE DE PÉDIATRIE

**Objectif :**
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# APPEL À PROJETS 2021

## Bourse dermato-pédiatrique

## Dotation 10 000 €

**OBJECTIF** : Soutenir des projets de formation et de recherche en dermato-pédiatrie

**INSCRIPTION** Réservée uniquement aux pédiatres et assistants en pédiatrie

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ouverture dépot candidature : 01.09.2020
date limite de dépot de dossier : 16.01.2021 (avant minuit)

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# Summary Report board meeting BVK – SBP 19/12/2019 - UZ Brussel

1. **Goals of the BVK/SBP**

We should redefine the goals based on the published statutes (2005):

- Promote **scientific** studies aboutall medical and social problems concerning children and adolescents
- Contact and **collaboration** with regional, national and international organisations
- Organization of and participation in **scientific congresses** on a national and international level.
- Development of an optimal preventive, social and curative health care, in **all aspect**, for children and adolescents
- **Representation** of the interests regarding the health of children and adolescents
- **Take actions** directly or indirectly related to these goals

2. **Role of the BVK/SBP members:**

- Membership : different competencies + experience (academic, non-academic, university, regional)
- Commitments : active participation
- Evaluation of projects on short, mid-term and long-term
- Role of executive committee and secretary
  - "Quick" actions
  - Delegation
  - Preparation of the meetings
  - Reporting
  - Financial running
- Meetings
  - Entire board : real life (2 – 3 /year)
  - Subgroups (tele-conference) (ad-hoc/theme)

**Comment**: "Why can't we have the meetings of all the associations on 1 day (BVK/SBP, VVK GBPF, VBS/GBS, Academy) for "x"hours and then afterwards report all to the Academy?"

*Can be discussed further during the ongoing "Fusion" meetings*

3. **Congress BVK/SBP 19/20 March 2020.**

Pierre Smeesters gives an actual state on the Congress.

There is enough financial ssupport.

The young assistants are involved, even more than last year.

New: a session "how to give a presentation in 180 seconds"

The use of a congress app with several functions could be implemented.

If there is place left, non-profit health organizations can be present for free.

Young assistants can explain the use of the congress app at the registration desk.

The lack of social media for publicity (Facebook, LinkedIn) has been noticed.

4. **Sub-specialties**

More and more pediatric sub-specialty associations and working groups contact the BVK/SBP for support/endorsement. Further initiatives for (official) standardization/recognition are needed

Recent:

* (Sub)speciality in "Clinical Infectiology" -> High Council

  Subgroup : BelgianGroupPediatricInfectiousDiseases (BGPID)

* Working groups/associations : asking for collaboration/endorsement BVK/SBP

- BPDA (Belgian Pediatric Dermatology Association), President : V Bernier, Vice-president: D Van Gysel, Secretary: J Pêtre, Treasuser: H De Maeseneer. Meeting well be planned with Belgian Association Dermatology and Venerology
- Belgian Working Group on Pediatric Rheumatology, President: L Goffin. Regulation will be provided
- Belgian Working Group on Congenital Heart Diseases, M Gewillig, D De Wolf, S Moniotte,…under discussion

We (BVK/ BSP; VVK; GBPF; VBS/GBS; Academy) could unify our forces to e.g. Certification/recognition by BVK/SBP + Belgian High Council physician-specialists and general practitioners (FOD/SPF) after accomplishment sub-specialty education, with agreement about training plans (European-based) of all educators.

Comment : "Attention! Regulations (Ministery of Education) are different in Flemisch/French/Brussels part of the country "

Some pediatric sub-specialty associations are linked to a society for adults : e.g. pediatric pulmonologists are part of the BeSP (Belgian Society Pulmonology)

5. **BVK/SBP Projects**

- GSK : Grant

  Proposed activities :

  - Masterclass/e-learnig: vaccines + side effetcs (e.g. fever)
  - Strategies to sustain or increase immunization levels.
- MSD : IPOS marketing research : Inquiry parents and HCP about Varicella
- Mustella - Expanscience
  - Prize "Dermato-pediatrics " at the congress
  - Prize: "Social pediatrics" 2020) : Announcement: begin 2020. Winner : december 2020. Awarding: BVK/SBP annual congress 2021.
- Ultragenics (+ Takeda + SanofiGenzyme) : Awareness campaign : "Rare diseases " (mucopolysaccharidosis).
- VBS/SBP: (Tyl Jonckheer)

  Enquëte : use of Optiflow by "general" pediatricians

  Demand for developing protocols/criteria
  - Use of antibiotics
  - Criteria for presence in delivery room
  - Use of IV perfusion/gastric tube for rehydration

6. **BJP**

Budget: positive!

All pediatricians can consult the BJP via the website

Online submission of articles : in preparation

**Not discussed:**

1. Announcements
   a. ECFN: BVK/SBP support (logo) / endorsement (website)
      i. Campaigns 2019:
         1. Global Call to Action for Newborn Care
         2. World Prematurity Day (WPD)
      ii. Position papers
         1. Respiratory syncytial virus (RSV) in preterm and ill infants
         2. Addressing the nutritional emergency of preterm birth – Optimal practice in neonatal parental nutrition
      iii. Toolkit
         1. "Shaping the future – Combining forces to improve newborn health"
   b. Announcements on the website
      i. "Interuniversity certificat in perinatology: transdisciplinary approach." New formation by UCL and ULB + scientific board of GIP (Anaïs Delmée, UCL "Inter-university certificat in perinatology: transdisciplinary approach." New formation by UCL and ULB + scientific board of GIP (Anaïs Delmée, UCL
      ii. EAPRASnet (European Academy of Paediatric Research in Ambulatory Settings Network): "On-line survey : availibility & use of diagnostic tests (POCT) clinical management of febrile infants in Europe"
   c. Steun tekst De Standaard : "Preventieve Gezondheidszorg", Wouter Arrazola De Onate & André Emmanuel
   d. Vitamine D drops + toxicity of propylgallaat (antioxidans E 310) (cfr NVK)
   e. Support research: "prizes"
      i. Annual congress :
         1. Best oral abstract presentation : 1 BVK/SBP + 1 Nestlé award
         2. Best poster presentation : 1 BVK/SBP + 2 Nestlé awards
      ii. BVK/SBP Young Investigator Award
      iii. Expanscience – Mustella
2. Financial support BVK/SBP : details can be provided on demand
3. Fusion initiatives Belgian pediatric societies : ongoing.
   a. Past meetings : June 22th, November 08th 2019
   b. Scheduled meeting: January 09th 2020 (Zoom)

# Type 1 diabetes and epilepsy: an intriguing link

Matthias De Wachter[1]; An-Sofie Schoonjans[1]; Christophe De Block[2]; Sarah Weckhuysen[3]; Annick France[4]; Berten Ceulemans[1]

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Matthias.DeWachter@uza.be

## Abstract

The link between epilepsy and type 1 diabetes has been underappreciated. The prevalence of epilepsy in type 1 diabetic patients is higher than in the general population. Prevalence varies among different studies, but a two- to sixfold increase compared to the general population is reported. Patients with type 1 diabetes and epilepsy often develop epilepsy before adolescence and have different types of seizures. Temporal lobe epilepsy and idiopathic generalized epilepsy are the most frequently reported epilepsy syndromes. The factors underlying this association remain to be elucidated, but metabolic, cerebrovascular, autoimmune and genetic factors are suggested to contribute. This review gives an overview of existing literature, starting from an illustrative case report. Future research in patient characteristics and etiological factors is needed. Understanding the genetics of these two diseases seems necessary to gain more insight in this intriguing link.

## Introduction

Both type 1 diabetes (T1D) and epilepsy are major causes of chronic disease, with considerable implications in social functioning, and require changes to daily life routine. They are both diseases with high morbidity and an increased mortality.[1,2]

T1D is a chronic immune-mediated disease, characterized by the destruction of the insulin-producing beta-cells in the pancreatic islets. The exact pathophysiologic mechanisms are unknown, although autoreactive T-cells (including CD4- and CD8-positive cells) are playing an important role. Auto-antibodies are the hallmark of this disease, including antibodies against insulinoma-associated protein-2 (IA-2A), islet cell (ICA), insulin (IAA), glutamic acid decarboxylase 65 (GAD65 ) and Zinc Transporter 8 (ZnT8).[3] T1D is also considered a disorder with complex genetic architecture. In the province of Antwerp (Belgium) the incidence of T1D in children younger than fifteen is 13.1 per 100,000 inhabitants per year.[4] Prevalence in Belgium is 0.05%. According to numbers of the International Diabetes Federation, worldwide prevalence is estimated around 0.04% in children and adolescents under the age of 20 years. T1D is associated with many other auto-immune disorders: auto-immune thyroid diseases, autoimmune gastritis, celiac disease and Addison disease.[5]

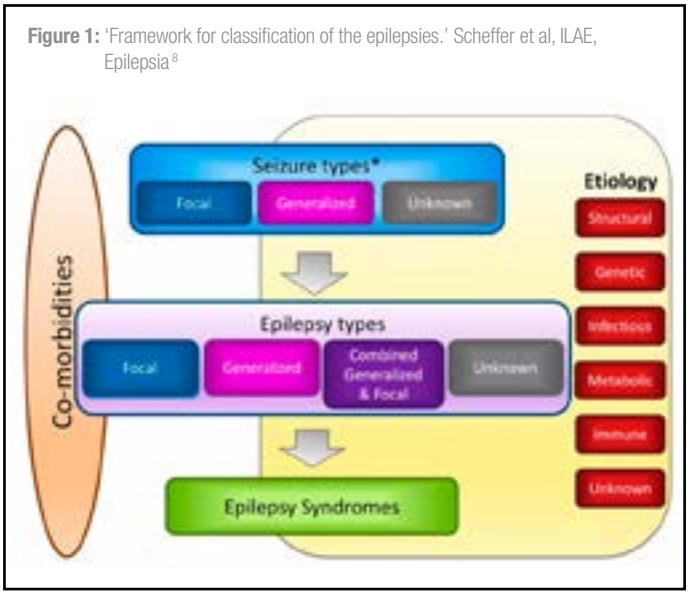
Epilepsy is characterized by an enduring predisposition to generate epileptic seizures, which are defined by a transient occurrence of signs and/or symptoms due to an abnormal excessive or abnormal synchronous neuronal brain activity.[6] The prevalence of active epilepsy in individuals under the age of 20 years is estimated at 0.45-0.50% in Europe.[7] In 2017 the International League Against Epilepsy (ILAE) updated its classification of epilepsy, in order to meet the continuously changing medical science and the growing insights in the etiology and its therapeutic implications. Epilepsy consists of a heterogenous group of disorders that can be classified into three levels: classification of seizure type, classification of epilepsy type, and the possible definition of a syndrome (Figure 1). The etiology includes genetic, structural, metabolic, immune and infectious causes. In general, most epilepsies with generalized onset seizures tend to have a genetic basis, while epilepsies with focal onset seizures have more heterogeneous etiologies. A well-recognized group of generalized epilepsies is named idiopathic generalized epilepsy (IGE), historically defined as 'no known or suspected etiology other than possible hereditary predisposition'. Nowadays IGE is considered to have a genetic basis, with a complex genetic inheritance.[8]

This manuscript will critically review existing literature on the association between epilepsy and T1D, describe pathophysiological and clinical features and discuss the key points for future research.

## Case report

A 12-year-old boy presented with polyuria, polydipsia and weight loss. He was referred by the general practitioner with glycemia of 628 mg/dL (normally <200 mg/dL). At the emergency department complaints of abdominal pain and slight

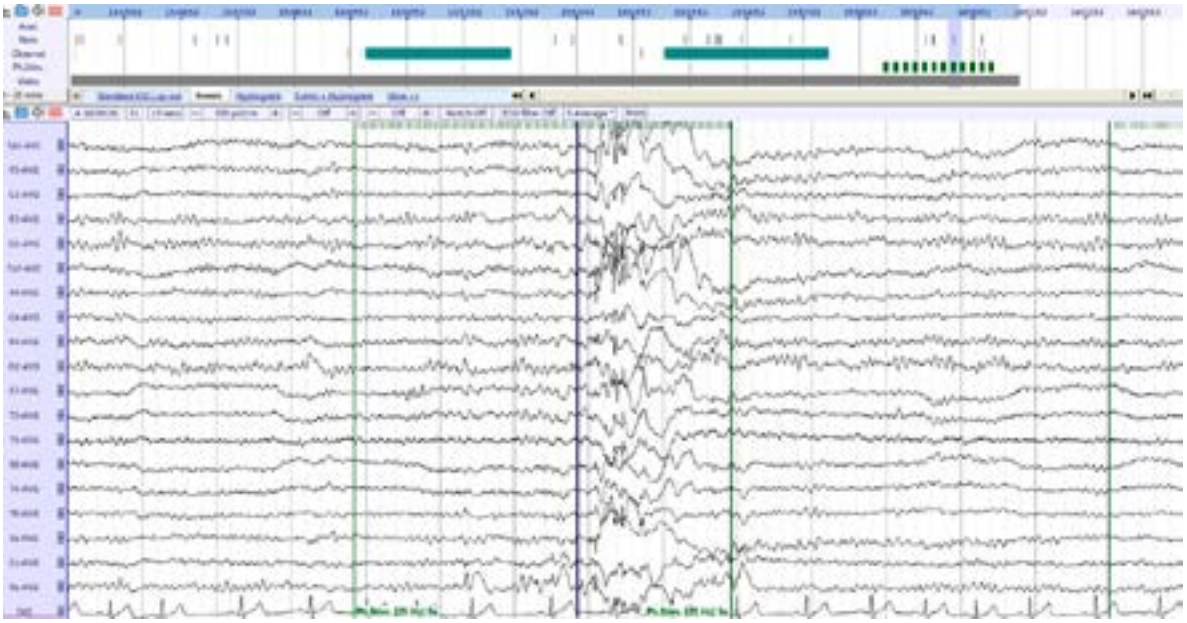
**Figure 1:** 'Framework for classification of the epilepsies.' Scheffer et al, ILAE, Epilepsia [8]




dizziness were also mentioned. Past history was trivial, apart from enuresis nocturna until the age of 8, for which he used oxybutynin. Physical examination was normal. Weight loss was estimated at 3.7 kg in 1.5 months. Blood analyses showed glycemia of 334 mg/dL, ketosis of 0.2 mmol/L (normally 0.1-0.5 mmol/L) and hbA1c of 8.7 % (normally 4.8-6%). Blood count, liver- and kidney function were normal. There was no acidosis. Based on this presentation diagnosis of T1D was made and intravenous insulin was started. The presence of antibodies against IA-2A, ICA, IAA and GAD65 confirmed the diagnosis. Glycemic values stabilized and treatment was switched to subcutaneous insulin. After completing diabetic teaching, he was discharged from the hospital. Strict and regular ambulatory follow-up was started at 3-month intervals.

Three months later the patient presented at our university hospital after a generalized tonic clonic (GTC) convulsion in the morning. Glycemia was 62 mg/dL after convulsions had stopped. Interictal electroencephalogram (EEG) showed a symmetric, age-normal background rhythm with generalized polyspike-waves during hyperventilation and intermittent light stimulation (see figure 2) . The patient's mother mentioned myoclonic jerks in the morning, leading to dropping his glucose meter. This clinical presentation and EEG recordings were consistent with the diagnosis of juvenile myoclonic epilepsy (JME). Glycemic control was excellent with a hbA1c of 6.3 %. At that time, no anticonvulsive treatment was started. Six months later, early morning GTC attacks persisted and levetiracetam was started. Glycemia during these attacks was normal. Convulsions diminished

**Figure 2:** 'Icterictal EEG': Interictal EEG of the presented case shows typical polyspike-wave discharges during intermittent light stimulation



but after a seizure-free period of 9 months GTC seizures returned. Interictal EEG showed generalized spike waves and valproic acid was added. Four months later he was admitted to the pediatric intensive care unit because of a convulsive status epilepticus, treated with benzodiazepines. A few weeks later he had a cluster of 3 GTC attacks, a hypoglycemia (48 mg/dL) was measured between the first two. Again benzodiazepines halted the seizures. Clobazam was added to his anticonvulsive therapy. Despite this triple therapy he experienced another heavy GTC seizure after 14 days and lamotrigine was added, levetiracetam stopped. Magnetic resonance imaging (MRI) of the brain and an epilepsy gene panel (IPG Gosselies) were normal. At the age of 15 he became seizure-free. First clobazam was stopped, and later on lamotrigine. Presently he has been seizure-free for over 3 years on valproic acid monotherapy.

## Discussion

*Evidence for increased co-occurrence of epilepsy and T1D*

Epileptic seizures in diabetic patients were historically classified as hypoglycemic symptomatic seizures. This case illustrates the difficulties in differentiating euglycemic and hypoglycemic seizures in patients without continuous glucose monitoring. Although the presented case had two documented hypoglycemic attacks, semeiology of most seizures and interictal EEG findings are consistent with an epileptic syndrome in this patient with T1D.

The first description of a possible association between T1D and epilepsy goes back to 1977, when Eeg- Olofsson et al. found more frequent epileptic activity on EEG in children with T1D, compared to a control group of healthy children.[9] Different seizures types are found among T1D patients and both focal and generalized epilepsy are described in prevalence studies. IGE and temporal lobe epilepsy (TLE) are reported most frequently, although specific numbers differ depending on which study is consulted.[10-12] The first prevalence study, in a cohort of patients with IGE, found a significantly higher prevalence (1%) of T1D in the IGE group compared to the general population.[13] This was later confirmed in a cohort of adults with pharmacoresistant epilepsy, which also had a T1D prevalence of 1%.[11] Considering cohorts of T1D patients, prevalence of epilepsy was 21/1000 in a small group of T1D patients (n=285), confirmed by studies performed in larger cohorts, also showing a triple risk of developing epilepsy. [12, 14, 15] A German study showed similar results in a large group of 45851 T1D patients.[16] In most studies T1D precedes onset of epilepsy in the majority of patients.[10, 12, 13, 17] A recent study in a multi-ethnic group of T1D patients found a high frequency of epilepsy (5.9%).[10] Other studies however did not show a significant difference in epilepsy prevalence in T1D patients.[18, 19] Conclusions of prevalence studies are summarized in table 1. All these different prevalence studies are difficult to compare, not only because of the diversity of study population but also due to differences in inclusion criteria, differences in the choice of controls or baseline prevalence of epilepsy. A recent meta-analysis study indeed included only 3 studies, due to lack of validity of the other studies.[20] The authors found a combined Hazard Risk of 3.29 (CI 2.61-4.14), concluding that patients with T1D have a higher risk to develop epilepsy compared to individuals in the general population.

### Type 1 diabetes and epilepsy: a common pathway?

Literature about the possible etiological explanations for the coexistence of epilepsy and T1D is limited. Basically 4 different hypotheses were postulated: metabolic disturbances, cerebrovascular damage, autoimmune dysregulation and genetic predisposition.[14]

I. *Metabolic disturbances*

Seizures directly resulting from hyper- and hypoglycemia should not be categorized as epilepsy, but need to be categorized as symptomatic seizures.[8] Although exact mechanisms of these seizures are not known, many theories were postulated.[21] In hyperglycemia, gamma-aminobutyric acid (GABA) metabolism can be altered, lowering GABA levels and thereby lowering the seizure threshold. Metabolic disturbances associated with hyperglycemia, like dehydration and hyperosmolality, can decrease seizure threshold as well. In hypoglycemia, absence of energy substrates can lead to production of excitatory substances, resulting in hyperexcitability of the brain.[21] Brain activity is studied extensively in patients with T1D.[9,22,23] They can have EEG abnormalities in an acute hypo- and hyperglycemic state. In patients with acute hyperglycemia and diabetic ketoacidosis, EEG abnormalities correlated significantly with the severity of biochemical presentation (glycemic level, blood osmolality, dehydration, acidosis and ketosis). The EEG abnormalities included disorganization of background activity, slow wave characteristics and, less common paroxysmal activity.[23] Most importantly, long-term EEG abnormalities, ranging from asymmetry in the background rhythm to paroxysmal spike waves, were observed in patients with T1D without any neurological symptoms in euglycemic conditions.[22] The severity of these abnormalities varies and is correlated with the frequency of severe previous hypoglycemic attacks.[22] Although EEG abnormalities are common in T1D patients, it is not known whether there is a correlation between these EEG abnormalities and the development of seizures. Conclusively, although it is clearly demonstrated that acute hypoglycemia and hyperglycemia increase seizure susceptibility, the role of long-term metabolic disturbances in the development of non-symptomatic epileptic seizures is less clear.[21] In patients with high glycemic values, glucose itself can be proconvulsive. Additionally, metabolic disturbances following hyperglycemia can contribute to the development of seizures.[24] Recurrent hypoglycemia could possibly force the brain to use adaptive energy mechanisms (lactate), which can sustain seizures in patients with T1D patients.[25] Nevertheless, while metabolic factors do play a role in the susceptibility of developing seizures, they seem insufficient to explain the development of epilepsy in well-controlled T1D patients. Schober et al. found no difference in hbA1c, nor in insulin use in T1D patients with or without epilepsy. Also, the occurrence of hypoglycemic events was comparable in both groups after correction for confounders. It should be noted that this study did not use continuous glucose monitoring.[26] Hypoglycemia unawareness is present in up to 40% of subjects with T1D,[27] and as such, many hypoglycemic events might have passed

unnoticed when using capillary glucose measurements.

II. *Cerebrovascular damage*

Microvascular complications are common in both T1D and type 2 diabetes mellitus (T2D). The brain is a frequent target for these complications, leading to changes in cerebral blood flow and histopathological changes.[28] Epilepsy in T1D patients as a consequence of a cerebrovascular complication would suggest that all patients have an onset of T1D before epilepsy. In most studies, onset of T1D precedes onset of epilepsy in approximately 80% of patients.[10-12, 17] In only one study just a minority of patients had T1D before epilepsy (table 1).[19]. Furthermore, as vascular complications are more common in T2D, one would expect a stronger correlation between epilepsy and T2D, which could not be confirmed.[28, 29]

III. *Autoimmune dysregulation*

Within this domain there is a specific interest for the role of anti-glutamic acid decarboxylase 65 antibodies (GAD65-ab). GAD65 catalyzes the conversion of glutamic acid, an important excitatory neurotransmitter in the central nervous system, into GABA, an important inhibitory neurotransmitter. GAD65 is produced in the central nervous system and in the beta cells of the pancreatic islet cells, the ovaries and the testes.[30, 31] GAD65-ab can be found in up to 80% of patients with newly-diagnosed T1D.[32] GAD65-ab are associated with multiple neurological diseases, among them: stiff-person syndrome, cerebellar ataxia, and epilepsy.[33,34] The mechanism by which GAD65-ab cause epilepsy is not entirely clear. There might be a direct pathogenic role in which they interfere with the function of GABA. Their presence can disturb the balance between excitation and inhibition in the brain, leading to epileptic seizures.[21, 35] It is also possible that the presence of GAD65-ab is a secondary phenomenon after release of GAD65 in the circulation due to disruption of the GABAergic neurons, also leading to production of other autoantibodies.[36] In the general population prevalence of GAD65-ab positivity is scarcely investigated, but estimated around 2% or less.[37] Few studies have tried to look at GAD65-ab in patients with both T1D and epilepsy, lacking consistent data, mainly due to small sample sizes.[10, 18, 19, 26]. Several studies did not find a difference in GAD65-ab positivity in T1D patients with or without epilepsy.[10, 16] Low titers of GAD65-ab were

**Table 1:** Framework for classification of the epilepsies.' Scheffer et al, ILAE, Epilepsia

| Author | Year | Study population | controls | Results | Type study | Conclusions | Remarks |
|---|---|---|---|---|---|---|---|
| Aguiar et al [10] | 2019 | 375 T1D | * | 22EPI/375 (5.9%)<br>IGE: 8/375 (2.1%)<br>TLE: 4/375 (1.1%) | Cross-sectional | An elevated epilepsy frequency in a cohort of T1D patients | - no control group<br>- prevalence of EPI in GP not mentioned<br>- exclusion of patients with history of severe hypoglycemia<br>- includes patients with structural etiology of epilepsy; frequency of EPI with unknown origin was 3.2%<br>- onset of T1D before onset of EPI in 83% |
| Dafoulas et al [15] | 2017 | 4922 T1D | 19688 GP | Incidence:<br>132/10000<br>Vs<br>44/10000 | Retrospective | HR 3.02 (95%CI: 1.95-4.69) of developing EPI in T1D cohort compared with GP | - ≤ 40 years of age<br>- T1D ≤ 18 years of age: significant higher prevalence (HR 3.02 vs 3.44)<br>- exclusion of patients with epilepsy before diagnosis of T1D<br>- includes patients with cerebral palsy |
| Chou et al [14] | 2016 | 2568 T1D | 25680 GP | Incidence:<br>33.7/10 000<br>Vs<br>10.4/10 000 | Retrospective | HR 2.84 (95%CI: 2.11-3.83) of developing EPI in T1D cohort compared with GP | - ≤ 18 years of age<br>- no information about etiology of epilepsy |
| Keezer et al [11] | 2015 | 2016 TRE | * 3.4-4.4/1000 | 20 T1D/2016 (1.0%) | Retrospective | A more than twofold increase in prevalence of T1D | - no control group<br>- adults with pharmacoresistant EPI<br>- No IGE in T1D group<br>- onset of T1D before onset of EPI in 80% |
| Falip et al [19] | 2014 | 229 T1D | * | 2 EPI/229 (0.8%) | Retrospective | Epilepsy is not more frequent in patients with adult onset T1D | - no control group<br>- prevalence of EPI in GP not mentioned<br>- complex study design combining 2 inclusion methods<br>- only adult onset of T1D<br>- no patient characteristics reported<br>- only TLE<br>- onset of T1D before onset of EPI in 34% |
| Ramakrishnan et al [12] | 2012 | 285 T1D | * 3.6/1000 | Prevalence EPI:<br>21/1000<br>6 EPI/285 (2.1%)<br>IGE: 5/285 (1.8%) | Retrospective | A three- to almost a sixfold increase in the prevalence of T1D in children with T1D | - no control group<br>- ≤ 16 years of age<br>- limited information about classification of epilepsy<br>- only a probable diagnosis of IGE<br>- onset of T1D before onset of EPI in 83% |
| Schober et al [26] | 2011 | 45851 T1D | * 2.1-4.1/1000 | 705 EPI/45851 (1.6%) | Observational | Increased prevalence of epileptic non-hypoglycemic seizures for children and adolescents with T1D | - no control group<br>- ≤ 20 years of age<br>- No difference in glycemic control between epilepsy and no epilepsy |
| Mancardi et al [17] | 2010 | 249 T1D | * | 6 EPI/249 (2.4%)<br>IGE: 4/249 (1.6%) | Retrospective | Higher prevalence of epilepsy (including IGE) compared with GP | - no control group<br>- prevalence of EPI in GP not mentioned<br>- ≥ 18 years of age<br>- onset of T1D before onset of EPI in 83% |
| O'Connell [18] | 2008 | 1384 T1D | * 5-10/1000 | 15 EPI/1384 (0.9 %) | Cross-sectional | No higher prevalence of epilepsy or IGE | - no control group<br>- ≤ 19 years of age<br>- high reported prevalence of epilepsy in general population<br>- strict inclusion/exclusion criteria leading to limited inclusions<br>- onset of T1D before onset of EPI in 87% |
| McCorry et al [13] | 2005 | 518 IGE | 150 000 GP | 7 T1D/518 (1%)<br>Vs<br>465 T1D/ 150000 (0.3%) | Retrospective | OR 4.4 (95%CI: 2.1-9.2) of having T1D in the IGE cohort compared with GP | - 15-30 years of age<br>- onset of T1D before onset of EPI in all patients with available information |

Table 1: prevalence studies of T1D and epilepsy; T1D: type 1 diabetes; EPI: epilepsy; IGE: Idiopathic generalized epilepsy; TLE: temporal lobe epilepsy; GP: general population; PRE: pharmacoresistant epilepsy; vs: versus; HR: hazard risk; OR: odds ratio; 95%CI: 95% confidence-interval
* prevalence of epilepsy according to literature (lacking control group)

found in 7 of 8 T1D patients with epilepsy, but these titers were not compared with T1D patients without epilepsy.[18]

IV. *Genetic predisposition*

Ramakirshnan et al. were the first to explicitly suggest the possibility of a genetic predisposition, due to the excess of IGE, not only in their cohort, but also in the first published prevalence study.[12, 13] IGE is considered to have a genetic basis, with a complex genetic inheritance. McCorry et al. found that the onset of T1D preceded the onset of epilepsy concluding that this must be because of a different onset of 2 different pathologies or simply because T1D causes epilepsy.[13] T1D preceded onset of epilepsy also in other studies.[10, 12, 13, 17] T1D is considered a disorder with complex genetic architecture. In T1D 50% of the genetic risk is due to alleles at the HLA-region on chromosome 6p21, which encodes the major histocompatibility complex proteins. Certain haplotypes of this complex are associated with an increased risk of developing T1D. Genome-studies have found other loci as well, although the molecular mechanism of action remains unclear for most of them.[38] So far, no common genetic risk factors for both epilepsy and T1D have been identified, but promising research involving genes coding for glucose metabolism and major histocompatibility complex is ongoing.[10, 39] There are a few rare genetic syndromes due to mutations in KCNJ11 and IER3IP1 associated with neonatal diabetes mellitus, epilepsy, and developmental delay, but they are not associated with T1D.[40, 41]

## Conclusion

Although literature concerning the potential relationship between epilepsy and T1D is scant, available information is supportive of a more than fortuitous association between these two diseases. There is large variability in reported prevalence of epilepsy in T1D patients, possibly because differentiating between hypo- and euglycemic seizures is challenging. Currently, continuous glucose monitoring is available in many patients with T1D and provides information about fluctuations in glycemic values, which can improve differentiation between hypoglycemic and euglycemic seizures in patients with T1D. As such, the underlying etiology of seizures in T1D patients can be better defined and proper treatment can be considered. Both the metabolic and cerebrovascular etiological hypotheses offer insufficient explanation considering the characteristics of reported patients, although it is clear that fluctuations in glycemic values could be a trigger for epileptic seizures. Hypothesis on auto-immune and genetic etiologies are plausible, but so far hard evidence is lacking. Genomic research in both T1D and epilepsy is rapidly growing and offers possibilities to identify a common genetic pathway. It is also possible that multiple factors are contributing to the coexistence of both diseases. In conclusion, more studies are needed to define the characteristics of T1D patients with epilepsy. These studies need to focus on reporting seizure type, classification of epilepsy, history of hypoglycemic attacks, use of continuous glucose monitoring, glycemic control, and presence of specific auto-antibodies like GAD65-ab.

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# Neonatal electroencephalography: revival of an old technique

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## Abstract

In preterm neonates or critically ill newborns, there is an increased focus on neuromonitoring with the ultimate goal to improve neonatal outcome. Therefore neonatal EEG has regained his place in modern neonatal care. Both amplitude-integrated and standard EEG techniques can be used for this purpose. Neonatal EEG has a few specific applications on the NICU. It can be used to detect seizures and follow-up on the effect of treatment, determine the degree of encephalopathy in newborns with hypoxic ischemic encephalopathy (HIE) and assess ongoing brain maturation in preterm born babies.

## Introduction

Neonatal care has improved considerably in the past years, leading to improved survival rates in the neonatal intensive care unit (NICU). Despite these major advances in perinatal care, there is still a wide range of long-term consequences affecting survivors. Direct injury to the brain, related to premature birth or disturbance of normal brain maturation due to an acute event in the neonatal period, accounts for the subsequent occurrence of developmental impairments. The risk and severity of these complications rises with decreasing gestational age, lower birth weight and the extent of the brain injury. The neonatal intensive care faces the challenge to protect the developing brain during this critical period of brain development at the NICU. As a result there is an increased focus on neuromonitoring and neuroprotection in the NICU. Neonatal electroencephalography (EEG) has regained a prominent place in the care of sick newborns. EEG can offer a window on brain function in newborns, even if the neurological status is difficult to evaluate from a clinical point of view.

## aEEG and EEG are complementary techniques

Continuous EEG monitoring provides direct information on brain function in the newborn. The classic system of conventional EEG can be used in preterm and term newborns[1]. A limited amount of electrodes can be used in the small babies (10-17), applied according to the International 10-20 System. The conventional EEG can give information on background activity in terms of amplitude, symmetry, synchrony and frequency. The development of different sleep stages are easily appreciated. Information on abnormal neuronale activity eg seizures is very detailed in time and space. It allows very good insight in artefacts, especially when combined with video monitoring. It is a non-invasive technique, but requires training of the technician and experience of the reader. To facilitate the use of functional brain monitoring in the NICU, amplitude-integrated EEG (aEEG) can be used as a screening method.

aEEG is measured with a limited amount of electrodes (2-4). The EEG is frequency filtered and displayed on a semi-logarithmic scale (linear 0-10 µV, logarithmic 10-100 µV) and time compressed. The result is an 'activity band', shown on a display allowing an easy visual interpretation by pattern recognition. It is faster and easier to use, and therefore can be used in very preterm born and critically ill babies. Interpretation requires minimal training in comparison with the standard EEG technique. It can also be used for evaluation of background activity, but there is less sensitivity for focal abnormalities and asymmetry. Sleep-wake is visualised in a sinusoidal pattern and this way active sleep and quiet sleep can be monitored. Seizure activity can be picked-up, keeping in mind that short seizures or those in low amplitude can be missed and artefacts can be misinterpreted as seizures[2].

It is important to keep in mind that many frequently used medications in the NICU eg midazolam, fentanyl, phenobarbital, can have an effect on the background activity in the EEG. Especially when EEG is used for evaluation of degree of encephalopathy and prognostication. aEEG is becoming a routine part of the clinical evaluation of the sick newborn at the NICU. It should be used as a complement to the standard EEG, and close collaboration between neonatologists and clinical neurophysiologists is necessary for optimal performance and interpretation of EEG data.

## Neonatal seizures

The occurrence of neonatal seizures is a common clinical condition in neonates. Seizures are often the first sign of neurological dysfunction in the newborn and are mostly acute symptomatic. This means that the occurrence of seizures points towards an underlying brain injury such as hypoxic ischemic encephalopathy, stroke or intraventricular hemorrhage. Seizures can have a long lasting effect on brain development and can lead to long-term neurodevelopmental problems[3].

Clinical diagnosis remains difficult. Bed-side clinical observation has been demonstrated to be inaccurate for neonatal seizure detection. Many seizures in preterm and term newborns are subclinical or have very subtle clinical signs. Dissociation between clinical and electrophysiological phenomena is often observed in neonatal seizures, especially after initiation of treatment with phenobarbital.

On the other hand, EEG has also an important function in the differential diagnosis of paroxysmal events in the newborn. Many paroxysmal events that can be observed in preterm and term newborns have no correlate on EEG. These events are not epileptic in origin and should not be treated with anti-epileptic drugs. Typical examples are benign sleep myoclonus and automatisms that can be seen due to brainstem release phenomena in critically ill newborns eg smacking or bicycling movements.

EEG remains the golden standard for detecting all seizures in the neonate. aEEG can be helpful in screening for epileptic seizures, keeping in mind the limitations of the technique (Fig 1). EEG monitoring should be requested in high risk neonates keeping in mind that more than half of the seizures in this patient group will be subclinical. After treatment, monitoring of the response to anti-seizure medication and evaluation for re-emergence of seizures during or after weaning can be evaluated with the help of further EEG monitoring.

The underlying cause of the seizures will be the most important factor for outcome prediction. However, there is growing evidence that recurrent seizure activity will amplify the negative effect on the developing brain, regardless of underlying etiology[4]. Therefore detection and treatment of seizures has become more aggressive in the NICU. Further research is necessary to define the optimal treatment strategy and ultimately improve long-term outcome in newborns with neonatal seizures.

## Hypoxic ischemic encephalopathy

Hypoxic ischemic encephalopathy is still a major cause of morbidity and mortality in the newborn. The severity and duration of the insult will determine the degree of brain damage[5]. Neurodevelopmental sequelae include cerebral palsy, epilepsy and cognitive problems. After the first phase of the insult, the hypoxia induces secondary changes to the brain, leading to further brain damage in the first hours after birth. This enables a therapeutic window of time when neuroprotective measures could prevent this additional secondary brain damage. Therapeutic hypothermia has become standard of care in newborns with a moderate to severe degree of encephalopathy. The goal is to decrease the core temperature of the newborn to 33-35°C for 72 hours within the first 6 hours after birth. Decreasing the temperature markedly protects against the secondary reperfusion injury

and improves outcome[6]. It is of great interest to identify in a fast and reliable manner the candidates for therapeutic hypothermia. However it remains difficult to predict which newborns will develop a significant degree of encephalopathy or epileptic seizures in the first hours after birth. The decision to start therapeutic hypothermia can be based on clinical or electroencephalographic scores. Clinical scores (eg Thompson score) are easy to apply but can be variable in the first hours postnatally[7]. As the EEG is very sensitive to abnormalities in brain function, it is a suitable and objective method for quantifying the severity of encephalopathy and the evaluation of recovery after initiation of treatment. Both aEEG and EEG can identify moderate and severe degrees of encephalopathy and facilitate the decision to initiate therapeutic hypothermia.

For future neuroprotective measures, milder forms of encephalopathy will be important to discriminate and in this group routine EEG measurement will prove to be superior to aEEG. Routine EEG monitoring is most sensitive in determining the degree of encephalopathy. The earliest abnormality is the absence of normally occuring sleep/wake cycling. More severe brain dysfunction will lead to discontinuous background patterns in the EEG (Fig2). Depending on the severity, the discontinuous periods become prolonged (> 10 seconds) and suppressed (<10μV)[8]. Bed-side interpretation of neonatal EEG remains difficult however. Therefore there is a need for the development of a reliable decision-support EEG analysis based on the automated grading of neonatal background EEG. First steps have been made in the development of real-time automatic background analysis software[9].

**Figure 1:** Example of epileptic seizure. Notice the upward deviation of the lower margin of the aEEG activity band (upper part) and the rhythmic sharp activity in the EEG (lower part).

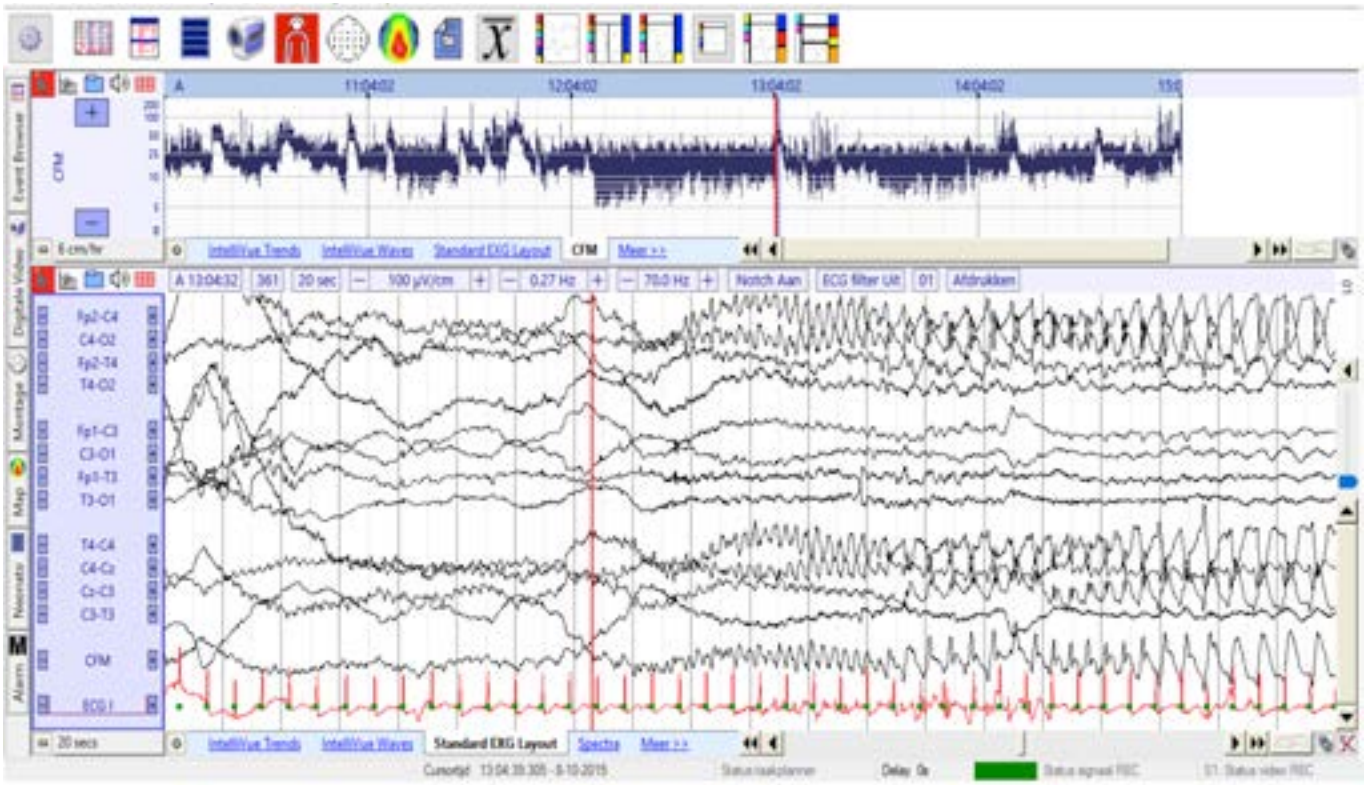
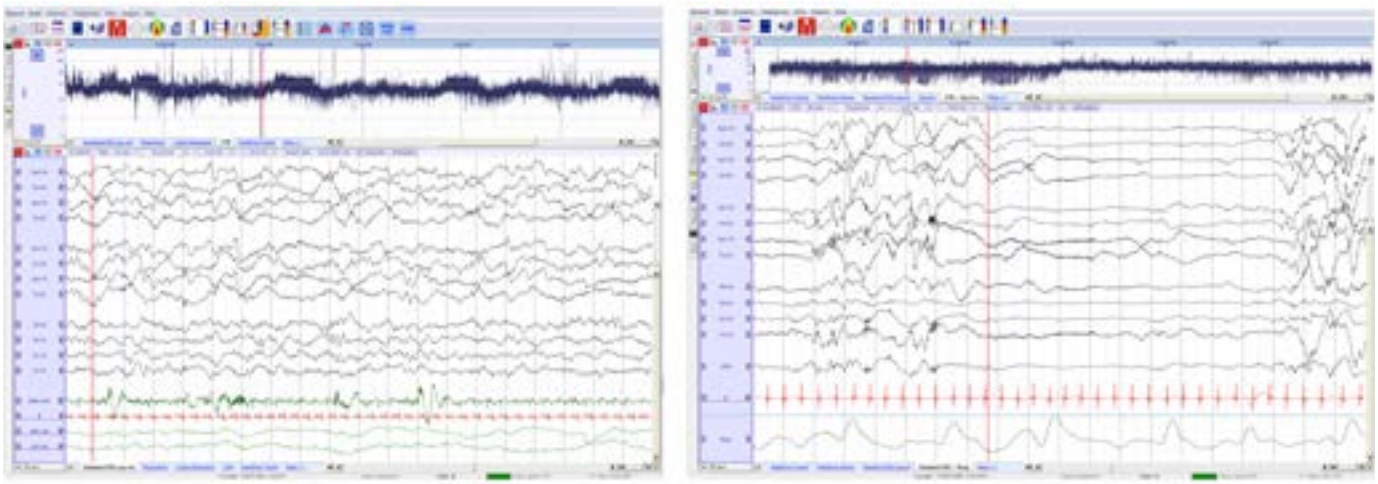


**Figure 2:** aEEG activity band (upper part) and routine EEG (lower part) Left: normal EEG of term newborn baby Right: discontinuous EEG pattern in a baby suffering from HIE.



## EEG for evaluation of brain maturation

Preterm birth accounts for almost 11% of all live births worldwide annually. Medical advances have led to improved survival rate, but these children remain at high risk for long-term disabilities. In preterm neonates, the neuronal network is still in development. The human brain develops rapidly during gestation as the degree of cortical folding increases from week to week. These changes can be seen from a structural perspective but are also reflected in the electrophysiological activity. The first electrical activity to be seen are spontaneous activity transients or SATs. At this point the background is still discontinuous and bursts have a simple appearance. With advancing age and neuronal development, the EEG pattern will become more continuous, bursts of activity become more complex and sleep-wake cycling appears[10]. Therefore, serial EEG monitoring can follow-up on brain maturation according to postmenstrual age (Fig 3) .

There is growing evidence that background EEG activity, reflecting the complexity of the neuronal network during development, can predict cognitive outcome in preterm born children[11,12]. Less mature EEG patterns and sleep architecture have been reported in preterm infants when compared with term infants at matched term ages. Further research is necessary to improve sensitivity and specificity of various EEG features to predict neurodevelopmental outcome, but it will prove to be valuable in the future. Early prediction is a first step towards development of early intervention strategies and additional neuroprotective measures.

## Conclusion

Neonatal EEG knows a revival in the NICU. The focus on neuromonitoring has the purpose to further improve neurodevelopmental outcome of preterm and ill newborn babies. EEG monitoring can be used for diagnostic and prognostic purposes. Electrophysiological markers have a value in unraveling pathophysiological mechanisms during development of the neuronal network in newborns and can guide further development of neuroprotective measures in the NICU.

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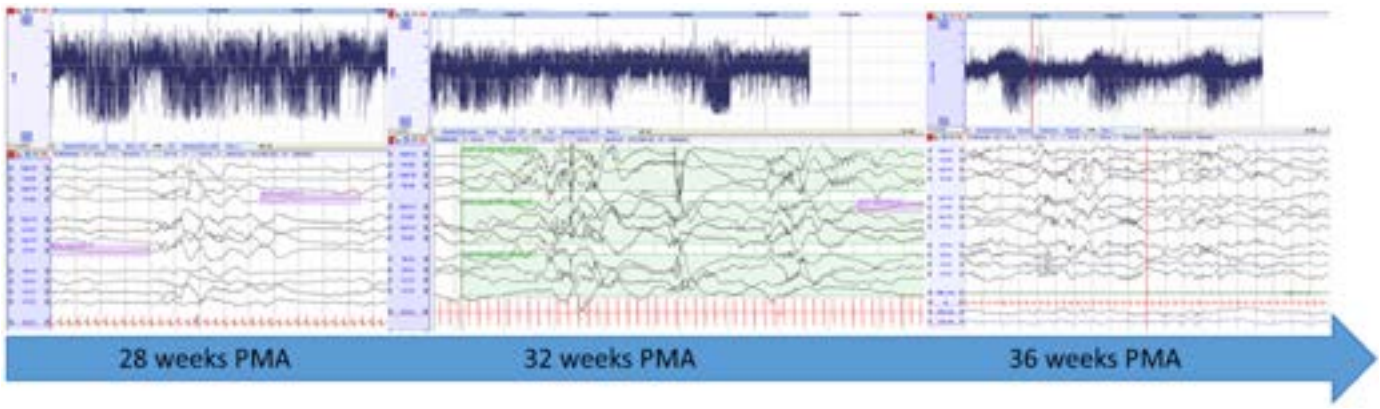
**Figure 3:** aEEG (upper part) and EEG (lower part) pattern illustrating normal evolution with advancing postmenstrual age.



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# Seizures are not the major issue in self-limited focal epilepsies: focus on cognitive disorders

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## Abstract

Benign epilepsy of childhood with centro-temporal spikes is the most common type of self-limited focal epilepsies (SFE), which account for 10% of all epilepsy in the pediatric age range and is supposed to be of polygenic origin. The term benign refers to the fact that children are supposed to be of normal intellect, have no brain lesion that could explain their epilepsy and that epilepsy usually remits by the age of sixteen. But seizures in SFE are the tip of the iceberg. Indeed, cognitive and learning deficits are frequent and may negatively impact children's academic achievements, mental health and quality-of-life. In this article, we will review the evidence of widespread cognitive dysfunction in SFE, present the tools to identify these cognitive deficits, how interictal epileptiform discharges may play a role in these cognitive deficits and discuss the concept of epileptic encephalopathy with continuous spike and waves during slow-wave sleep.

## Introduction

Benign epilepsy of childhood with centro-temporal spikes (BECTS), or more recently, epilepsy with centro-temporal spikes (ECTS) is the most common electroclinical epilepsy syndrome, accounts for 5–10% of all epilepsy in the pediatric age range and is supposed to be of polygenic origin[1,2]. Distinctive features of BECTS include its specific electroencephalography (EEG) signature (centro-temporal spikes activated by sleep)(see figure 1), seizure semiology (brachio-facial seizures) and age dependent onset (3-13 years). The term "benign" refers to the fact that children with BECTS are generally of normal intellect at the epilepsy onset, have no history of neurological insult or condition that could explain their epilepsy, have no obvious focal neurological deficits and in virtually all children seizures remit by the age of sixteen.

## The evidence of widespread cognitive dysfunction in self-limited focal epilepsies

However, the situation is not so favorable as it seems. In a recent meta-analysis Wickens et al. have shown that children with BECTS display a profile of pervasive cognitive difficulties and thus challenge current conceptions of BECTS as a benign disease[1]. Accordingly, revised terminology of the international league against epilepsy (ILAE) replaces the term "benign" with "self-limited" and use the abbreviation ECTS in place of BECTS[1,3]. Moreover, the most common self-limited focal epilepsy (SFE) is ECTS but others like the self-limited occipital, frontal, temporal, and parietal lobe epilepsies are also included in this broad group[3]. Language dysfunction is recurrently raised as an issue of concern in the SFE literature. Smith et al. reported poorer auditory processing, single-word reading, and expressive and receptive language in children with SFE [4]. Wickens et al. have also shown a large effect for poorer outcomes in the verbal intellectual quotient (IQ) i.e. acquired verbal knowledge and language-based abilities[1]. In addition to language deficits, systematic reviews have concluded that children with SFE display worse memory and attentional functioning compared to normal controls[5,6].Kavros et al. allocated different tests within attention-based theory and could conclude that there was a deficit in all theoretical attention systems including alertness and executive networks[5]. Other studies have also revealed poorer cognitive outcomes in other major cognitive factors, including visual processing, processing speed, fluid reasoning and motor coordination[1]. In a school-aged prospective population based study of children with a first recognized seizure and a normal IQ (>or =70), 27% to 40% exhibit neuropsychological (NP) deficits at onset of the disease(3). Finally, long-term studies have shown persistent cognitive impairments in ECTS even after the remission of the disease[1].

Considering the focal nature of SFE, it is surprising to find a profile of diffuse cognitive difficulties while we might have expected that the cognitive deficits would be limited to the localization of the interictal epileptiform discharges (IED). All these observations may suggest a considerable impact of the overarching epileptic disease process in brain functioning.

## What are the tools to identify these cognitive deficits?

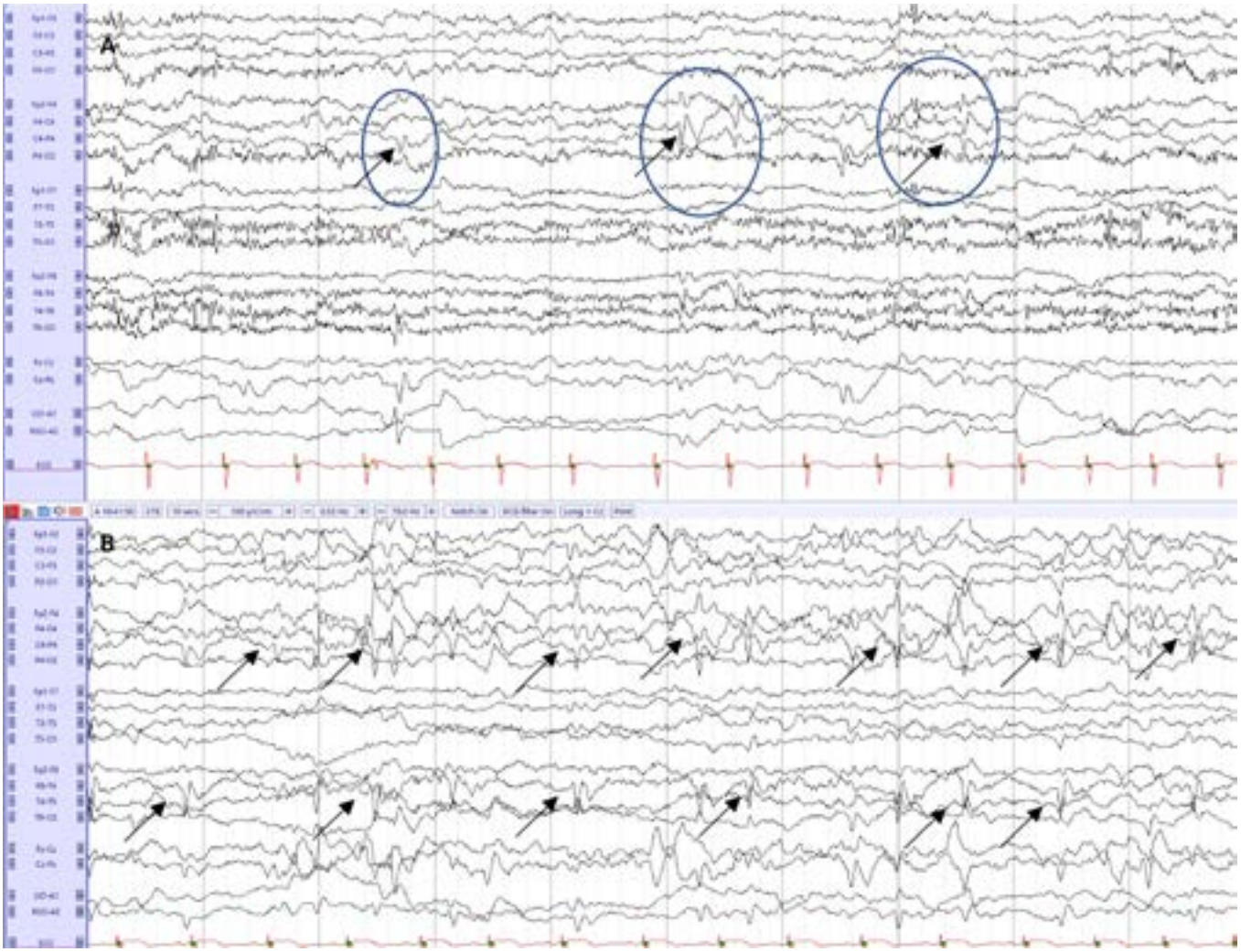
It is crucial to rapidly identify and characterize cognitive and learning deficits in these young patients as they may negatively impact children's academic achievements, mental health and quality-of-life.

Based on the medical history of the patient, the first red flag that should alert the physician is the presence of learning and/or behavioral difficulties.

On the first consultation with the child's physician, parents questionnaires are interesting screening tools. Diagnostic and Statistical Manual of Mental Disorders (DSM) V questionnaire for the detection of attention deficit disorder with or without hyperactivity (ADHD) is a useful tool but is limited to children older than six years of age. The Massa score, that was already used in two previous study assessing EEG criteria predictive of complicated evolution in SFE[7,8] assesses academic underachievement and behavioral problems (table 1). The cognitive function is classified as "typical" (sum score $\leq$ 2) or "at risk" (sum score $\geq$ 3) according to the sum of academic and behavioral scores. The Child Behavior Checklist (CBCL, Achenbach, 1991) is a widely used caregiver report form identifying emotional and behavioral problems together with academic and social skills in children. Normative data are available integrating information from multiple societies. If these parents questionnaires indicate cognitive problems, the second step is to perform an individual neuropsychological assessment consisting of the administration of several tests that have been standardized and normed in healthy populations[9].

Several studies have shown that the Wechsler Intelligence Scale for Children (i.e. IQ scale) or the Wechlser nonverbal scale (i.e. nonverbal IQ) for children

**Figure 1:** Electroencephalography (EEG) data collected from a 9-years-old male with epilepsy with epilepsy with centro-temporal spikes (ECTS) showing A) Wake EEG : right sided centro-temporal spikes (grade 1-arrows and circle) and B) Sleep EEG : right sided centro-temporal spikes activated by sleep (grade 3-arrows).




with language difficulties are sensitive to epilepsy-related cognitive problems in clinically referred children with epilepsy[10]. Besides IQ, it is crucial to explore memory function, expressive and receptive language skills, attention and executive functions, perceptual and motor abilities with a standardized protocol. This creates a cognitive profile of strengths and weaknesses across multiple domains that assess the mental capacity of the child and provide the basis for a cognitive rehabilitation program if needed[9]. The protocol used in our institution is detailed on table 2 .

## The concept of epileptic encephalopathy in SFE

Evidence is growing that apart from the genetic predisposition, the repetition of seizures and the use of antiepileptic drug (AED), focal interictal epileptiform discharges (IED) may play an important and underestimated role on behavior and cognition difficulties in children with SFE. Indeed, the prevalence of focal IED in the electroencephalogram (EEG) of cohorts of non-epileptic children with neurodevelopmental disorders (i.e. ADHD, specific language impairment, etc.) has been reported significantly higher than in the normal population[11]. Even in SFE patients with infrequent seizures where AED are unnecessary, cognitive problems may be severe[12]. Moreover, several studies have shown that the severity of cognitive deficits has been associated with the intensity of IED in the awake and NREM (non-rapid eye movement) sleep state[13]. Despite this literature supporting a negative impact of IED on behavior and cognition, well controlled-studies designed to evaluate the effect of an AED aiming to reduce IED are still lacking. Therefore, in typical SFE, AED are primary prescribed to prevent seizures recurrences and not to treat IED.

There is an exception to this rule in children. A subgroup of SFE patients may evolve to epileptic encephalopathy (EE) with continuous spike and waves during slow-wave sleep (CSWS). This epileptic syndrome associates EE with almost continuous and diffuse IED during NREM sleep. Patients with EE present cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology suggesting that the IED itself contributes to the cognitive deficits [2,14]. Clinical manifestation of EE includes plateauing of development or regression, either global or limited to certain functions such as language (e.g. caused by acquired auditory agnosia secondary to left temporal IED in Laudau-Kleffner Syndrome for example) or behavior, typically arising or worsening at times of abundant IED even in the absence of seizures[14]. ECTS and ECTS complicated by EE with CSWS are at the two edges of a spectrum where the most frequent and diffuse IED during NREM sleep (figure2) result in the more severe behavioral and cognitive deficits[3,13]. In EE with CSWS, improvement of sleep EEG with AED and particularly corticosteroids, results in considerable cognitive improvement, as illustrated in table 3, as well as normalization of epilepsy-related regional metabolic changes[12,15-19]. On the contrary, if treatment is delayed or failed, irreversible cognitive sequelae may persist life-long, even if epilepsy remit by adolescence[20,21,22]. This is the reason why these patients should be identified rapidly, to bring as soon as possible the best treatment. A regular standardized neuropsychological assessment that will confirm the cognitive regression and a sleep EEG obtained during a whole night of sleep or a nap are required to confirm the diagnosis of EE with CSWS. Regarding the EEG, two criteria are of interest and must be analyzed. The first one is the spike wave index (SWI), corresponding to the percentage of SW activity in a defined period (for example the first 20-minute NREM sleep) that will objectivize the intensity of spiking, usually occupying at least more than 85 % of the NREM sleep (see figure 2). The second criteria is the diffusion of the IED to other parts of the brain. For this purpose, our team has developed a qualitative EEG grading system based on 5 grades (see table 4)[12]. This grade was adapted from papers aimed to characterize the EEG findings in children with typical and

atypical forms of ECTS, including the modification after adjunction of an AED[7,23]. Interestingly, several studies found that some typical ECTS patients without cognitive regression or plateauing might have a SWI > to 85% but that none had a grade inferior to 3. On the contrary, other studies evidenced that some patients with a clear cognitive regression had a SWI < 85%. Moreover, we observed that the response to treatment characterized by a significant cognitive improvement was always associated with a fall-off of at least two grades in both awake and sleep EEG tracings but not always by a decrease in the SWI[12,16,24]. These observations suggest that the EEG grade correlates better than the classical sleep SWI with cognitive functioning in CSWS patients.

## How IED may cause cognitive deficits in SFE?

Two non-exclusive hypotheses are proposed to explain the impact of IED on cognitive deficits in ECTS. The first hypothesis suggests that the cause is transient cognitive impairment (TCI) i.e. each IED induces a transient modification of brain functioning depending on the localization and lateralization of the IED[13]. However, considering the difficulties to clinically identify TCI, it remains difficult to conceive that it is only through the repetition of transient time-locked effects that IED contribute to sustained cognitive deficits. The second hypothesis proposes more long-lasting effects of IED on brain functioning and plasticity via complex interactions within different neuronal populations, whose activities decrease or increase not only during but also before and after the IED[13].

Studies have demonstrated modification of brain connectivity associated with IEDs in widespread cortical areas involved in cognitive processing, including the frontal, temporal and occipital cortex, as well as areas involved in the default mode network (DMN)[25,26]. The DMN is composed by connected brain structures that are active when normal subjects are at rest and is deactivated when they engage in a task. In children with SFE, increased variability in the precuneus, a core component of the DMN, appears to be associated with an earlier age of seizure onset. A positive correlation has been reported between the segregation of DMN components, the extent to which the anatomic network components could function independently, and intelligence quotient (IQ), verbal comprehension, and perceptual reasoning has been reported[27]. Thus, IED-related inhibition of the default mode network would lead to a decrease in awareness.

As previously reported, language function is an area of interest in SFE because its deficits are very frequent. A dynamic functional connectivity study provided additional insights into the effects, and possibly the sequelae, of IEDs in SFE. Based on the putative cortical sources of the IEDs, Xiao et al selected regions of interest (ROIs) within the bilateral Rolandic opercula, a region engaged in language tasks. They measured the evolving connectivity strength between these ROIs and the rest of the brain during the course of >2000 IEDs. The investigators observed increasing connectivity between the IED sources and the left inferior frontal gyrus, left supramarginal gyrus, and left inferior parietal lobe over the course of the IEDs, three brain regions also crucial for language production[28]. The observation of periodic cortical excitations caused by IEDs overlapping brain regions showing decreased connectivity suggests that the momentary discharges might lead to persistent connectivity alterations. This is consistent with the remote inhibition hypothesis, a proposed explanation for the deficits seen in CSWS and Landau-Kleffner syndrome, positing that abundant IEDs lead to the inhibition of remote but functionally connected brain region[16].

Although children with SFE usually have IQ scores in the normal range, they present frequently deficits in executive functions i.e. attention, processing speed, working memory and inhibitory control compared to healthy individuals [1]. The dorsolateral prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex have traditionally been associated with executive function. Several studies implicate nonspecific frontal lobe involvement in children with SFE. Electrographic measures suggest an overall modification in the connectivity within frontal and frontotemporal regions that appears to be partly driven by the IEDs[27].

## Conclusion

There has been increasing evidence for the presence of widespread cognitive dysfunction in SFE. Many questions concerning the impact of IED on behavior and cognition, the pathophysiology and treatment of IED-induced deficits remain unanswered. Well-designed neurophysiological and pharmacological studies are warranted to address these crucial questions.


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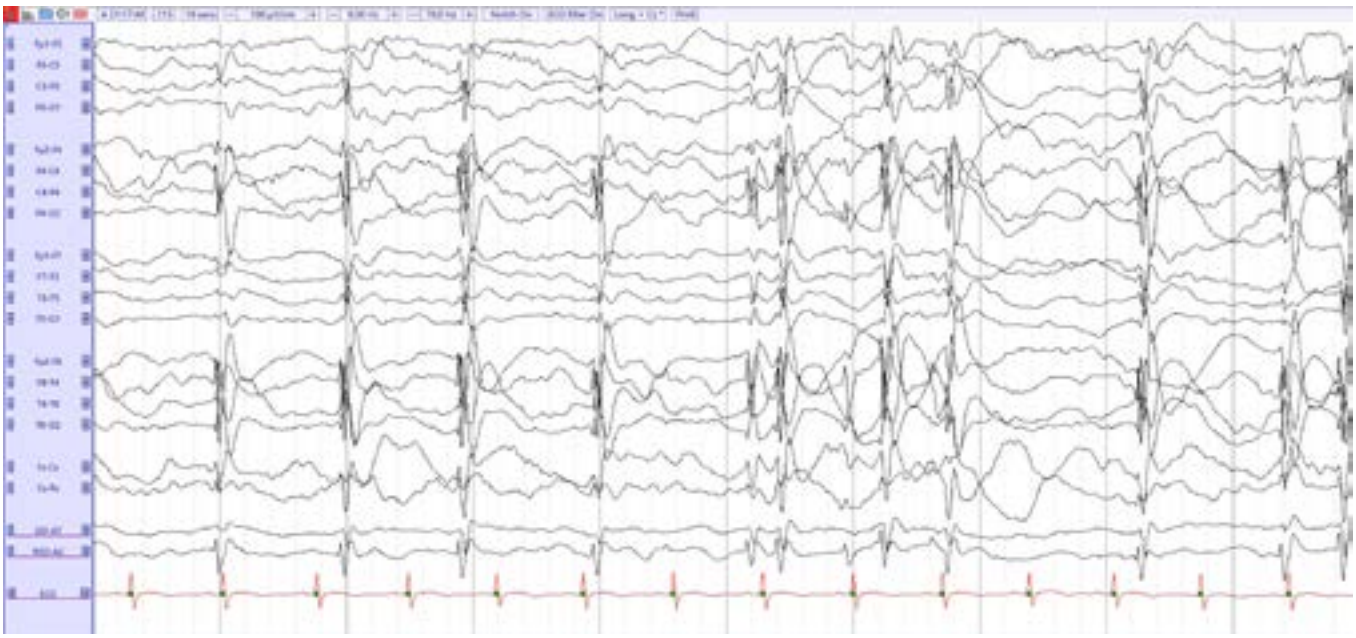
**Figure 2:** Sleep Electroencephalography (EEG) data collected from an 8-years-old male with epilepsy with centro-temporal spikes (ECTS) complicated by an epileptic encephalopathy with continuous spike and waves during slow-wave sleep (CSWS) with a spike-wave index (SWI) > 85% and frequent secondary generalization, evaluated as a grade 4.



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# Epilepsy as presenting symptom of neuroinflammatory disorders in childhood

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## Keywords

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## Abstract

Neuroinflammatory disorders in childhood are a growing spectrum of chronic conditions including autoimmune as well as autoinflammatory diseases. Nearly every component of the central and peripheral nervous system can be target of dysregulation of the innate or adaptive immune system. Clinical manifestations range from focal neurological deficits to decreased level of consciousness and coma. Seizures may be the main presenting symptom. This is especially the fact in acute disseminated encephalomyelitis and in the presence of neuronal autoantibodies. Also, in systemic autoimmune or autoinflammatory disorders, seizures may occur before any sign or symptom of systemic involvement. Autoimmune seizures often do not respond to conventional antiepileptic treatment but might respond to immunotherapy, and therefore an early correct diagnosis is important.

Most specific neuroinflammatory disorders remain rare in childhood, however, when considered as a group of disorders, they are not uncommon and more prevalent than previously thought. Increased clinical recognition and new diagnostic markers, especially autoantibodies, have increased the number of diagnosed patients and have led to better characterization of the different neuroinflammatory disorders. Correct diagnosis remains often challenging and can solely rely on clinical features in case of absent biomarkers. Timely diagnosis is essential as it may lead to early initiation of immunotherapy and improvement in long-term neurological outcomes.

## Introduction

The term 'neuroinflammatory disorders' is an umbrella for all diseases affecting the central and/or peripheral nervous system caused by inflammation. The group includes autoimmune as well as autoinflammatory disorders of the nervous system on the one hand, and, primary and secondary inflammation of the nervous system on the other hand. Even infections can be considered as part of the spectrum. They may occur in children of any age and are typically acute or subacute in onset. Nearly every component of the central and peripheral nervous system can become target of dysregulation of the innate or adaptive immune system.

Autoimmune and autoinflammatory diseases are both systemic diseases with a pathological process directed against own body cells and tissues characterized by chronic activation of the immune system which eventually leads to tissue inflammation in genetically predisposed individuals. Nevertheless, specific effectors of damage are different in the two groups of diseases. In autoinflammatory diseases, the innate immune system directly causes tissue inflammation without participation of the adaptive system. In autoimmune diseases the innate immune system activates the adaptive immune system which, in turn, is responsible for the inflammatory process. In the patients with autoinflammatory diseases, monocytes and macrophages of the innate immune system are responsible for inflammation and damage and not autoantibodies and autoreactive antigen-specific T cells as in autoimmune diseases.[1] However, it is Important to realize that both autoimmune and autoinflammatory disorders are the expression of immune dysregulation, and both may be the consequence of the same underlying genetic vulnerability. Moreover, it is increasingly evident that autoinflammatory as well as autoimmune disorders can be seen as complications of primary immunodeficiency.[2]

Primary neuroinflammatory disorders solely affect the nervous system. In secondary cases of neuroinflammation the inflammation occurs in the context of a systemic disease.

Clinical manifestations of childhood neuroinflammatory disorders range from focal neurological deficits to decreased level of consciousness and coma. Mostly, in the patients with focal neurological deficits only discrete lesions are seen on imaging whereas in the encephalopathic patients extensive abnormalities are seen on brain magnetic resonance imaging (MRI). A striking exception are the autoantibody driven encephalopathies in which MRI can even be normal in comatose patients.[3,4] New insights in etiopathogenesis of inflammatory disorders of the nervous system over the past decade have widened the spectrum of these diseases dramatically, and growing recognition of these conditions has increased the number of diagnosed patients. In this paper, the main focus is on auto-immune disorders of the nervous system in childhood presenting with seizures.

## Primary neuroinflammatory disorders in childhood

The best known and one of the more frequently occurring primary neuroinflammatory disorders in childhood consist of the group of immune-mediated acquired demyelinating syndromes. These can occur as 1-time event (monophasic) or as recurrent disease with several relapses. Monophasic syndromes constitute approximately 80% of cases of acquired demyelination during childhood and include acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis (TM) among other rarer monofocal or polyfocal presentations.[5] Monophasic syndromes are more likely to occur in younger children and in most of the children a preceding respiratory infection was reported.[6] About one fifth of the children will evolve towards a relapsing disease and most of them will ultimately be diagnosed with pediatric-onset multiple sclerosis (POMS).[5]

Other relapsing demyelinating syndromes consist of the group of neuromyelitis optica spectrum disorders (NMOSD) and acute disseminated encephalomyelitis followed by optic neuritis (ADEM-ON). ADEM-ON patients present with ADEM and subsequently relapse with a single or recurrent episodes of ON.[7] In about three-fourths of the children with NMOSD IgG antibodies targeting aquaporin-4 are detected which likely play a key pathological role in this disorder.[8] The majority of ADEM-ON patients has anti-myelinoligodendrocyte glycoptrotein (MOG) antibodies. In contrast with the aquaporin-4 antibodies in neuromyelitis optica spectrum disorders, anti-MOG antibodies are not diagnostic for ADEM-ON.[9,10] In the younger age group MOG antibodies are typically found in the patients with monophasic ADEM. However, up to one third to one half of the children with MOG antibodies will relapse within two years showing a disease course of recurrent optic neuritis, multiphasic demyelinating encephalomyelitis

(MDEM), ADEM-ON or NMOSD but not MS.[11,12] Seizure are rare in ON and TM, as well as in POMS and NMOSD. However in ADEM, seizures are one of the core symptoms and often the presenting symptom.

Antibody-mediated encephalopathies encompass a wide spectrum of newly recognized diseases. In general, the affected individuals present with subacute onset of cognitive and/or psychiatric abnormalities besides focal neurological signs, seizures or movement disorders. MRI features suggestive of encephalitis and cerebrospinal fluid (CSF) pleocytosis are supportive features for the diagnosis. For the definitive diagnosis, testing of specific autoantibodies against neuronal cell-surface (e.g. LGI1, CASPR2, DPPX, GQ1b), synaptic (e.g. NMDAR, AMPAR, GABAbR, GABAaR, mGluR5, dopamine 2 receptor, glycine receptor), or intracellular (e.g. Hu, Ma2, GAD) antigens may be helpful.[13]

N-methyl-D-aspartate receptor (NMDAR) encephalitis was first described by Dalmau in 2007 as paraneoplastic neuropsychiatric disorder affecting young women with ovarian teratoma.[14] Nowadays, NMDAR encephalitis is recognized as one of the most common autoimmune encephalitis in children surpassing the frequency of any single viral cause of encephalitis in young people.[15] In contrast to the typically psychiatric presentation in adulthood, children present more likely with seizures or movement disorders. In childhood, paraneoplastic cases are exceptional.[16]

Limbic encephalitis is characterized by (1) subacute onset of memory deficit, seizures or psychiatric symptoms; (2) bilateral brain abnormalities highly restricted to the medial temporal lobes; (3) CSF pleocytosis and/or electroencephalogram (EEG) abnormalities involving the temporal lobes; and (4) reasonable exclusion of alternative causes. Limbic encephalitis can occur as paraneoplastic phenomenon, but in childhood occurs in the vast majority of cases as non-paraneoplastic phenomenon. In paraneoplastic cases, typically Hu and Ma2 antibodies are detected, in non-paraneoplastic cases LGI1, GABAbR and AMPAR antibodies but also other antigens.[13] As in NMDAR-encephalitis, children present more likely with seizures than adults.

Rasmussen encephalitis (RE) is an unihemispheric epileptic syndrome caused by unilateral cerebral inflammation leading to unihemispheric brain atrophy. Cytotoxic CD8+ T lymphocytes seems to play a major role but the full pathogenic cascade in not clear yet. RE is characterized clinically by refractory focal seizures, most typically epilepsia partialis continua, in conjunction with progressive deterioration of neurological function.[17]

Seizures can be autoimmune in nature associated with the presence of neuronal autoantibodies (e.g. LGI1, CASPR2, NMDAR, AMPAR, GABAbR, GABAaR, mGluR5, glycine receptor, GAD) without typical 'autoimmune encephalitis' phenotype. These patients present primarily with seizures in the absence of other features of encephalitis such as encephalopathy, although the seizures and electrographic abnormalities might be severe enough to produce an 'epileptic' encephalopathy. Typically, it affects previously neurologically normal children, seizure onset is explosive with rapid evolution into status epilepticus or severe seizure clusters and seizures are focal. Autoimmune seizures often do not respond to conventional antiepileptic treatment but might respond to immunotherapy, and therefore an early correct diagnosis is important.[18]

## Secondary neuroinflammatory disorders in childhood

Inflammation of the nervous system is seen in several systemic autoimmune and autoinflammatory disorders. In autoimmune diseases, in general, dysregulation of adaptive immunity leads to production of autoantibodies and/or autoreactive T cells. In contrast, autoinflammatory disorders are predominantly hereditary disorders of innate immunity. For an overview of systemic disorders with possible central nervous system inflammation see table 1.[3] Of all disorders listed in the table, systemic lupus erythematosus (SLE), neurosarcoidosis and deficiency of adenosine deaminase 2 (DADA2) most frequently manifest with inflammation of the nervous system and can present with seizures.

## Diagnostic challenges

The huge diversity of clinical presentations of neuroinflammatory disorders makes an early and correct diagnosis often a real challenge. Moreover, the immature developing immune system in childhood influences the presentation of clinical entities as defined in adulthood. This highlights the need for more specific and sensitive biological markers to enable early correct diagnosis.

**Table 1:** Systemic disorders with CNS inflammation

| |
|---|
| Systemic autoimmune rheumatic diseases<br>– Systemic lupus erythematosus (SLE)<br>– Antiphospholipid antibody syndrome (primary and secondary)<br>– Sjögren syndrome<br>– Acute rheumatic fever<br>– Linear scleroderma/morphea/ "en coup de sabre"<br>– Sarcoidosis (neurosarcoidosis)<br>– Macrophage activation syndrome or hemophagocytic lymphohistiocytosis as complication of underlying systemic autoimmune syndrome (e.g. systemic juvenile idiopatic arthritis, SLE) |
| Systemic vasculitis with CNS involvement<br>– IgA vasculitis (Henoch-Schönlein purpura)<br>– ANCA-associated vasculitides<br>· Granulomatosis with polyangiitis (formerly Wegener granulomatosis)<br>· Microscopic polyarteritis<br>· Eosinophilic granulomatosis (formerly Churg-Strauss syndrome)<br>– Behçet disease<br>– Kawasaki disease<br>– Takayasu arteritis<br>– Polyarteritis nodosa<br>– Cogan syndrome<br>– Susac syndrome |
| Autoinflammatory syndromes with hereditary immune dysregulation<br>– Aicardi-Goutières syndrome<br>– Neonatal onset multisystem inflammatory disease and Muckle-Wells syndrome<br>– Deficiency of adenosine deaminase 2 (DADA2)<br>– Primary familial hemophagocytic lymphohistiocytosis |

The field of auto-antibodies directed against neuronal tissue is one of the most exciting fields of neuroinflammation. The discovery of antibody-mediated encephalitides has changed the diagnostic and therapeutic approach to many neurological or psychiatric syndromes previously considered as idiopathic.[19] In antibody-mediated encephalitides, routine investigation often reveals only atypical signs of inflammation. Cerebral imaging may even be normal hampering correct diagnosis. Nowadays, diagnostic testing of specific autoantibodies against neuronal cell-surface antigens (e.g. LGI1, CASPR2, DPPX, GQ1b), synaptic (e.g. NMDAR, AMPAR, GABAbR, GABAaR, mGluR5, dopamine 2 receptor, glycine receptor), or intracellular (e.g. Hu, Ma2, GAD) antigens is accessible in daily practice enabling correct diagnosis. The increasing awareness of antibody-mediated encephalitides and the relatively easy accessibility of autoantibody testing makes that the diagnosis is increasingly made. However, it should be mentioned that antibody titers correlate imperfectly with the course of the disease and may remain detectable after clinical recovery indicating the need to identify biomarkers for prognosis and treatment decisions.[20] Moreover, when results of antibody assays are discordant with the phenotype or when the diagnosis is made in an atypical demographic group, the clinical phenotype should remain the gold standard for diagnosis.

Another related hot topic nowadays is the value of MOG antibodies as diagnostic tool. MOG antibodies are typically present in monophasic demyelinating disorders, particularly, in the younger children with ADEM, and, the presence of MOG antibodies are thought to be an argument against MS diagnosis. However, up to one half of children with MOG antibodies will relapse within two years and some of these patients can meet the McDonald Criteria for multiple sclerosis. It is still under debate whether patients tested positive for MOG antibodies who fulfill the diagnostic criteria for MS should be considered as having MS, or, whether they should be considered having a MOG antibody related disease. This is more than a theoretical discussion as illustrated by the fact that patients with MOG antibodies, even when they fulfill the diagnostic criteria for MS, do not tend to respond well to the classical immunomodulatory therapies used in MS.[10]

Detection of specific autoantibodies is often considered to be pathognomonic for a certain disease, but the diagnosis is not always straightforward. First, a whole clinical spectrum may be associated with one specific auto-antibody like is the fact in a MOG antibody related disease. Second, the role of the autoantibody is not always clear and autoantibodies may be present in healthy individuals.[21]

Besides autoantibodies, several possible biomarkers, in serum as well as in CSF, are under investigation for clinical assessment and monitoring of neuroinflammatory disorders. Chemokines and other cytokines are among the major inflammatory mediators, and many are detectable in CSF and qualify as biomarkers that delineate the inflammatory process.[22] Various combinations of panels of immunobiomarkers have been proposed for detection of active intrathecal inflammation although many pitfalls are still to overcome. In the future, the implementation of this technique may not only be important in a diagnostic setting but will equally be important to clarify which factors influence the levels of central inflammatory activity, ultimately allowing to stratify better and to treat the patients more efficiently.[23]

In secondary neuroinflammatory disorders, the diagnosis can be straightforward in case the systemic autoimmune disorder is known in the patient. However, the diagnosis may be challenging if the neurological manifestation is the presenting symptom at the time that any sign or symptom of systemic involvement is lacking. In Systemic lupus erythematosus neurological manifestations are common and can be seen as initial presentation in up to one quarter of the patients.[24] In every patient with neuropsychiatric presentation without clear explanation, a systemic work-out is warranted including an inflammatory bilan and testing for autoantibodies in order to possibly diagnose a systemic autoimmune disorder. Autoantibodies are central in the diagnosis of systemic lupus erythematosus and several autoantibodies were found to correlate with neuropsychiatric symptoms. However, it should be mentioned that the prevalence of anti-nuclear antibodies in healthy subjects may reach 20% at certain ages, and many non-lupus patients with mild neurological symptoms, such as weakness or headache, might have weakly positive anti-nuclear antibodies.[25]

Although a growing palette of diagnostic biomarkers is available, clinical recognition of disease entities remains crucial for the diagnosis. This is especially true when pathognomonic diagnostic markers are missing. The clinician must judge on clinical grounds to request the correct diagnostic tests.

Figure 1 shows how to manage the diagnostic challenges in neuroinflammatory disorders in childhood.

## General considerations in the treatment of neuroinflammatory disorders

It is important to consider a neuroinflammatory process as possible underlying cause of neurological diseases in childhood including seizures, as it will allow to start early with immunotherapy leading to improvement of long-term neurological outcome. As these diseases have a common underlying pathophysiological mechanism, similar therapies can be used to treat diverse autoimmune and autoinflammatory diseases.

First of all, treatment of neuroinflammatory disorders aims to obtain rapid control of the inflammation. For induction of remission, high-dose corticosteroids pulses given during three to five days are used as first-line therapy in severe inflammation of the nervous system. Habitual, high-dose corticosteroids are given intravenously. However, recent evidence from adult trials support the fact that oral high-dose is as effective as intravenously high-dose.[26-28] Especially in childhood, oral therapy would offer more comfort but evidence in patients under the age of 18 is lacking. In addition to steroids, depending on the underlying inflammatory pathways, repetitive pulsed doses of cyclophosphamide intravenously may be added in particular cases. Standard-dose oral corticosteroid treatment can be the first choice in less severe cases, or, is used as tapering regimen after intravenous therapy. Corticosteroids are cost-effective but have many well-known side effects.[29] Intravenous immunoglobulins (IVIG) and plasma exchange or plasmapheresis are good alternatives in the steroid resistant patients, specifically in antibody mediated neuroinflammation.[30,31] IVIG is expensive and in Belgium, in the field of neuroinflammation, only reimbursed for treatment of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Plasma exchange or plasmapheresis requires specific expertise, especially in young children.

For maintaining remission, choices have to be made not only concerning choice of treatment substance but also concerning treatment duration. The choice of treatment duration depends upon the characteristics of the diseases (time needed to cool down the inflammatory process, relapsing disease or not) and severity at presentation. The choice of immunosuppressive agent is directed by the underlying inflammatory pathways as far as these are known.[9] Most neuroinflammatory disorders are thought to be T cell driven, thus T cell targeted therapy is commonly used. Most frequently used T lymphocyte targeted treatment are azathioprine or mycophenolate mofetil. The later has not only an effect on T cells but also on B cells.[32] In (auto)antibody driven diseases B cell targeted therapy is warranted with rituximab as most specific choice.[29] Oral steroids in tapering regimen and periodic IVIG can also be part of the long-term treatment.

An overview of the commonly used immunomodulatory therapies in childhood neuroinflammation for induction therapy as well as for maintenance therapy are listed in table 2 with their mechanism of action, most common side effects and monitoring advice.[3,4,32-36] In general, if possible, the advice is to administer missing vaccines or designated vaccines for patients with immune depression before starting immunomodulatory therapy. For life vaccines this should be at least 2-4 weeks before therapy. Also, screening for tuberculosis, hepatitis B and C virus and HIV is required. During treatment, monitoring routinely for signs and symptoms of bacterial, fungal, protozoal, new or reactivated viral or opportunistic infections is recommended.

Along with genetic unraveling, innovative imaging and neuropathological and cell-based diagnostic approaches have led to an explosion of research concerning molecular underpinnings of neuroinflammatory diseases and rational design of molecular therapies. Patient specific "treat-to-target" strategies which take advantage of patient's specific immune dysregulation might possibly allow to avoid systemic side effects of powerful "broad-spectrum" medications, such as high-dose corticosteroids. Multiple targeting strategies have been developed as there are designer monoclonal antibodies directed against cell markers or soluble components of the inflammatory pathway. Many biopharmaceutical immunomodulators are in a phase of being developed, tried in preclinical setting, tried in clinical studies or are already approved for clinical use. First trials were in non-neurologic disorders such as Crohn's disease and rheumatoid arthritis among others. However, the treatment of those disorders has boosted trials in neuroinflammatory disorders.[37] Designer molecules with potential use in neuroinflammatory disorders are listed in table 3.

## Conclusion

Neuroinflammatory disorders in childhood are a growing spectrum of chronic conditions including autoimmune as well as autoinflammatory diseases. Nearly every component of the central and peripheral nervous system can be target of dysregulation of the innate or adaptive immune system. Clinical manifestations range from focal neurological deficits to decreased level of consciousness and coma. Seizures may be the main presenting symptom. Although most specific neuroinflammatory disorders remain rare at least in childhood, when considered as a group of disorders, they are not uncommon and more prevalent than previously thought. Increased clinical recognition, advances in assay development with new diagnostic markers especially autoantibodies has increased the number of diagnosed patients and has led to better characterization of the different neuroinflammatory disorders. Correct diagnosis remains often challenging and can solely rely on clinical features in case of absent biomarkers. Since most neuroinflammatory disorders are treatable diseases, timely diagnosis is essential as it may lead to early initiation of immunotherapy and improvement in long-term neurological outcomes. However, formal consensus-based treatment protocols or protocols based on evidence from clinical trials are to be established yet. Currently, new options in treatment are expanding including targeting of key biological pathways. The new diagnostic tools together with new genetic insights and new therapies opens a new time area in childhood neuroinflammatory diseases which enables better prognosis.

**Table 2:** Common therapies for childhood neuroinflammatory disorders

| Medication<br>Dosage | Mechanism of action | Side effects | Monitoring |
|---|---|---|---|
| **Acute management** | | | |
| IV methylprednisolone<br><br>20-30 mg/kg/d (max 1g/d) for 3-5 d | Impact on differentiation, activation and survival of leucocytes; suppression of synthesis of proinflammatory cytokines; inhibition of immune cell trafficking | Common: hot flashes, palpitations, insomnia, mood alterations, gastro-intestinal symptoms, hypertension<br>Rare: cardiac arrhythmias | Pre/postinfusion cycle: renal and liver function tests, glucose and electrolytes<br>During infusion: blood pressure, heart rhythm |
| IVIG<br><br>2 g/kg divided over 1-5d | Inhibition of cytokine and autoantibody production, neutralizing of cytokines, inactivation of compliment, modulation of innate immune effector cells and B cells | Common: headache, gastro-intestinal symptoms, flu-like symptoms<br>Less common: aseptic meningitis, renal toxicity, hemolysis<br>Rare: hypersensitivity reactions or anaphylaxis (especially in IgA deficient) | Prior to first dose: IgA level and testing for pre-existing infections in selected cases<br>Prior to every dose: complete blood cell counts, Coombs test, renal and liver function tests<br>Monitor patient closely during infusion |
| Plasma exchange<br><br>5-7 procedures; if incomplete recovery may be continued longer | Removal from plasma of circulating immunoglobulins and inflammatory mediators | Common: hypersensitivity reactions or anaphylaxis, hypocalcemia, hypomagnesemia, metabolic alkalosis<br>Rare: hypovolemia, thrombosis, bleeding, increased risk of infections | Pre-post procedure: complete blood cell counts, ionized calcium, magnesium, potassium, phosphate, plasma total carbon dioxide, bicarbonate, albumin, coagulation screening |
| **Maintenance** | | | |
| Prednisone; variable length oral taper starting at 1-2 mg/kg/d in 1 or 2 divided doses (max 60 mg/d)<br><br>and/or<br><br>IV methylprednisolone 10-30 mg/kg/d (max 1g/d) for 1-3 d monthly | As above | Common: gastro-intestinal symptoms, hot flashes, cushingoid facies, diabetes, hirsutism, hypertension, acne, weight gain, mood disturbances, insomnia, striae, leukocytosis, increased susceptibility to infections, impaired wound healing<br>Rare: palpitations, cardiac arrhythmias/ myopathy, electrolyte abnormalities, venous thrombosis, psychosis, myopathy, avascular necrosis, pseudotumor cerebri<br>Long term: osteoporosis, cataracts, growth inhibition, skin atrophy | Monitor complete blood cell counts, renal function tests, glycemia, electrolytes, blood pressure, heart rhythm, weight, growth, bone density, ophthalmological screening<br>Strongly consider vitamin D and calcium supplementation<br>Consider proton pump inhibitors for gastric protection<br>Taper down to lowest possible dose, administer once daily in the morning and consider alternate day therapy<br>Administer adequate stress doses when necessary |
| IVIG<br><br>1-2 g/kg divided over 1-5 d every 3-8 weeks at lowest dose that maintains clinical efficacy | As above | As above | As above |
| **Immunosupressive agents** | | | |
| Cyclophosphamide<br><br>IV pulse doses 500-1000 mg/m² once monthly for 7 doses | Alkylating agent, impairs DNA synthesis and induces apoptosis in lymphocytes and other actively proliferating cells | Common: gastro-intestinal symptoms, nausea, vomiting, hair thinning/alopecia, hemorrhagic cystitis, myelosuppression<br>Rare: infusion reactions/anaphylaxis, diarrhea, stomatitis, urinary tract and renal toxicity, opportunistic infections, hepatotoxicity, hyponatriemia, risk of malignancy, infertility | Exclude or correct any urinary tract obstructions prior to treatment<br>Monitor complete blood cell counts, renal and liver functions, bilirubin, electrolytes, urinalysis, signs/symptoms of malignancy and/or infection, cardiac and respiratory function<br>Increased hydratation is recommended during pulse doses<br>Caution: several drug interactions |
| Azathioprine<br><br>2-3 mg/kg/d (max 150 mg/d) | Synthetic purine analogue, blocks de novo purine synthesis, cytotoxic to stimulated T and B lymphocytes | Common: malaise, gastro-intestinal symptoms, cytopenia (dose-related), hepatotoxicity<br>Rare: serious infections (including opportunistic infections and progressive multifocal leukoencephalopathy), malignancies risk (cumulative dose and treatment duration related), Extremely rare: secondary hemophagocytic lymphohistiocytosis | Monitor complete blood cell counts, renal and liver functions, electrolytes, bilirubin, signs/symptoms of malignancy and/ or infection<br>Divide dose or administer after meals to reduce gastro-intestinal symptoms<br>Caution: several drug interactions |
| Mycophenolate mofetil<br><br>800-1200 mg/m²/d<br>divided in 2 doses (max 2 x 1 g/g) | Inhibition of inosine monophosphate dehydrogenase with reduction of de novo synthesis of guanosine nucleotides, antiproliferative effect on T and B cells, induction of apoptosis and necrosis of activated T-lymphoctes and monocytes, reduction of cytokine production, immunoglobuline production, chemotaxis and cell-cell interaction | Common: nausea and diarrhea, mild neutropenia, anemia, malaise, hair thinning/ alopecia<br>Rare: renal and liver toxicity, metabolic dysfunction, hypertension, cardiac arrhythmia<br>Extremely rare: serious infections (including opportunistic infections and progressive multifocal leukoencephalopathy), increased risk of malignancies | Monitor complete blood cell counts, renal and liver functions, electrolytes, cholesterol, signs/symptoms of malignancy and/ or infection, cardiac and respiratory function<br>Caution: several drug interactions |
| Rituximab<br><br>375 mg/m² for 2-4 doses weekly | Chimeric monoclonal antibody against CD20, B-cell depletion, transient T-cell inactivation | Common: infusion related reactions (hypersensitivity reactions or anaphylaxis, throat irritation, nausea, gastro-intestinal symptoms, hypo-/hypertension, fever, chills, headache, insomnia), headache, fatigue, gastro-intestinal symptoms<br>Rare: prolonged hypogammaglobulinemia, anaphylaxis, renal and liver toxicity, cytopenias, increased risk of infections<br>Extremely rare: progressive multifocal leukoencephalopathy | Monitor complete blood cell counts, renal and liver functions, bilirubin, electrolytes, signs/symptoms of malignancy and/or infection, cardiac and respiratory function<br>Caution: several drug interactions<br>Monitor patient during infusion and discontinue infusion in case of severe reaction<br>Do not use in patients with active hepatitis B infection |

**Figure 1:** Schematic overview of tests available to achieve a correct diagnosis. A diagnostic work-out starts with the cilinical recognition of disease entity in order to limit tests to targeted examinations.

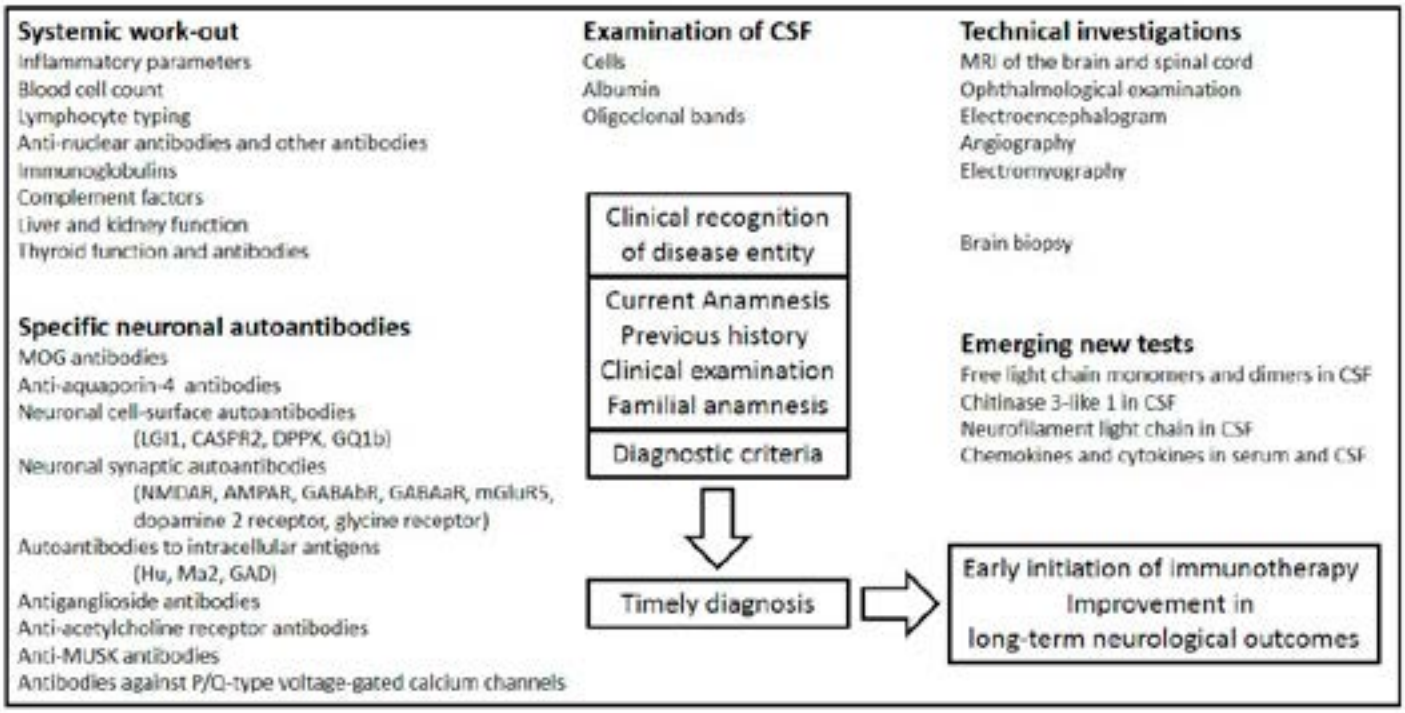


**Table 3:** Overview of designer molecules with potential use in neuroinflammatory disorders

| Name | Type of designer molecule | Route of administration | Target | Mechanism of action |
|---|---|---|---|---|
| Rituximab | Chimeric human-mouse monoclonal antibody | Intravenous infusions | Anti-CD20 | B-cell-depletion |
| Ocrelizumab | Humanized monoclonal antibody | Intravenous infusions | Anti-CD20 | B-cell-depletion |
| Ofatumumab | Fully human monoclonal antibody | Intravenous infusions | Anti-CD20 | B-cell-depletion |
| Ublituximab | Chimeric human-mouse monoclonal antibody | Intravenous infusions | Anti-CD20 | B-cell-depletion |
| Inebilizumab | Humanized monoclonal antibody | Intravenous infusions | Anti-CD19 | B-cell-depletion |
| Natalizumab | Humanized monoclonal antibody | Intravenous infusions | Anti-α4 integrin | Blocks leukocytes crossing the blood vessel |
| Alemtuzumab | Humanized monoclonal antibody | Intravenous infusions | Anti-CD52 | Depletes circulating B- and T-lymphocytes |
| Eculizumab | Humanized monoclonal antibody | Intravenous infusions | Anti-complement protein C5 | Inhibits cleavage of C5 into C5a and C5b |
| Infliximab | Chimeric human-mouse monoclonal antibody | Intravenous infusions | Anti-tumor necrosis factor α | Neutralizes the activity of tumor necrosis factor α |
| Adalimumab | Fully human monoclonal antibody | Subcutaneous injections | Anti-tumor necrosis factor α | Neutralizes the activity of tumor necrosis factor α |
| Tocilizumab | Humanized monoclonal antibody | Intravenous infusions | Anti-interleukin 6 receptor | Blocks IL-6 signaling |
| Satralizumab | Humanized monoclonal antibody | Subcutaneous injections | Anti-interleukin 6 receptor | Blocks IL-6 signaling |
| Anakinra | Recombinant interleukin 1 receptor antagonist | Subcutaneous injections | Interleukin-1 receptor | Neutralizes Il-1 signaling |

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# Cannabis : new treatment option in childhood epilepsy?

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## Nihil nove sub sole

Medicinal use of cannabis extracts (especially from *cannabis sativa*) is not new. Already in 1800 BC, cannabis was used in the treatment of nocturnal convulsions. More recently, in 1881, the famous neurologist W. Gowers described the use of cannabis in refractory epilepsy[1]. In the 60ies of the previous century, the most important components were identified. The cannabis plant contains more than 100 phytocannabinoids[2]. The 2 most important components to understand the use of medicinal cannabis are cannabidiol (CBD) and tetrahydrocannabidiol (THC). Especially cannabidiol has an anti-epileptic effect. It has also anxiolytic and anti-psychotic effects. In contrast, THC is less anti-epileptic but rather muscle relaxant and anti-nociceptive, hence its use for pain and spasticity in for instance multiple sclerosis. It is addictive, hallucinogenic and psychedelic and explains the (increasing) recreational use of cannabis. It is important to notice that, apart from CBD and THC, other components (such as other phytocannabinoids, terpenes, ketones,…) are also present in plant extracts and that these also can have an effect on different brain systems. In addition, different cannabis plant exist. For example, the *cannabis sativa* plant contains higher concentrations of THC, whereas the *cannabis indica* plant contains more CBD. Further plant selection can generate plants with almost exclusively CBD and little or no THC. Synthetic cannabis derivates are also available and are now also being tested for medicinal use. The working mechanism of CBD as an anti-epileptic drug is multifactorial. CBD inhibits presynaptic GPR55 receptors and desensitises TRPV1 receptors with decreased calcium influx as a result. It also inhibits the ENT1 adenosine re-uptake receptors which increases the extracellular adenosine concentration. Altogether, this leads to reduced excitation of the post-synaptic neuron. CBD does not work through the well-known endocannabinoid system, in contrast to THC [3].

## The story of Charlotte Figi

The use of cannabis as anti-epileptic drug actually only started a few years ago with the very mediatized story of Charlotte Figi [4]. Charlotte was known with the Dravet syndrome and was, as expected, refractory to the then available anti-epileptic drugs. She had daily seizures. After the start of a cannabis extract (high in CBD and low in THC), there was a dramatic (albeit temporary) decrease of her seizure frequency. Also because the State of Colorado rapidly legalised the use of medicinal cannabis, also in other forms of epilepsy, there was an exponential growth in cannabis use for epilepsy. This lead to a small but very influential case series study [5], in which it was 'shown' that cannabis extracts can reduce seizure frequency in more than 70% of the patients. This was a survey done in parents of children with refractory epilepsy, and different extracts at different dosages were used, all without any strict medical supervision. In a way, this sort of studies plus the increasing pressure of patient organizations forced the scientific community to further study in depth the potential indication of cannabis for epilepsy. It is not impossible that many positive effects are due to a large placebo effect size. For instance, one could calculate that the efficacy of cannabis was significantly higher in patients moving to Colorado (to get legal medicinal cannabis) than in patients already living in Colorado (65% improvement versus 38%) [6].

## Cannabidiol as a novel anti-epileptic drug

A first more scientific study was published in 2016 [7]. In that study, 137 children with different types of refractory epilepsy were included. All patients were treated with add-on cannabis (99,5 % cannabidiol and minimal concentration of THC, Epidiolex®GWPharma). The results confirmed that in a majority of the children a decrease in seizure frequency was seen. This decrease was typically between 40 and 60% and 10% of the children was seizure free in the last 4 weeks of the 12 week trial. Three percent was seizure free during the full maintenance period in the trial.

Posthoc analysis showed that 49% of the 32 children with Dravet syndrome were responders, with a minimum seizure frequency decrease of 50%. It also became clear that the efficacy of this CBD product was higher when there was a combination with clobazam. In the group of patients in whom clobazam was one of the baseline drugs, there were 51% responders whereas this was only in 27% of those without clobazam as co-medication. This exploratory study was followed by a first placebo-controlled randomized trial with Epidiolex®in patients with Dravet syndrome [8]. In comparison to placebo, add-on CBD was significantly more effective. There was a mean seizure frequency reduction by 38,9% in the treated group versus 13,3% in the placebo group. The effect size of add-on CBD is comparable to the effect size seen with the existing anti-epileptic drugs for Dravet syndrome. Of notice is also that the dosage of CBD was 20mg/kg/day in this study. In a next placebo controlled trial with CBD, but now in Lennox Gastaut syndrome[9], these results were confirmed. In the treated group there was a seizure frequency reduction of 37% , while this was 17% in the placebo group. This latter study also showed there was no extra benefit above the dosage of 10 mg/kg/day.

## What about side effects?

Several studies have now been published, so that it becomes possible to understand the side effect profile of CBD. In many children there is an increase of liver transaminase enzymes, up to 3x the normal values. This can be temporary and it disappears when CBD is stopped. There is an important interaction with clobazam. Because CBD is a potent inhibitor of CYP2C19, CYP2D6 and CYP2C9, combined use of CBD with clobazam leads to a significant increase of clobazam and nor-clobazam levels, with sometimes increased somnolence [10]. When CBD is started in patient also taking clobazam, alertness and somnolence should be followed carefully and it is advised to decrease the dosage of clobazam. Another common side effects is diarrhoea, most likely because CBD is administered as an oily solution. The negative effect of THC on the developing brain is well-known [11]. THC binds irreversibly on the presynaptic CB1 (endocannabinoid) receptors, with a long lasting effect on the development/'pruning' of postsynaptic glutamate receptors. This can lead to excessive glutamate excitation. Epidemiological studies looking at the effect of prenatal cannabis/THC use on the foetus, newborn and young infant show that THC can cause subtle developmental problems. More particularly, increased disinhibition, more visuo-spatial and memory problems were observed in 3 large cohort studies [12]. In this respect, cannabis products with no or very little THC can be considered safe. There are also non-controlled studies, which one tries to show that a substantial concentration of THC, together with CBD, is necessary for good efficacy (the 'entourage effect'). Because the possible negative effect of THC on brain development and the lack of rigorous studies, one cannot support these hypotheses so far [13].

## Situation in Europe and Belgium

Cannabidiol, and more specifically Epidiolex®(almost pure CBD), was approved in 2019 by FDA and EMA as an add-on drug for Dravet and Lennox-Gastaut syndrome (above the age of 2 years). The EMA has specified further that the use of CBD should always be combined with clobazam. This is not a requirement of the FDA. Since 2019, In Belgium, it is legal to prescribe CBD oil for the treatment of epilepsy. The final dose is 5 to 10 mg/kg/day. In contrast to other European countries, however, there is no reimbursement yet. At this moment, and for a correct dosage of CBD, the cost for the patient is more than 500 euro per months (depending on weight). It remains the question whether the observed efficacy (seizure frequency reduction by 40-50%) justifies the high price.

## Summary

- Cannabidiol reduces the number of seizures in patients with Dravet syndrome or Lennox-Gastaut syndrome. For other epilepsy types, there are no controlled studies available.

- The effect size of add-on CBD is comparable to the effect size of the available anti-epileptic drugs in these 2 syndromes.

- The minimum effective dose is 5-10 mg/kg/day

- Liver toxicity and interactions with other drugs (especially clobazam) should be carefully followed.

- THC has a negative effect on the developing brain and its use should be discouraged.

- The use of other non-pharmacologically tested forms/concentrations/ combinations of cannabis cannot be supported.

- In Belgium it is legal to prescribe CBD, but at this moment there is no reimbursement for this costly product.

**Note**

Epidiolex® is the trade name of the CBD product (not available in Belgium at the moment

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| 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 ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT** Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue préremplie Vaccin méningococcique groupe B (ADNr, composant, adsorbé) - EU/1/12/812/001 Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09 **COMPOSITION QUALITATIVE ET QUANTITATIVE** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Protéine recombinante NadA de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Protéine de fusion recombinante fHbp de ***Neisseria meningitidis*** groupe B [1, 2, 3] 50 microgrammes Vésicules de membrane externe (OMV) de ***Neisseria meningitidis groupe*** B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4 [2] 25 microgrammes [1] produite dans des cellules d'***E. coli*** par la technique de l'ADN recombinant [2] adsorbée sur hydroxyde d'aluminium (0,5 mg $Al^{3+}$) [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H) **DONNÉES CLINIQUES INDICATIONS THÉRAPEUTIQUES** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par ***Neisseria meningitidis*** de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **POSOLOGIE ET MODE D'ADMINISTRATION** Posologie **Tableau 1. Résumé de la posologie**

| Age lors de la première dose | 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 | Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique [d] |
| **Adolescents (à partir de 11 ans) et adultes*** | | | |

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée au-delà de l'âge de 24 mois. [c] Voir rubrique 5.1 du RCP complet. La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet. * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, sous-cutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **CONTRE-INDICATIONS** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **MISES EN GARDE SPÉCIALES ET PRÉCAUTIONS D'EMPLOI** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vaso-vagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contre-indication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles post-vaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits hétréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à ***Neisseria meningitidis*** du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était co-administré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et ***Haemophilus influenzae*** de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastro-intestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu sous-cutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculo-squelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vaso-vagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections gastro-intestinales Très fréquent : nausées Affections musculo-squelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration. **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance 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** 03/2019 (v09) **MODE DE DELIVRANCE** Sur prescription médicale.

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# A pilot study for early screening of emotional, behavioural and autism spectrum disorders in children with functional constipation

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## Keywords

Childhood constipation – functional constipation – autism spectrum disorder– developmental disorder – emotional problems – behavioural problems

## Abstract

**Background and objective:** A significant group of children with functional constipation (FC) continues to have symptoms despite recommended standard therapy. Underlying psychiatric problems could explain therapy resistance. However, a work-up for psychiatric problems is only recommended after unsuccessful 6 months standard therapy. Earlier detection and check-up could lead to faster start-up of a more adequate therapy. Therefore, we investigated the prevalence of emotional, behavioural and social problems in the FC-population at the first contact with a paediatric gastroenterologist in a tertiary care hospital.

**Design and Setting:** A cross-sectional pilot study was carried out. Parents and/or children (4-18 year) completed behavioural questionnaires (Social Responsiveness Scale -2 (SRS-2) and Aseba questionnaires) at first contact. Parental stress and negative life-events were also considered by respectively the 'Opvoedingsbelasting Vragenlijst' and the 'Vragenlijst Meegemaakte Gebeurtenissen'.

**Results:** 6 out of the 29 participants were known with previously diagnosed/suspected behavioural- or developmental problems. 12/23 participants who had never been diagnosed/suspected to suffer these problems completed the behavioural questionnaires, 7/12 reported behavioural problems. Deficiencies in social responsiveness were reported in 4 out of 15 participants who completed the SRS-2.

**Conclusion:** This study stresses the need of awareness for possible socio-emotional and behavioural problems in children with chronic FC. It also emphasizes the need for a more intensive cooperation between child and adolescent psychiatry units and paediatric gastroenterology. A concise questionnaire as a screening tool for emotional, behavioural and social problems early in the diagnosis of FC could improve quality-of-care for these children.

## Introduction

The diagnosis of functional constipation (FC) in children leads to several diagnostic and therapeutic challenges[1].

Most children respond well to standard recommended treatment, but there is a considerable group of patients that will continue to have symptoms[1]. In this group, paediatricians sometimes presume the presence of an underlying psychopathology such as a developmental disorder, mood disorder, behavioural disorder [1-3]. A longer treatment period has shown strong association with behavioural problems, suggestive for treatment resistant constipation [4].

It is known that functional defecation disorders (FDD) can be associated with behavioural and developmental disorders, such as Autism Spectrum Disorder (ASD) and Attention Deficit and Hyperactivity Disorder (ADHD), though these disorders are often initially unrecognized [5,6]. Also, there are no clear guidelines reported regarding the timing when to search for underlying psychopathology in FC.

Research using Social Responsiveness Scale (SRS) and Social Communication Questionnaire-Lifetime (SCQ-L), screening tools for social difficulties, did not identify ASD diagnosis, in children with functional constipation [5]. At the other hand, they found a total increase in emotional and behavioural problems in their research group. Prior studies found that 28 % of children with FDD referred to a tertiary centre scored positive on ASD screening questionnaires [1,5]. A high prevalence of behavioural problems (37 %) in children with FC has been described as well [4,7].

According to the Guidelines for children with FC of the North American and European Societies of Paediatric Gastroenterology, Hepatology and Nutrition, the diagnosis of emotional, behavioural and/or developmental disorders (ASD or ADHD) will be considered after an unsuccessful six-month standard treatment[5].

We hypothesized that it could be useful to incorporate an earlier screening for emotional, behavioural and autism spectrum disorders into the diagnostic work-up of children with functional constipation referred to a tertiary care hospital. FC may have an important impact on the Quality of Life (QoL) in families of these children. Therefore we also measured parental stress and negative life-events from the child's perspective using the 'Opvoedingsbelasting Vragenlijst' (OBVL) for measurement of parental stress and the 'Vragenlijst Meegemaakte Gebeurtenissen' (VMG) for possible stressful life events from the child's perspective [8,9].

## Materials and Methods

### 1.1 Participants

This study included Dutch and French-speaking children, age 4-18 years, presenting for the first time at KidZ Health Castle (KHC) Brussels with suspicion of functional constipation complaints. Children could present ambulatory or could be hospitalized and were eligible regardless of previously diagnosed behavioural and developmental problems and regardless of any previous treatment for FDD.

The diagnosis of FC was made based on the Rome IV criteria. Given that the 2 month interval listed in the Rome IV criteria for older children may unfairly delay treatment in some children with constipation, children who had difficulty with defecation for at least 2 weeks were also included [3].

Children with an underlying organic cause that could have contributed to the development of constipation and children with functional non-retentive faecal incontinence (FNRFI) were excluded.

### 1.2 Study design and setting

A cross-sectional study was carried out between January 2018 and June 2018. After informed consent was obtained, the behavioural and QoL questionnaires (1.3 Measurements) were given to the consenting parents for the parents, children and teachers. The study was approved by the Medical Ethics Committee of UZ Brussels. This study is registered at ClinicalTrials.gov. Registration number: NCT03614000.

### 1.3 Measurements

1.3.1 *Social Responsiveness Scale - 2 (SRS–2)*

The SRS-2 is a validated 65-item scale for the screening of ASD. It requires parents to rate the child's behaviour during the previous 6 months. The questionnaire assesses interpersonal behaviour, communication and repetitive/stereotypic behaviour characteristics of ASD. The form can be completed by teachers or parents and takes approximately 15 to 20 min to complete. Each question is scored on a 4-point Likert scale, ranging from 0 (not true) to 4 (always true). The total raw score ranges from 0-195. A total score ≥ 51 is suggestive for the presence of ASD with a sensitivity of 0.90 and a specificity of 0.88 for both males and females. Total raw scores can be transformed into gender-normed T-scores (because of the significant effect of gender on the total score) with higher scores indicating a greater severity of behavioural symptoms. T≥76: serious deficiencies in social responsiveness, 61-75: mild to moderate deficiencies in social responsiveness, 40-60: Normal degree of social responsiveness, <40: high level of social responsiveness [10].

1.3.2 *The Aseba Questionnaires (CBC-L, TRF, YSR)*

This screening instrument evaluates emotional and behavioural problems. It measures indications for the presence of psychopathology and it contains between 110 and 113 items/symptoms of psychopathology, grouped in 8 different syndrome dimensions (anxious-depressed, withdrawn-depressed, somatic complaints, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour). The syndrome dimensions are grouped in three global scales: internalizing problems, externalizing problems and the total problems. There are different questionnaires, to be filled out by different informants. The Child Behaviour Checklist (CBCL) and the Teacher's Report Form (TRF) are completed respectively by the parents and the teacher or social worker of children aged 6 to 18 years. The Youth Self Report (YSR) can be completed by the youngsters, aged 11 to 18 years. There is also a CBCL and TRF for children between 1.5 and 5 years. T-scores ≥ 64 are defined as clinical range, 60 ≤T ≤63 as borderline clinical range and T<60 as normal range for emotional and behavioural problems [11].

Both aforementioned questionnaires have proven to be standardized, reliable and valid instruments, widely used in daily practice, with good psychometric properties and discriminant validity. The duration for completing these questionnaires is 15 minutes each.

1.3.3 *The VG&O (Vragenlijst Gezin en Opvoeding*)

The VG&O is a set of 4 questionnaires, developed for parents, that gives a subscale of parental stress (OBVL, Opvoedingsbelasting Vragenlijst), family functioning (VGFO, Vragenlijst Gezinsfunctioneren Ouders), educational habits (Verkorte Schaal voor Ouderlijk Gezag, VSOG) and life events (Vragenlijst Meegemaakte Gebeurtenissen, VMG). The VG&O is available in Dutch, French and many other languages as well. In this study, only the first (OBVL) and last part (VMG) are used.

The OBVL contains 34 questions about how a parent experiences his or her child, about the interaction with the child, and about the feelings and health of the parent. For every question there are 4 possible answers, from "Not true" = 1 to "Very true" = 4. With a score form, five subscores and a total score can be calculated. These scores can be converted in T-scores using a norm table. The Cronbach's alpha for the total score of perceived parental difficulties is estimated between 0.89 and 0.91. This means the reliability of the questionnaire is good, which suggest a minimum chance of random errors [9]. T-scores ≥ 64 are defined as pathological, 60 ≤ T ≤ 63 as borderline, and T < 60 as normal [11].

The VMG maps (potentially) stressful events within families such as birth, moving to a new house and illness. The parents then indicate whether this event was experienced as positive or negative by the child [8,9].

The duration for completing these questionnaires is 10 minutes each.

### 1.4 Outcomes

The primary outcome measures were: i) the prevalence of (internalizing and externalizing) behavioural problems as assessed by the Aseba questionnaires; ii) the prevalence of behavioural and social responsiveness problems as assessed by the Social Responsiveness Scale-2.

Secondary outcome measures were: i) the number of positive screens for parental stress as assessed by the OBVL questionnaires; ii) the number of positive screens for negative life-events as assessed by the VMG questionnaire.

### 1.5 Data processing

For the SRS-2, Aseba and OBVL questionnaires both the raw total scores and T-scores were calculated. In case of the SRS-2, a T-score > 60 was considered positive for the presence of mild/moderate/severe deficits in social responsiveness. The Aseba questionnaire was considered positive for the presence of borderline/clinical range behavioural and emotional problems if ≥1 of the components (CBCL, TRF and/or YSR) has a T-score ≥ 60; a distinction was made between the T-scores for internalizing and externalizing behavioural problems. Regarding the OBVL, a T-score ≥ 60 was considered positive for the presence of mild/moderate/severe problems. A separate score was provided for the VMG questionnaire with 0=absence of negative life-events, 1=presence of negative life-events.

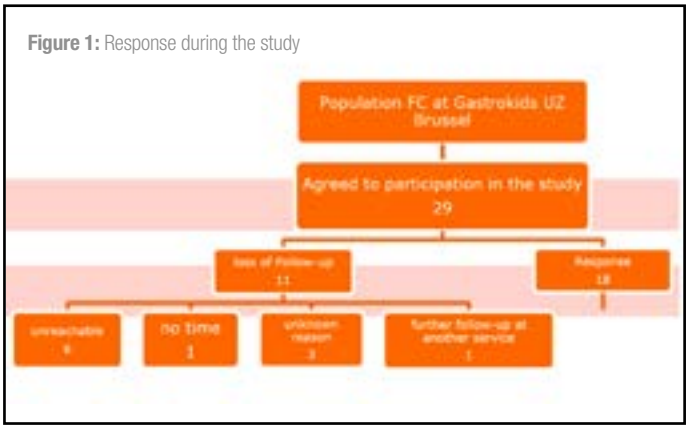
### 1.6 Analytic plan

Microsoft Excel was used for all statistical analyses. The population characteristics were determined. Given the extensive size of the non-response group, a comparison was made between the response and non-response group. The groups were compared by analyses using several categoric variables. Fisher exact tests were used for variables with an observed or expected frequency of <5.

## 2. Results

Twenty-nine of the thirty-two children (4-15 years) and their parents, who presented at our tertiary clinic for suspected FC, both ambulatory and hospitalized, agreed to participate. The response rate is shown in Figure 1. They were contacted by phone after one week as a reminder to return the completed questionnaires. The participants who didn't return the set of questionnaires, were contacted a second time by phone, then by text message and if they still weren't reachable, an email was sent with more information.

**Figure 1:** Response during the study




We had to deal with two types of non-response: we didn't receive data from 11 children because the parents were unreachable after leaving the hospital (n=6), or because they ultimately didn't want to participate in the study for unknown reason (n=3), or because they couldn't make time for the questionnaires (n=1). One of the non-responders had further follow-up at another paediatric service for suspected conversion disorder.

Of the 29 participants, the median duration of constipation-symptoms at first contact in our tertiary clinic was nine months. They arrived at our paediatric gastroenterology department through referral from the general practitioner, the paediatrician or emergency service with persistent complaints of suspected FC.

We included both outpatient (n=15) and in-patients (n=14). A greater number of respondents was seen among the in-patients (n=10 vs. 8), as well as a greater presence of emotional and behavioural problems (n=8 vs. 5) (Table 1). Eleven out of 14 in-patients were seen by a psychologist, as part of the in-patient treatment protocol. In this group; different psychiatric and psychological factors as well as life events emerged during the talk with the

**Table 1:** Demographics and clinical characteristics of all participants with and without symptoms of ASD or emotional and behavioral problems according to respectively SRS-2 or Aseba questionnaires.

| | Total | Non-response | Response: | *Both SRS-2 and Aseba negative* | *only positive SRS-2* | *Only positive Aseba* | *both SRS-2 and Aseba positive* |
|---|---|---|---|---|---|---|---|
| n | 29 | 11 | 18 | 5 | 0 | 9 | 4 |
| **gender** | | | | | | | |
| male | 14 | 6 | 8 | 2 | / | 5 | 1 |
| female | 15 | 5 | 10 | 3 | / | 4 | 3 |
| **Place of recruitment** | | | | | | | |
| Hospitalized (H) | 14 | 4 | 10 | 2 | / | 8 | 0 |
| Outpatient (O) | 15 | 7 | 8 | 3 | / | 1 | 4 |
| **Age and duration of symptoms** | | | | | | | |
| Median age (in years) | 9 | 9 | 9 | 6 | / | 10 | 9,5 |
| **Median age start symptoms (in years)** | 7,01 | 7,34 | 7,51 | 4,42 | / | 8,885 | 7,5 |
| **Median duration of symptoms at first contact (in months)** | 9 | 27 | 6 | 24 | / | 3,5 | 22 |
| **emotional, behavioral and developmental disorders** | **6** | | | | | | |
| **suspected emotional or behavioral disorder** | 1 | NA | 1 | | | | 1 |
| suspected ASD* | 2 | NA | 2 | | | 2 | |
| suspected ADHD* | 1 | NA | 1 | | | 1 | |
| previously diagnosed DCD | 1 | NA | 1 | | | 1 | |
| previously diagnosed ADHD | 2 | NA | 2 | | | | 2 |

*1 participant with presumption of both ADHD and ASD diagnosis. NA: Not Applicable

psychologist: new diagnose of ASD in patient with Marfan syndrome (n=1), gender dysphoria (n=1), parental mental illness (n=2). Other psychological factors and possible negative life-events: bullying at school (n=3), learning difficulties (n=4), change of school (n=2), school absenteeism (n=3); transgressive behaviour (n=1); parental acute illness (n=1), moving to a new house (n=1), domestic violence (n=1); sleeping difficulties (n=1); therapeutic non-compliance (n=3). In the outpatient setting, no psychosocial evaluation by a psychologist took place.

Out all 18 respondents, some did not submit the SRS-2 or one of the Aseba questionnaires (Table 2). Some of the OBVL and VMG were returned unfilled (n=2). This explains the difference in numbers that are used to discuss the results.

Parents of 18 patients completed one or both behavioural questionnaires. Among these 18 respondents, a total of 13 participants had a positive screening for one or both questionnaires. Thus, in almost half of the participants evidence for the presence of emotional-, behavioural- or social problems was found: nine participants had positive Aseba questionnaires, four participants scored positive on both SRS-2 and Aseba (Table 1).

Medical histories revealed that 6/29 participants presented with previously diagnosed or suspected behavioural or developmental problems. One patient presented with a developmental coordination disorder (DCD). ADHD was diagnosed in two participants and suspected in another. The diagnosis of both ADHD and ASD was suspected in one participant. Another patient was suspected for a behaviour problem.

Both behavioural questionnaires were positive in the participant with suspected behavioural disorder (n=1) and in the participants with previously diagnosed ADHD (n=2). A positive Aseba questionnaire was found in all participants with suspected ASD (n=2), ADHD (n=1) and previously diagnosed DCD (n=1).

The remaining 23 participants had not been diagnosed or previously suspected of any psychiatric problem. Twelve of them completed the set of questionnaires; emerging emotional, behavioural or social difficulties in seven, of whom four were found to have internalizing behavioural problem, two were found to have both internalizing and externalizing problems and one also had difficulties in social responsiveness.

### 2.1 SRS-2 Questionnaires

Out of the 29 participants, 15 parents filled out the SRS-2 (Table 2).

Among these 15 respondents, four scored above the cut-off value for this ASD screening questionnaire: In 2/4 children, both previously diagnosed with ADHD, serious deficiencies in social responsiveness were reported (T≥76);

2/4 children had a T-score 61 ≤T≤ 75, one of them was suspected of a behavioural disorder by the paediatrician (Table 2).

Eleven children screened in the group of normal level of social responsiveness: one girl was previously diagnosed with DCD; two boys were suspected for ASD (one of them was also suspected for ADHD).

### 2.2 Aseba Questionnaires

18 out of the 29 participants have filled in the CBCL and/or TRF and/or YSR. In Figure 2 and 3, the T-scores from the Aseba questionnaires are shown.

Of the 14 children younger than 12 years old, 13 parents completed the CBCL questionnaire (Figure 2): four reported results exceeding the cut-off for clinically significant problems (T≥60) on both the internalizing and externalizing scale, four reported results above the cut-off value for problems on the internalizing scale, and five parents reported results that didn't exceed the clinical cut-off.

Nine teachers completed the TRF: three reported results above the cut-off for clinically significant problems on both the internalizing and externalizing scale, two reported results exceeding the cut-off for problems on the internalizing scale and four teachers reported results that didn't exceed the clinical cut-off.

Both parents and teachers reported results exceeding the cut-off for clinically significant internalizing and/or externalizing problems in 4/14 children.

In 9/14 children parents and/or teachers reported results above the clinically significant cut-off for internalizing and/or externalizing problems.

Of the four children ≥ 12 years old, all parents completed the CBCL questionnaire (Figure 3): one reported results exceeding the cut-off

**Table 2:** Results of SRS-2, Aseba (CBCL, YSR, TRF), OBVL and VMG questionnaires in response-group.

| PATIENT | Gender | Age | Place of recruitment | Previously diagnosed or suspected emotional, behavioral or developmental disorder | SRS-2 T-score | CBCL T-score | | TRF T-score | | YSR T-score | | OBVL T-score | VMG | Evolution of FC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | I | E | I | E | I | E | | | |
| **1** | M | 6 | H | suspected ASD | 51 | **68** | 48 | X | X | / | / | **61** | 0 | - |
| **2** | F | 9 | O | previously diagnosed ADHD | **78** | **68** | **67** | **67** | **68** | / | / | 53 | 0 | + |
| **3** | M | 10 | H | | 59 | **72** | 50 | X | X | / | / | 58 | **1** | + |
| **4** | M | 5 | O | | 57 | 43 | 40 | X | X | / | / | **67** | 0 | + |
| **5** | M | 9 | H | | 59 | **65** | 50 | **66** | 53 | / | / | **61** | 0 | + |
| **6** | M | 4 | O | | 53 | 43 | 32 | 48 | 46 | / | / | 54 | 0 | - |
| **7** | F | 12 | H | previously diagnosed DCD | 58 | **59** | 40 | **75** | 59 | 47 | 34 | 46 | **1** | + |
| **8** | F | 7 | O | | 47 | 46 | 47 | 54 | 52 | / | / | 39 | **1** | - |
| **9** | F | 10 | O | | X | X | X | **61** | 43 | / | / | X | X | + |
| **10** | F | 11 | O | previously diagnosed ADHD | **79** | **73** | **60** | **70** | **66** | / | / | **74** | **1** | + |
| **11** | M | 15 | H | Suspected ASD, suspected ADHD | 48 | **76** | 51 | **70** | 42 | **61** | 44 | 42 | **1** | X |
| **12** | F | 6 | H | | 55 | 46 | 51 | 44 | 43 | / | / | 55 | **1** | - |
| **13** | F | 12 | H | | X | 6 | 0 | X | X | **62** | 42 | X | X | + |
| **14** | M | 6 | O | | **63** | **61** | **68** | 53 | 54 | / | / | 58 | 0 | X |
| **15** | F | 7 | H | | 42 | 59 | 34 | X | X | / | / | 58 | **1** | - |
| **16** | M | 8 | H | | 55 | **61** | **62** | 59 | 54 | / | / | **61** | **1** | + |
| **17** | F | 12 | H | | X | **69** | **65** | X | X | **68** | 54 | 52 | **1** | - |
| **18** | F | 10 | O | suspected behavioral disorder | **66** | **73** | 58 | **72** | **68** | / | / | **66** | **1** | + |

Values in bold are positive scores. SRS-2 T-score: T≥76: serious deficiencies in social responsiveness, 61-75: mild to moderate deficiencies in social responsiveness, 40-60: Normal degree of social responsiveness. <40: high level of social responsiveness. CBCL/TRF/YSR: T≥64: clinical range, 60≤T≤63: borderline clinical range, <60: normal range for emotional and behavioral problems. OBVL: T≥ 64: pathological, 60 ≤ T ≤ 63: borderline, and T< 60: normal. VMG: 0=absence of negative life-events, 1=presence of negative life-events. M: male, F: Female.
X: Missing values, /: YSR couldn't be completed because participant < 12 years, I: internalizing behavior, E: externalizing behavior, H: hospitalized, O: outpatient, ASD: autism spectrum disorder, ADHD: attention deficit and hyperactivity disorder, DCD: development coordination disorder.
+/-: improvement/relapse of FC complaints after 6 months.

**Figure 2:** Results of Aseba questionnaires for participants <12 years.
This graph shows the T-scores from the Aseba questionnaires (CBCL and TRF) for the 14 participants younger than 12 years. The degree of internalizing and externalizing behavioural problems is displayed separately. T-score <60: normal range, 60≤T≤63: borderline clinical range, T ≥ 64: clinical range.

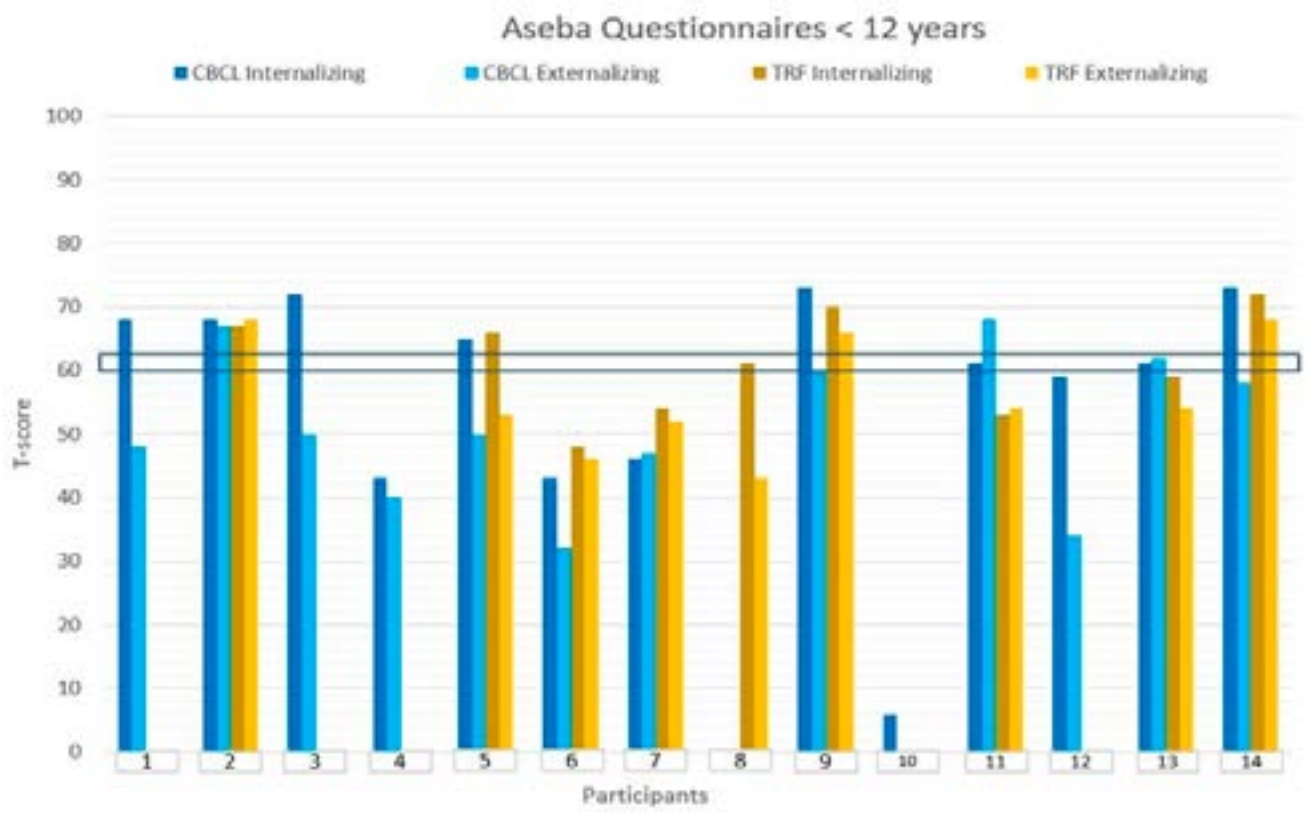
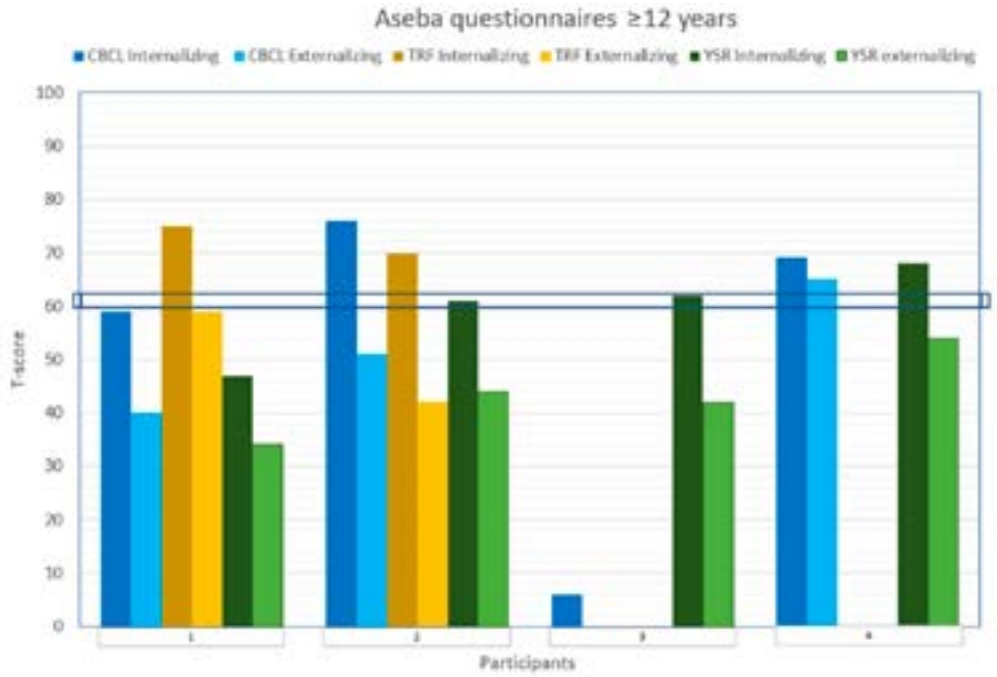


**Figure 3:** Results of Aseba questionnaires for participants ≥12 years.
This graph shows the T-scores from the Aseba questionnaires (CBCL, TRF and YSR) for the 4 participants ≥12 years. The degree of internalizing and externalizing behavioural problems is displayed separately. T-score <60: normal range, 60≤T≤63: borderline clinical range, T ≥ 64: clinical range.




for clinically significant problems (T≥60) on both the internalizing and externalizing scale, another reported results above the clinical cut-off for internalizing problems, and two parents reported results that didn't exceed the clinical cut-off.

The two teachers who completed the TRF reported results above the cut-off for clinically significant internalizing problems. In one of them, both the parents and the child himself also noted results above the clinical cut-off for internalizing problems.

All four children completed the YSR: In 3/4 children, the results exceeded the cut-off value for significant problems on the internalizing scale.

In 1/4 children, parent as well as teacher and child reported results above the cut-off for clinically significant internalizing problems.

In all children ≥ 12 years, the parents, teacher and/or child reported results above the clinically significant cut-off for internalizing and/or externalizing problems.

The four respondents who showed problems in social responsiveness based on the SRS-2 (T>60), also scored above the cut-off value (T≥60) for both internalizing and externalizing problems in ≥ 1 of the Aseba questionnaires (CBCL, TRF and/or YSR) (Table 2).

### 2.3 OBVL Questionnaires

Of the 16 parents that completed the OBVL for parental stress, six scored above the cut-off value. In this group, the majority (5/6) showed a positive screening for emotional, behavioural and/or social problems: three children had a positive Aseba-questionnaire, two children scored positive on both SRS-2 and Aseba (Table 2).

Of the 13 participants that screened above the cut-off value for either emotional, behavioural or social problems, five of them scored above the cut-off value for parental stress.

### 2.4 VMG Questionnaires

Of the 16 parents that completed the VMG for negative life-events in perception of their child, 10 experienced ≥1 negative life-event. In this group, 7/10 children had a positive screening for emotional, behavioural and/or social responsiveness problems.

Of the 13 participants that screened above the cut-off value for either emotional, behavioural or social responsiveness problems, seven of them experienced ≥1 negative life-event.

## 3. Discussion

Previous studies found a higher prevalence of ASD-symptoms (28%) in children with FDD who were admitted to a tertiary centre. In a Dutch study with children referred to a gastrointestinal outpatient clinic for FC, the prevalence of behaviour problems (36% internalizing, 27% externalizing) was 3- to 4-fold higher than the Dutch general paediatric population (9%) [11].

Therefore, this current study examined the prevalence of emotional, behavioural or social problems in children with FC (age 4-18) referred to our specialized clinic. Consistent with above-mentioned research, the results indicate a high presence of these problems in this selected paediatric FC population [4,6,12].

Practitioners with experience in the treatment of constipation in children reported that management of the behavioural aspects of constipation are as important as the medical and dietary approaches [13].

To the best of our knowledge, this pilot study is the first using a broad set of questionnaires screening for ASD (SRS-2), internalizing and externalizing disorders (Aseba), parental stress (OBVL) and negative life-events (VMG) at first contact for children referred to a specialized tertiary care centre.

S. Kuizenga-Wessel found that positive ASD screening surveys (SCQ-L and SRS) didn't correctly identify ASD in the majority of children with FC, though the tools did help to identify other types of disorders such as externalizing behaviour disorders, anxiety disorders, learning disorders, adjustment disorder, and posttraumatic stress disorder [5].

The 4/15-ratio of positive ASD screens in our study population of children with FC closely matches previous findings [1,5]. However, in our study, gender-normed T-scores with a cut-off value of T≥ 60 suggestive for the presence of ASD were used, instead of raw total scores ≥ 51. We decided to use T-scores, because they are more frequently used in clinical practice.

In this study, the four respondents with problems in social responsiveness also show internalizing and externalizing problems, based on the Aseba. Kuizenga-Wessel S. et al stated that positive SRS screens are not able to correctly identify ASD, but do identify children with previously undiagnosed behavioural problems [5]. We didn't conduct a thorough diagnostic assessment of the children showing positive scores on the questionnaires. We only know that two of them where suspected with having ADHD and 4 of them had a suspected behavioural disorder.

Two of the participants showed an elevated score on the social responsiveness scale. Diagnosis was confirmed in one, based on a multidisciplinary investigation. Nevertheless, the SRS-2 T-scores were normal in both. The Aseba questionnaires, on the other hand, did indicate the presence of internalizing problems. We can only speculate that a wider view and generalized screening tools are needed to signal possible emotional, behavioural or developmental difficulties.

In line with the assumption that constipation is often linked with fear of defecation and in agreement with previous studies [2,14,15], we found that the majority of problems were reported on the internalizing scale. However, it is important to be alert to the presence of externalizing problems too [6,14].

With an overall prevalence of 44.8 % (13/29) this study could overestimate the prevalence of emotional, behavioural or social problems in children with FC. Possible explanation could be that parents concerned for the presence of psychiatric problems in their children may be more likely to return the questionnaires. Other explanation might be the inclusion of children previously diagnosed/suspected with behavioural or developmental problems. On the other hand, patients presenting at our tertiary centre for a first consultation often have a long search for effective treatment options behind them, resulting in a higher overall prevalence. Given different research, showing a higher prevalence of GI-symptoms in children with developmental delay and ASD, further investigation of this bi-directional axis is needed[16,17].

The use of parent, teacher as well as the child himself as informants is interesting because it reveals the perception of problems in the various informants, giving a more accurate and broader view of the child's functioning [18]. Nevertheless, the use of this extensive set of questionnaires made it more time-consuming and complex for the concerned parents and doctors.

In this study, we found that a substantial number of parents (5/13) of children with either behavioural, emotional, or social problems indicated the presence of parental stress. A considerable number of children with positive screens experienced adverse life-events. Of the 16 parents that completed the OBVL and VMG questionnaires, an overall prevalence of 37.5% and 62.5% for the presence of respectively significant parental stress and negative life-events was reported.

These psychosocial factors may play an important role in the families' QoL and the pathophysiology of FC [2,19,20] and should be considered when evaluating children with FC. No previous studies have used the OBVL or VMG in the context of FC. The use of these questionnaires could also help parents to identify with these questions and therefore feel more recognized in their parenting role, promoting the involvement of parents in the care process of their child.

This pilot study has a couple of limitations and weaknesses. The first one is the small number of patients included, which ensures that this study rather has a descriptive value. Limited statistical analysis could be performed, but the rather small sample doesn't allow to generalize findings. Secondly, only patients from KHC Brussels, a university hospital, were included, implying these findings may not be generalized to primary care.

To achieve more representative results, it is recommended to consider a larger sample and longer duration of the study.

In further research it is recommended to reconsider the extent of the questionnaires if we want to use them on a regular basis in all children referred to a tertiary care hospital. Since the Aseba questionnaires contain more than 100 items, they are time consuming in practice. In future studies, the SDQ (Strengths and Difficulties Questionnaire) could be considered to evaluate the presence of internalizing and/or externalizing behavioural problems. This is a freely available and limited screening tool with 25 items for parent, teacher and child that can be used in assessment situations where there is little time [21]. Regarding the screening for characteristics of ASD, the less extensive SCQ (Social Communication Questionnaire) could be used. However the rather focus on ASD-symptoms during the first four years of life and a lower specificity (0.80) could make this questionnaire less suitable.

As discussed in the introduction, FC leads to several diagnostic and therapeutic challenges. This study has shown the importance to be aware of the significant prevalence of emotional, behavioural and social problems, but also raises new questions related to the early detection of these problems. Due to the small sample, no generalizable statements can be made, but it is an interesting starting point for further research.

Clinical paediatric practice currently lacks a tool to recognize children with emotional, behavioural and developmental problems at an early stage; based on expert opinion, small nuances in the daily functioning of a child are often unnoticed in a short-term paediatric consultation; a conversation with the parents and child often provides insufficient information about the child's well-being and functioning. A more intensive multidisciplinary approach and a treatment tailored to the needs of each child is required.

## 4. Conclusion

This study emphasizes the need of awareness for possible emotional-, behavioural- and/or social problems in children with severe chronic FC. It also raises new questions related to the early detection and treatment of these problems. Adding a concise behavioural screening after first contact with the gastroenterologist for all children referred for FC in a tertiary care hospital may improve the quality of care for these children. Furthermore, it is important to emphasize the need for psychological support provided for all hospitalized FC-patients at the KHC Brussels, as part of the treatment protocol. After discharge from the hospital, an assessment by the psychologist and paediatrician should be made whether psychological care should be continued.

## 5. Acknowledgements

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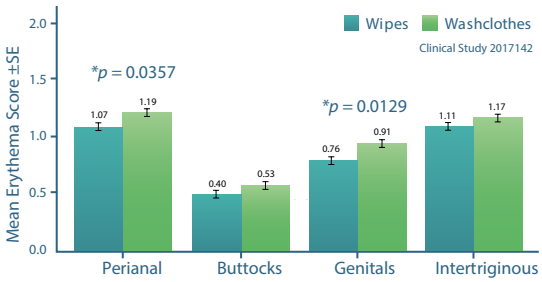
Pampers Aqua Pure wipes were demonstrated to be at least as mild/gentle as washcloth and water over the two-week usage period. Skin of subjects using the wipes also showed significantly lower pH than skin of subjects using washcloth and tap water, which could provide long term benefits for skin health.

### Average Erythema Score by Grading Site

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- Sodium Citrate
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# Long term outcomes of infant colic: a systematic review

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## Keywords

infant colic, excessive crying, childhood, outcomes

## Abstract

**Introduction:** Infant colic, or excessive crying, affects up to 20% of infants and is generally regarded as a benign, self-limiting condition. Increasing evidence suggests that it may precede several negative outcomes in childhood, including behavioural problems and physical illnesses.
**Methods:** A systematic literature search yielded 23 prospective studies on infant colic with various health and/or behavioural outcomes. Study quality was evaluated with the STROBE 22-point scale.
**Results:** 69 551 infants were included, of which 6 441 were diagnosed with infant colic at a median age of 3 months. The heterogeneity in the definition of infant colic that was used, precluded a formal meta-analysis of the studies. Outcomes were measured between 15 months and 18 years, with a mean upper age of 6 years, and were categorized in behavioural problems (based on cohort age), mental health, physical health, cognition and family functioning.
**Discussion:** This review shows that infant colic is associated with a higher risk of behavioural problems, including hyperactivity and attention problems, mood problems and conduct disorders. Further associations were found with psychological disorders, poorer cognitive functioning and certain physical disorders in childhood, such as atopy and migraine. There was little evidence for a significant effect on family functioning. Given the limited amount of research per outcome variable, further studies are required to assess the strength of these associations.

## Introduction

Infant colic is generally defined as excessive, inconsolable crying in the first months of life with no apparent cause. However, approximately twenty unique definitions of infant colic are in use, ranging from objective durations of crying (e.g. Wessel criteria) to subjective definitions, such as "any amount of crying that worries the parents"[1-2]. Several etiologies have been proposed, but the exact etiology is still unknown. It is regarded as a self-limiting condition that resolves by the age of 6 months[1]. Reports on its prevalence range between 5% and 19% of infants[3].

Incessant crying is often a source of anxiety and stress for parents, who find it hard to manage[4]. It is associated with adverse short-term outcomes, including postnatal depression, premature termination of breastfeeding, abusive head trauma and shaken baby syndrome[5-8]. Crying problems in infants are the reason for about 20% of paediatric consultations, which creates a significant economic impact on health services[2,9].

Infant colic is also linked to adverse long-term outcomes like behavioural problems, several physical health problems and family functioning in an increasing number of studies. However, the results of some of these reports are conflicting, especially in retrospective studies. The aim of our systematic review was to identify which outcomes in childhood can be associated with infant colic in prospective studies.

## Methods

### Selection of studies

A systematic literature search for studies regarding the effects of infant colic on outcomes in childhood was conducted using PubMed, Embase and CINAHL. A structured question was designed based in the PEO system to evaluate if infants (P) who present with colic or excessive crying (E) that persists beyond 3 months is associated with adverse development in childhood (O). Either MeSH terms or relevant keywords with the appropriate Boolean operators were used in the databases. Additional studies were identified by reviewing bibliographies of relevant articles. The initial screening was based on titles and abstracts, the subsequent screening and analysis was based on the full-texts of the studies.

### Eligibility criteria

Articles were only included if they met the following criteria: (1) children who were included had a history of infant colic or excessive crying that was objectified during infancy, without the concurrence of other regulatory problems, namely feeding or sleeping problems; (2) at least one follow-up assessment concerned the child's health or behaviour and was performed at an age older than 12 months; and (3) the study was prospective in nature. Editorials, systematic reviews, case series, retrospective studies and animal studies were excluded. Only articles in English were included. Both articles with quantitative outcome data as well as articles with qualitative outcome results were included.

### Study quality control and data extraction

Quality of the studies was assessed using the STROBE 22-point scale (Strengthening The Reporting of Observational Studies in Epidemiology)[10]. All relevant data were extracted using a standardized form, which included all definitions, inclusion and exclusion criteria, study methodology and relevant outcome measures.

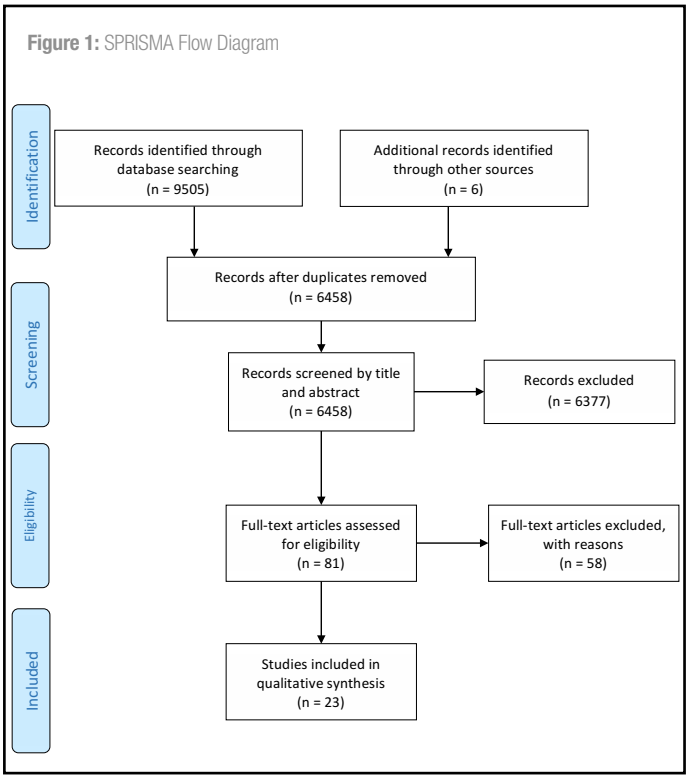
## Results

### Study selection, quality and methodology

The initial literature search of the aforementioned databases provided 9505 articles. 6 additional articles were included through review of bibliographies of relevant articles. After removing duplicates, 6458 articles were assessed by title and abstract. 81 of these articles were evaluated as full-text. 23 eligible studies were finally identified (Figure 1) and checked for methodological quality (Figure 2).

All studies combined included a total of 69.551 children, of whom 6.114 had excessive crying and 63.437 were controls. The median study size was 160 (Interquartile Range (IQR): 1600). The population was community based in 20/23 studies and clinical in 3/23 studies. Some studies used the same study cohorts, such as the Danish National Birth Cohort (DNBC) and the Amsterdam-Born Children and their Development (ABCD). Eighteen of the studies provided sociodemographic characteristics of the study sample.

**Figure 1:** SPRISMA Flow Diagram




Infant colic was diagnosed between 31 days and 9 months of age. The median upper age for the assessment of excessive crying was 3 months (IQR: 4). Information on infant crying was obtained using diaries, interviews, clinical assessments or questionnaires (Table 1). Most information was provided by caregivers (parents), in six studies additional information was provided by experts (paediatricians and health nurses). Diagnostic criteria for infant colic are not consistent, and several different definitions were used. Thirteen studies used the criteria for excessive crying proposed by Wessel et al (crying three or more hours per day, three or more days per week, during three or more weeks in the first three months of life) or the modified Wessel criteria (crying/fussing for 3 hours or more per day, for 3 days or more per week, for 1 week)[11]. Various other definitions were used, including "parental complaint" and "crying more than others of the same age". The heterogeneity in the definition precludes a formal meta-analysis of the studies.

## Outcomes

Follow-up after infant colic took place between 15 months and 18 years of age. The median upper age for follow-up was 6 years (IQR: 7). 14 articles studied the effects of infant colic on behaviour, 4 on mental health, 8 on physical health, 2 on cognition and 7 on family functioning (Table 2). Follow-up information was acquired through questionnaires in 17 studies, clinical assessments were used in 6 studies, and interviews were used in 5 studies. Some studies used the same questionnaires, including the Child Behavior Checklist (CBCL), the Strengths and Difficulties Questionnaire (SDQ), the Developmental Coordination Disorder Questionnaire (DCDQ'07), and the Behavioral Style Questionnaire (BSQ). Parents provided information on the outcome variable in 18/23 studies, experts (such as physicians) in 10 studies, and teachers in 2 studies. The children themselves provided information through questionnaires in 3/23 studies, these children were between 8 and 18 years old at follow-up.

### Behavioural outcome and Mental health

Fourteen of the included articles studied behavioural outcomes. We report the qualitative assessment of these studies based on the cohort age.

*≤ 5 years old*

Three studies *(St-James et al:*15 months old, Bayley, BSQ and Infant Behaviour Record (IBR); *Bell et al*: 2-3 years old, Autism Behaviour Checklist (ABC) and parental reports; *Elliot et al*: 2-4 years old, using CBCL) did not detect significant differences[12-14].

*Santos et al (*4years old, CBCL score) and *Papousek et al* (30months old, diary, Infant Characteristics Questionnaire (ICQ), CBCL/2-3) found that in general children in the excessive crying group had more internalising problems and externalising behavioural problems[15-16].

Ex-colicky children were found to be more aggressive, socially withdrawn, anxious and/or depressed and had higher scores on the emotionality subscale of the temperament questionnaire (*Rautava et al.,* 3years old, parent questionnaire, CBCL/2-3, Denver Developmental Screening (DDS) test)[17]. According to *Rautava et al.* ex-colicky children had more difficulties falling asleep, more temper tantrums and more sleeping disorders, but showed no statistically differences in child development[17]. *Cannivet et al* (4years old, parental questionnaire) found that "extreme criers" were less likely to enjoy meals[18].

*≥ 6 years old*

Two studies by *DeSantis et al* (3-8years Coping Inventory, CBCL, Child Behavior Checklist Teacher Report Form CBCL-TRF) and *Milidou et al* (7years, DCDQ'07) did not find any association between infant colic and behavioural problems[19-20].

Six studies found associations with emotional symptoms, conduct problems, hyperactivity and/or attention deficits, externalising behaviour problems, peer problems and eating problems. Significant associations were found between excessive crying in infancy and a higher risk for overall behavioural problems and hyperactivity/inattention problems by *Rao et al (*5years old , Personality Inventory for Children (PIC))[21], *Smarius et al* (5-6years old , Preschool Anxiety Scale (PAS) and Short Mood and Feelings Questionnaire (SMFQ))[22], *Wolke et al* (8-10years old, SDQ, Total Academic Achievement Score (TAAS), Emotionality, Activity, Sociability Temperament Survey (EASTS) and Childhood Temperament Impression (CTI) scale)[23], *Neu et al* (6-8years, BSQ, CBCL and Matching Familiar Figures Test (MFFT))[24] and *Lemcke et al* (8-14years old, accessed data from Danish hospital registries and the National Prescription Registry to identify participants from the Danish National Birth Cohort that had later been diagnosed with Attention Deficit and Hyperactivity disorder (ADHD))[25]. *Neu et al* confirmed that ex-colicky children had ADHD Checklist scores twice as high as the control group[24]. The same conclusion was drawn by *Lemcke et al*[25]. They found a significant association between children who had cried longer and more often (>4 hours per day, > 4 days per week) under the age of 6 months old, and children who were diagnosed with ADHD. An association was also found for children who cried more than 30 minutes per day in the first three months of life and ADHD in childhood.

*Brown et al* (5-8 years, SDQ scales) showed that ex-colicky children were found to have a higher risk of scoring in the abnormal range compared to the control group, for emotional problems, with girls having a higher risk than boys, although only boys showed a higher risk for conduct disorders[26]. Conduct problems were confirmed by *Smarius et al* and *Wolke et al* found an association with mood problems, emotional and peer problems[22-23]. The latter group also mentioned eating problems in the preschool cohort. *Savino et al* clinically evaluated previously colicky children at the age of 10 years and found a higher prevalence of sleep disorders, aggressiveness, fussiness and feelings of supremacy[27].

### Physical health

Eight of the included articles assessed the effect of infant colic on physical health.

Three studies found no difference. The analysis of *Brown et al* (school-aged children) showed no difference in prevalence of childhood illnesses between the colic group and controls in the state of Victoria, Australia[26]. *Smarius et al* investigated 5-7year olds[28]. These underwent a clinical evaluation, including measurement of blood pressure, heart rate, heart rate variability and indicators of cardiac autonomic nervous system activity. No significant differences were found between measurements in former colicky infants and the control group. *Castro-Rodríguez et al* studied the prevalence of asthma and/or atopy in children (3-13 years) who had infant colic[29]. They used the following biomarkers, aside from the results of a completed health questionnaire: total serum IgE levels, skin allergy prick tests, and peakflow variability. They found no associations between a history of infant colics and asthma, wheezing, eczema, allergic rhinitis and the atopy markers.

Five studies did find an association with atopic disease, allergic disorders, recurrent abdominal pain, functional gastro-intestinal diseases, ear infections and migraine with aura. *Kalliomäki et al* (0-2 years, relative with atopic disease, completed Barr charts and skin prick test at 2 years of age) found that high risk colic children, were more likely to develop atopic disease[30]. *Savino et al* clinically evaluated children at the age of 10 for allergic diseases and concluded allergic

**Figure 2:** STROBE quality assessment

| Authors | 1a | 1b | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smarius M., van Eijsden M., et al | - | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 20,5 |
| Bell G., Hiscock H, et al. | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | - | 20 |
| Hestbaek L., Sannes M., et al. | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | 20 |
| Santos I., Matijasevich A., et al | + | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 20 |
| Brown M., Heine RG., et al | - | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | 19,5 |
| Milidou I., Lindhard C., et al | - | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | 19,5 |
| Smarius L., Strieder T., et al | - | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 19,5 |
| Lemcke S., Parner E., et al | + | + | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | 19 |
| Neu M., Robinson J., et al | - | + | + | + | + | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | 18,5 |
| Castro-Rodriguez J., Stern D., et al. | + | + | + | + | - | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | 18 |
| Elliot M., Pederson E.L., et al | - | - | + | + | + | + | + | + | + | - | + | + | + | + | - | + | + | + | + | - | + | + | + | 18 |
| Savino F., Castagno E., et al | + | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | + | - | + | + | - | 18 |
| Sillanpää M., Saarinen M., et al | + | + | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | - | + | 18 |
| Räihä H., Lehtonen T., et al | - | + | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | - | + | 17,5 |
| Rao M., Brenner E., et al | - | + | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | - | 17,5 |
| DeSantis A., Coster W., et al. | - | - | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | - | 17 |
| Partty A., Kalliomaki S., et al | - | - | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | - | + | 17 |
| Rautava P., Lehtonen L., et al | - | + | + | + | - | + | + | + | + | - | - | + | + | + | + | + | + | + | - | - | + | + | + | 16,5 |
| Wolke D., Rizzo P., et al | - | + | + | + | - | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | - | 16,5 |
| Canivet C., Jakobsson B., et al. | - | - | + | + | - | + | + | + | + | - | - | + | + | + | - | + | + | + | + | - | + | + | + | 16 |
| Papousek M., Wurmser H., et al | - | - | + | + | - | + | + | + | + | - | - | + | + | + | - | + | + | + | + | + | - | + | + | 16 |
| St James-Roberts I., Conroy S., et al | - | + | + | + | - | - | + | + | + | + | - | + | + | + | - | + | + | + | - | - | + | + | + | 15,5 |
| Kalliomäki M., Laippala P., et al | - | - | + | - | - | - | + | - | + | - | - | + | + | + | - | + | + | + | + | - | - | - | + | 11 |

| *Article section* | Item number | Summary of recommendation |
|---|---|---|
| *Title and abstract* | 1a | Study's design in title/abstract |
| | 1b | Summary in abstract |
| *Introduction* | 2 | Scientific background and rationale |
| | 3 | Specific objectives, hypotheses |
| *Methods* | 4 | Key elements study design in beginning |
| | 5 | Setting, location, relevant dates |
| | 6 | Eligibility criteria, methods of participant selection, matching criteria |
| | 7 | Define outcomes, exposures, predictors, potential confounders, effect modifiers |
| | 8 | Methods of assessment/measurement of outcome variables |
| | 9 | Efforts to address potential sources of bias |
| | 10 | How study size was achieved |
| | 11 | How quantitative variables analysed |
| | 12 | Statistical methods |
| *Results* | 13 | Number of participants at each stage |
| | 14 | Characteristics of participants: sociodemographic, clinical, … |
| | 15 | Outcome data |
| | 16 | Main results, unadjusted estimates |
| | 17 | Other analyses done (e.g. subgroup analyses, interactions, …) |
| | 18 | Key results |
| | 19 | Limitations |
| | 20 | Overall interpretation of results |
| | 21 | Generalizability |
| *Other information* | 22 | Funding |

**Table 1:**

| Study | $N_{IF}$ | $N_{control}$ | $Age_{baseline}$ | Sample | M-tech | Inform | Diagnosis criteria | SOC |
|---|---|---|---|---|---|---|---|---|
| Bell G., Hiscock H, et al[12] | 167 | 671 | 4 – 9 months old | Community based (Baby biotics, Baby Business) | D | M | Modified Wessel et al | Yes |
| Brown M., Heine RG., et al[13] | 127 | | Less than 9 months | Clinically based | D | M | Parental complaint 24h cry chart | Yes |
| Canivet C., Jakobsson B., et al[14] | 50 | 102 | 12 weeks or 5 – 7 months | Community based | D/I | M | Wessel et al. | No |
| Castro-Rodriguez J., Stern D., et al[15]prospective study from an unselected population. Infantile colic and concurrent feeding method were determined from the 2-month well-infant visit form completed by the physician for 983 children who were enrolled at birth. Markers of atopy (total serum immunoglobulin E and allergy skin prick test | 90 | 893 | 2 months | Community based | CA/I | M/E | Physician's opinion + parental responses to questioning | Yes |
| DeSantis A., Coster W., et al[16] | 14 (persistent) | 14 (transient) | 4-12 weeks old | Clinically based | D/I | M | Number of hours crying and/or fussing | Yes |
| Elliot M., Pederson E.L., et al[17] | 10 | 72 | 6-8 weeks | Community based | I/Q | M/E | Wessel et al. | Yes |
| Hestbaek L., Sannes M., et al[18]"title":"Large cohort study finds a statistically significant association between excessive crying in early infancy and subsequent ear symptoms","type":"article-journa l","volume":"103"},"uris":["http://www.mendeley. com/documents/?uuid=339b5733-a3b6-39eb-9418-e39ec2d86d4f"]}],"mendeley":{"formattedCi tation":"<sup>18</>","plainTextFormattedCitation ":"18","previouslyFormattedCitation":"<sup>18</ p>"},"properties":{"noteIndex":0},"schema":"https:// github.com/citation-style-language/schema/raw/ master/csl-citation.json"} | Excessive crying: 1474 Extremely excessive crying = 709 | 24799 | Under 6 months | Community based (DNBCS) | I | M | Wessel et al. | No |
| Kalliomäki M., Laippala P., et al[19] | 116 total | | 7 & 12 weeks | Community based | D | M | Number of hours crying and/or fussing A cry not responsive to an intervention | No |
| Lemcke S., Parner E., et al[20] | - | - | 6 months | Community based (DNBC) | I | M | Wessel et al | Yes |
| Milidou I., Lindhard C., et al[21] | 1895 | 26045 | Under 6 months | Community based (DNBC) | I | M | Modified Wessel et al | Yes |
| Neu M., Robinson J., et al[22] | 20 | 20 | 4 – 16 weeks old | Community based | I/Q | M | Crying / unexplained fussiness > 2,8 hours per day, at least 3 days at 1 month old | Yes |
| Papousek M., Wurmser H., et al[23] | 60 | 45 | 1 – 6 months old | Clinically based | D | M | Wessel et al. | No |
| Partty A., Kalliomaki S., et al[24] | - | - | 7 and 12 weeks old | Community based | D | M | Number of hours crying and/or fussing A cry not responsive to intervention | Yes |
| Räihä H., Lehtonen T., et al[25] | 56 | 58 | 2 months old | Community based | D | M | Wessel et al | Yes |
| Rao M., Brenner E., et al[26] | 48 | 264 | 6 weeks, 13 weeks, 6 and 9 months | Community based | I/Q | M/E | daily uncontrolled crying without any obvious cause, persisting for at least two weeks | Yes |
| Rautava P., Lehtonen L., et al[27] | 338 | 527 | 3 months old | Community based | Q | M/E | Colic questionnaire, scores 1–3 (no colic), 4 (moderate colic) or 5 (severe colic) | Yes |
| Santos I., Matijasevich A., et al[28] | 438 | 3236 | 3 months | Community based | I | M | Crying more than others of same age | Yes |
| Savino F., Castagno E., et al[29] | 48 | 48 | 31 – 87 days old | Clinically based | I/CA | M/E | Wessel et al. | Yes |
| Sillanpää M., Saarinen M., et al[30] | 160 | 1107 | Under 3 months old | Community based | I/CA | M/E | a score of 5 on the visual analogue scale. | Yes |
| Smarius L., van Eijsden M., et al[31] | 61 | 2092 | 13 weeks old | Community based (ABCD) | D | M | Wessel et al. | Yes |
| Smarius L., Strieder T., et al[32] | 102 | 3287 | 13 weeks old | Community based (ABCD) | D | M | Wessel et al | Yes |
| St James-Roberts I., Conroy S., et al[33] | 67 | Evening criers = 38 Moderate criers = 55 | 4 – 5 weeks old | Community based | I/D | M | Wessel et al | No |
| Wolke D., Rizzo P., et al[34] | 64 | 64 | 3,8 months old | Clinically based | D | M | Modified Wessel et al. | Yes |

$N_{IF}$= amount of participants with infant colic, M-tech = method of measurement of infant colic, D = diary, I = interview, CA = clinical assessment, Q = questionnaire, Inform = informant of infant colic information, M = caregiver, E= expert, T = teacher, SOC = socio-demographic information available?

Table 2:

| Study | $N_{outcome}$ | $N_{Control}$ | $Age_{outcome}$ | M-tech | Outcome | Inform |
|---|---|---|---|---|---|---|
| Bell G., Hiscock H, et al[12] | 99 | 182 | 2-3 years old | Q (CBCL) | Behaviour,<br>Family Functioning | M |
| Brown M., Heine RG., et al[13] | 75 | | 5-8 years old | Q (SDQ, CHQ, Forsyth child vulnerability scale, Recent life events questionnaire, RAND-36 health status inventory)<br>CA (physical health assessment, clinical mental assessment)<br>I | Behaviour,<br>Physical health, Mental health | M/E |
| Canivet C., Jakobsson B., et al[14] | 50 | 102 | 4 years old | Q (Rutter Preschool questionnaire, Family Climate Scale) | Behaviour,<br>Family Functioning | M |
| Castro-Rodriguez J., Stern D., et al[15]prospective study from an unselected population. Infantile colic and concurrent feeding method were determined from the 2-month well-infant visit form completed by the physician for 983 children who were enrolled at birth. Markers of atopy (total serum immunoglobulin E and allergy skin prick test | 90 | 893 | 6 – 13 years old | CA (asthma, wheezing, allergic rhinitis, eczema, atopy markers, peak flow variability)<br>I | Physical health (Astma) | M/E |
| DeSantis A., Coster W., et al[16] | 14 | 14 | 3-8 years old | Q (Sensory profile, CBCL and TRF) | Behaviour | M/T |
| Elliot M., Pederson E.L., et al[17] | 10 | 72 | 2-4 years old | Q (CBCL, Feetham Family Function Survey, Family APGAR) | Behaviour,<br>Family Functioning | M |
| Hestbaek L., Sannes M., et al[18]"title":"Large cohort study finds a statistically significant association between excessive crying in early infancy and subsequent ear symptoms","type":"article-journal","volume":"103"},"uris":["http://www.mendeley.com/documents/?uuid=339b5733-a3b6-39eb-9418-e39ec2d86d4f"]}],"mendeley":{"formattedCitation":"<sup>18</P","plainTextFormattedCitation":"18","previouslyFormattedCitation":"<sup>18</sup>"},"properties":{"noteIndex":0},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} | Excessive crying = 1474<br>Extremely excessive crying = 709 | 24799 | 6 months - 7 years | I | Physical Health (Ear infections) | M |
| Kalliomäki M., Laippala P., et al[19] | 116 total | | 2 years | CA (atopic eczema, allergic rhinitis, asthma) | Physical health (Atopic disease) | E |
| Lemcke S., Parner E., et al[20] | | | 8-14 years old | CA (ICD-10, DSM-IV) | Mental health (ADHD) | E |
| Milidou I., Lindhard C., et al[21] | 1895 | 26045 | 7 years | Q (DCDQ'07) | Behaviour (Development) | M |
| Neu M., Robinson J., et al[22] | 20 | 20 | 6-8 years old | Q (BSQ, CBCL, MFFT, PSI, ADHD checklist) | Cognition, Behaviour,<br>Family functioning | M/E |
| Papousek M., Wurmser H., et al[23] | 60 | 45 | 30 months old | Q (ICQ, CBCL) | Behaviour (Temperament, emotional problems) | M |
| Partty A., Kalliomaki S., et al[24] | - | - | 13 years old | Q (modified Rome III Diagnostic Questionnaire for pediatric FGID) | Physical health (Functional GI disorders) | M/C |
| Räihä H., Lehtonen T., et al[25] | 54 | 52 | 3 years old | Q (McMaster Family Assessment Device) | Family Functioning | M |
| Rao M., Brenner E., et al[26] | 9 | 156 | 5 years old | Q (WPPSI-R test, PIC) | Behaviour,<br>Cognition (IQ) | E |
| Rautava P., Lehtonen L., et al[27] | 338 | 527 | 3 years old | Q (CBCL, DDST)<br>I | Behaviour,<br>Family Functioning | M |
| Santos I., Matijasevich A., et al[28] | 438 | 3236 | 4 years old | Q (CBCL) | Behaviour | E |
| Savino F., Castagno E., et al[29] | 48 | 48 | 10 years old | CA<br>I | Physical health (Gastro-intestinal disorders, allergic diseases)<br>Mental health (Psychological disorders) | E/M |
| Sillanpää M., Saarinen M., et al[30] | 96 | 691 | 18 years old | Q (chronic illness, ICHD criteria migraine) | Physical health (Migraine) | M/C |
| Smarius L., van Eijsden M., et al[31] | 61 | 2092 | 5 – 6 years old | CA (VU-AMS, BP with automatic oscillometric method) | Physical health (Blood pressure, heart rate, heart rate variability and indicators of cardiac autonomic nervous system activity) | E |
| Smarius L., Strieder T., et al[32] | 102 | 3287 | 5 – 6 years old | Q (SDQ) | Behaviour | M |
| St James-Roberts I., Conroy S., et al[33] | 67 persistent | 38 evening<br>55 moderate | 15 months old | Q (BSQ, IBR, Bayley Scales of Infant development) | Behaviour | M/E |
| Wolke D., Rizzo P., et al[34] | 64 | 64 | 8 – 10 years old | Q (CTIS, SDQ, TAAS) | Behaviour (Hyperactivity problems) | M/T/C |

M-tech = method of outcome measurement, D = diary, I = interview, CA = clinical assessment, Q = questionnaire, Inform = informant of infant colic information, M = caregiver, E= expert, T = teacher, C = child, SOC = socio-demographic information available?

disorders were more prevalent in ex-colicky children[27]. They also found that those children were significantly more likely to have recurrent abdominal pain. *Partty et al (*13 years, Rome III Diagnostic questionnaire) demonstrated that children who had had colic-type crying during their seventh and twelfth week of life were more likely to develop an abdominal pain-related functional gastro-intestinal disease at 13 years of age[31]. *Hestbaek et al* showed, on the basis of maternal reports, a statistically significant association between history of infant colic and ear infections, the use of antibiotics for ear infections and myringotomy in 18-month-olds and 7-year-olds[32]. *Sillanpää et al* questioned parents of formerly colicky infants on illnesses at the ages of 3, 12, 15 and 18[33]. At the age of 18, the adolescents themselves completed a questionnaire about their health, and more specifically questions about headaches. Infant colic was significantly associated with migraine with aura (RR of 2.7, 95 % CI 1.5–4.7), but not with migraine without aura.

Cognition

Two articles reported on cognitive functioning in ex-colicky children. *Neu et al* ( 6-8 years, Wechsler-Bellevue Intelligence Scale-III (WISC-III)) found that ex-colicky children only had lower perceptual scores, although the study by *Rao et al* (5 years, Wechsler Preschool and Primary Scale of intelligence (WPPSI-R)) found a significant association between prolonged crying and lower scores of total IQ (intelligence quotient), performance IQ and hand-eye coordination[24,21].

Family Functioning

Seven articles that studied the effect on family functioning were included.

Five of these found no significant differences between groups. *Bell et al* (2-3 years) found no significant impact on family functioning or on maternal mental health, and neither did *Canivet et al* (4 years) on 'family climate'[13,18]. *Brown et al* (5-8 years) reported no significant difference in family cohesion scores, *Neu et al* (6-8 year) showed no differences in parental distress, parent-child dysfunctional interaction and child difficultness and *Räihä et al* ( 3 year olds) did not report differences in the family's ability for problem solving, communication, affective responsiveness, affective involvement, behaviour control and general functioning[26,24,34].

Two studies found that infant colic was associated with a poorer subjective family functioning and with more major family disruptions. *Rautava et al* (3 years) found that children in the colic group had fewer siblings, their mothers perceived their household responsibilities as more substantial, and the mothers perceived contributions of the fathers to the household as insufficient more often[17]. The fathers in the colic group deemed that their families had fewer shared leisure time, the mothers deemed this leisure time as subpar more often than the control group. *Elliot et al* utilized several questionnaires to assess family function[14]. These did not show significant differences between the colic group and the control group. However, an association was found between infant crying and major family disruptions, for example divorce.

## Discussion

To our knowledge, this is the first systematic review of the long-term effects of infant colic into childhood. We found that these children were more likely to exhibit behavioural problems, psychological disorders, poorer cognitive functioning and physical disorders in childhood. There was little evidence for a significant effect of infant colic on family functioning.

In children under the age of 5, of the seven articles included, two showed that toddlers with a history of infant colic had more problems with internalizing and externalizing behaviour than children in control groups, though only one study produced scores in the abnormal range. The second study also showed that ex-colicky toddlers had more behavioural problems involving aggression, social withdrawnness, anxiety and/or depression. A third study found these children to have more sleeping problems and more temper tantrums. *Canivet et al* used a parental questionnaire and showed that the children had a more emotional temperament, and that they had more eating problems[18]. Though the studies do not provide an unambiguous result, they suggest that toddlers with a history of infant colic are at higher risk to develop a variety of behavioural problems.

In school-aged children, various measurements of behavioural outcome were used. Six studies found an association, namely that ex-colicky children had more emotional symptoms and mood problems, hyperactivity and attention deficits, conduct problems and externalizing behaviour problems.

All four of the included studies on mental health showed an association between infant colic and mental health problems. Though the studied mental health outcomes varied, several recurring themes can be found. Three studies found that children with a history of infant colic had a higher risk of ADHD in childhood. One study confirmed scores twice as high in the ex-colic group as in the control group. They also had a higher prevalence of oppositional defiant disorder, aggressiveness, fussiness, feelings of supremacy, depressive disorder, generalised anxiety disorder and sleep disorders. These findings are comparable to the behavioural outcomes.

Both included articles on cognitive functioning used a Weschler based intelligence scale, and both showed that ex-colicky children had lower intelligence scores. However, it is important to bear in mind that these two prospective studies used a small number of participants in the colic group (*Neu et al*: 20, *Rao et al*: 9)[24,21]. There are no large scale studies available to confirm these findings.

Five of the eight included studies on physical health found a relationship with infant colic. However, certain articles that included the same outcome measures had opposing results, which precludes unequivocal conclusions. Only allergic (three studies) and gastrointestinal diseases (two studies) were analysed in more than one included study. Of the three studies that looked at atopy, asthma and other allergic disorders, only two of them could show an association. Both studies on gastrointestinal disorders found an association. Other somatic problems were studied in one single study, such as number of ear infections and migraine.

Poorer family functioning is most likely not a result of infant colic, with five out of seven included articles showing no effect. Still, various measurements of outcome were used, making it more difficult to objectify the results. One study found an effect only on subjective family functioning (assessments were made by the parents themselves). The other study reported that infant colic was related to more major family disruptions, such as divorce.

Limitations

Only prospective studies were used to avoid recall bias. Because infant colic is often measured subjectively, it is much more prone to recall bias. Due to various definitions of infant colic and various measurements of outcome, it was not possible to perform a formal meta-analysis. This made it more difficult to draw objective conclusions. Additionally, only a small number of studies were found for each outcome.

## Conclusion

Infant colic is associated with behavioral, psychological, cognitive and physical problems in childhood. Some suggest that infant colic can in later life be associated with or be an expression of an undiagnosed, underlying disease, such as atopy or migraine, or even expression of a certain temperament early on in life. Children with a history of infant colic have a higher risk of developing behavioral problems and ADHD later in childhood. These findings suggest that children with a history of infant colic should be followed more closely to timely detect the associated health issues and behavioral problems. Certainly, more research is needed to be able to understand the precise nature of the relationship between infant colic and these disorders in childhood. Further research is also needed to understand if certain treatments for infant colic would have an impact on the behavioral and health issues later in life.

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# Anicteric hepatitis and arthralgia: two unusual presentations of Mycoplasma pneumoniae in children

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## Keywords

Mycoplasma pneumoniae, arthralgia, hepatitis, infection, extrapulmonary manifestations

## Abstract

*Mycoplasma pneumoniae* is a leading cause of both upper and lower respiratory tract infections worldwide. Although it is a well-recognized pulmonary pathogen, the manifestations outside the respiratory tract are often overlooked or overshadowed by the respiratory symptoms. Here, we report two cases of unusual presentations of *Mycoplasma pneumoniae* infection in children where arthralgia and anicteric hepatitis were the major clinical manifestations. A correct diagnosis was delayed due to initial mild respiratory complaints and the unawareness of the extrapulmonary manifestations, which are non-specific, of a Mycoplasma infection. There was a complete resolution of the complaints after adequate therapy with macrolide antibiotics.

## Background

*Mycoplasma pneumoniae* causes a wide variety of clinical manifestations in children and adults ranging from severe atypical pneumonia to asymptomatic or mild infection of the upper respiratory tract. Although it is mostly known as a respiratory pathogen, many extrapulmonary abnormalities have been described involving the central nervous system, joints, skin, liver, mucosa, vascular system, eye, heart and gastrointestinal tract1. These manifestations are an important part of Mycoplasma infection but are often not recognized or detected too late, delaying diagnosis and subsequent adequate therapy. Here, we report a *Mycoplasma pneumoniae* infection in a 2-year old child, born in Bangladesh, presenting with predominant arthralgia of the upper extremities and anicteric hepatitis, where initial diagnosis was incorrect due to false positive IgM serology for *Borrelia burgdorferi*, initial mild respiratory complaints and the unawareness of the extrapulmonary manifestations of a *Mycoplasma* infection. The fact that the patient originated from Bangladesh made the initial differential diagnosis broad, since several infectious diseases had to be excluded. The second case presented with arthralgia and bronchial hypperreactivity.

## Case 1

A 2-year-old girl, born in Bangladesh, was brought to the clinic to consult a pediatrician because the mother noticed reduced usage of both arms without apparent trauma or sickness. These complaints were observed for the first time 4 months ago. The mother didn't recall any signs of local inflammation or fever. Apart from her brother, who was diagnosed with a primary phagocytic disorder, no other members of the family were known with genetic or autoimmune diseases. The patient herself tested negative for the same immune disorder as her brother. The clinical investigation revealed a healthy child with purulent rhinitis and postnasal drip with normal lung auscultation and no signs of hepatosplenomegaly. The limbs and locomotor system showed normal movement with slight stiffness of the left elbow. No neurological deficits were observed. A routine blood examination was performed to investigate the possibility of juvenile idiopathic arthritis (JIA). In addition, an X-ray of the left arm revealed good mineralization of the bone fragments without fracture or signs of synovial fluid effusion.

The complete blood count and inflammatory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal (Table 1). These results together with a normal rheumatoid factor and negative autoimmune screening made the diagnosis of JIA highly unlikely[2]. Surprisingly, liver enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)) were increased, while albumin, total bilirubin and alkaline phosphatase (ALP) remained within the reference range. Due to the immobility of the upper limbs, serology for *Borrelia burgdorferi* (Liaison, Diasorin) was determined, since oligoarthritis is a common manifestation of late Lyme disease[3]. In addition, Mycoplasma serology (Liaison, Diasorin) was added because of upper respiratory complaints. *Borrelia burgdorferi* immunoglobulin M (IgM) was positive while IgG was negative suggestive for a possible recent infection. Confirmation of IgM was done by immunoblot assay which indeed showed a positive antigen band for *Borrelia* species. Moreover, IgM antibodies (index:10.0) to *Mycoplasma pneumoniae* were detected while IgG antibodies were not (< 0.10 AU/mL). At this point, Lyme disease appeared to be the most plausible cause for the ongoing joint complaints and thus amoxicillin-clavulanic acid was prescribed for three weeks.

During the follow-up consultation three weeks later no improvement of the patient's symptoms was noted. The mother recalled an episode of fever and coughing last week with pain in the right elbow and wrist without swelling, redness or rash with spontaneous resolution after three days. Lung auscultation revealed crepitations in both lungs. The routine laboratory tests showed a fulminant increase of transaminases (AST:210 U/L, ref. range: 20-60 U/L, ALT:624 U/L, ref. range: 17-44 U/L). Again, ESR and CRP were normal. The increase of ALT more than 10 times the upper reference limit (44 U/L) and ALP less than 3 times the upper reference limit (291 U/L) was suggestive for acute hepatitis[4]. Since the mother was known with hepatitis C virus (HCV), serology was tested to confirm a diagnosis of HCV infection. However, the results were negative, as was serology for hepatitis A and B virus. Amoxicillin-clavulanic acid-induced liver toxicity was considered. Yet, cholestasis is the most reported anomaly and ALP and y-GT (gamma-glutamyltransferase) were only mildly elevated in this case[5]. The fact that

**Table 1:** Laboratory test results upon multiple consultations in the hospital (case 1).

| Parameter | Unit | Visit 3 (+10 weeks) | Visit 2 (+6 weeks) | Visit 1 | Reference range |
|---|---|---|---|---|---|
| Leukocytes | $10^9$/L | 9.90 | 7.50 | 9.89 | 5.50 - 15.50 |
| Hemoglobine | g/dL | 12.1 | 12.7 | 11.8 | 11.5 - 13.5 |
| Trombocytes | $10^9$/L | 278 | 275 | 268 | 229 - 435 |
| Neutrophils | $10^9$/L | 3.63 | 2.59 | 4.03 | 2.1-8.9 |
| Lymphocytes | $10^9$/L | 5.06 + | 4.04 | 5.02 + | 1.2-4.5 |
| CRP | mg/L | <5.0 | <5.0 | <5.0 | < 10.0 |
| Sedimentation | mm/h Westergren | | 2 | 2 | 0 - 20 |
| LDH | U/L | 770 | 916 | 747 | 313 - 618 |
| Ferritin | µg/L | 40 | 86 | 73 | 6 - 137 |
| Albumin | g/L | 42.1 + | | 42.4 + | 34 – 42 |
| GOT (AST) | U/L | 57 | 210 + | 75 + | 20 - 60 |
| GPT (ALT) | U/L | 71 + | 624 + | 212 + | 17 - 44 |
| Total bilirubin | mg/dL | 0.3 | 0.3 | 0.3 | 0.2 – 1.3 |
| Alkaline phosphatase (ALP) | U/L | 163 | 166 | 188 | 129 - 291 |
| Gamma GT (y-GT) | U/L | 15 | 26 + | | 12 - 58 |

liver enzymes were increased before treatment is another argument against drug induced liver toxicity. Because of recent travel to Bangladesh, where outbreaks of chikungunya have been reported in 2018[6], serology for this virus was requested. Bilateral polyarthralgia of the wrists and hands and increased transaminases are frequent findings in chikungunya infection, although fever and increased CRP would also be expected. In addition, a molecular panel for common respiratory pathogens was performed on a nasopharyngeal aspirate because of unresolved respiratory tract symptoms. PCR was positive for bocavirus, coronavirus, parainfluenza virus type 4 and *Mycoplasma pneumoniae*. Serology for the latter revealed rising IgM (index:>27.0, 56302 relative light units) and the seroconversion of IgG, albeit weakly positive (11 AU/mL). The existence of respiratory tract symptoms together with the arthralgia and proven recent infection with *Mycoplasma pneumoniae* was sufficient to start treatment with clarithromycin for ten days.

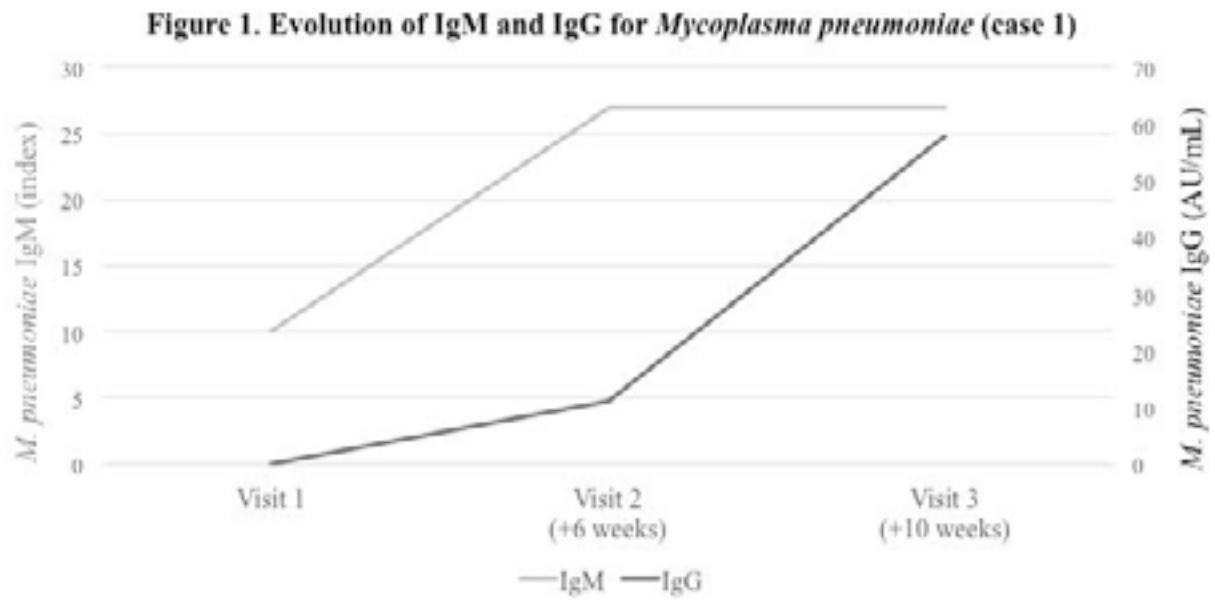
The patient returned three weeks after initiation of clarithromycin treatment with full recovery of locomotor function. Blood tests showed normalization of liver enzymes and rising IgM (index:>27.0, 93613 relative light units) and IgG antibodies for *Mycoplasma pneumoniae* (Figure 1). Serology and western blot for *Borrelia* species was negative suggesting a false positive result during the first visit.

## Case 2

A one-year-old boy was presented at the pediatric outpatient clinic with pain and non-use of his left arm since 1 day. He had a history of coughing and shortness of breath for the past 3 days. Anamnestically there would have been fever but this was not objectified. His medical history included a prenatal diagnosis of a small omphalocele, which closed 5 days after birth, circumcision and a fenestrated atrial septal defect which spontaneously closed. On clinical examination he had tachydyspnea at rest (45 breaths/min), with a saturation of 96%. Chest auscultation revealed bilateral wheezing with diffuse crepitation. The affected left arm felt warm, tender and the forearm was slightly swollen. Pronation and supination was painful.

The child was admitted for symptomatic treatment of a viral infection with bronchial hyperreactivity and for further observation of the left arm. Differential diagnosis included reactive arthritis of the left elbow or wrist. Laboratory test were not deviant e.g., normal leukocyte count (11.1 x10E9/L, ref. range: 5.5-15.5 x 10E9/L), CRP 0.6 mg/L (ref. range <10.0 mg/L). Due to a puncture problem, no hemoculture was taken at admission. Radiography of the left arm was normal. Nasopharyngeal aspirate revealed a positive PCR for Mycoplasma

**Figure 1** represents the evolution of IgM index and IgG index for Mycoplasma pneumoniae during three visits (case 1). Light grey line: Mycoplasma pneumoniae IgM, dark grey line: Mycoplasma pneumoniae IgG.



pneumoniae. He was treated with Salbutamol inhalation therapy and Azithromycin was started when PCR for Mycoplasma became positive. There was no fever during admission. He recovered completely, also the joint complaints disappeared quickly. In order to confirm a Mycoplasma infection, antibodies were determined 1 and 5 weeks after admission: IgM antibodies index decreased from > 27.0 AU/mL to 18 AU/mL, while the IgG antibodies remained stable (resp. 45 AU/mL and 40 AU/mL).

## Discussion

These two case reports describe an acute *Mycoplasma pneumoniae* infection in two children. One child presented with predominant arthralgia and anicteric hepatitis, the second with arthralgia and bronchial hyperreactivity. All complaints resolved without sequelae after appropriate antibiotic treatment. *Mycoplasma pneumoniae* is an important bacterial cause of respiratory tract infections in children. Although many infections are asymptomatic, tracheobronchitis and pneumonia are the most clinically important manifestations. Extrapulmonary disease involving the central nervous system, joints, skin, liver, mucosa, vascular system, eye, heart and gastrointestinal tract have been described. It is suggested that an aberrant host immune response plays an important role in the development of extrapulmonary manifestations[1,7]. In the first case, anicteric hepatitis was documented by elevated transaminases without signs of liver dysfunction. Liver involvement has been reported in a prospective Korean study in children with Mycoplasma infection, where 7.7% of infected patients were diagnosed with hepatitis. The results of this study clearly indicate increased AST and ALT levels without specific liver disorder and a relatively good prognosis with a longer mean duration of hospitalization[8]. *Mycoplasma* infection should thus be considered among the unusual causes of acute hepatitis among children whenever the most common hepatotropic viruses have been excluded[9]. Both cases also presented with a similar extrapulmonary manifestation involving the joints, which was twice the initial reason for consulting a pediatrician. Although, a separate aetiology is possible for the first case, considering the fact that the joints complaints were present few months before seroconversion, this seems unlikely because of complete resolution after adequate antibiotic therapy[10]. So far, no explanation for the late immune response was found.

## Conclusion

These two case reports reveal extrapulmonary manifestations, apart from the classical respiratory tract symptoms, which are non-specific for *Mycoplasma* infection, and could therefore delay a correct diagnosis and prompt start of adequate therapy. Treatment of extrapulmonary manifestations is needed as direct invasion of the organisms cannot be ruled out and decreasing overall bacterial loads can dampen the robust host immune system[10].

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# Relapsing hepatitis in children: an atypical presentation of hepatitis A virus infection in children.

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## Keywords

Hepatitis A virus, atypical manifestation, children

## Abstract

Hepatitis A virus (HAV) infections occur predominantly in children and are usually self-limited. Most children are asymptomatic but 30 percent of them develop the typical clinical triad including jaundice, light-colored stools and dark-colored urine. Apart from the well-known classical forms there are atypical manifestations of the disease such as prolonged cholestasis and relapsing HAV. This case report describes the case of a relapsing HAV in a 14-year old child.
It is crucial to remind those atypical presentations as it can avoid unnecessary invasive procedures such as liver biopsy.

## Introduction

Hepatitis A virus (HAV) infection is a disease caused by an RNA-virus affecting 120 million people annually worldwide. The risk of infection depends on socio-economic factors and the disease is more prevalent in developing countries. In Europe the number of declared cases has dramatically fallen although we still see a peak at the end of the summer when travelers are coming back from their holidays, often visiting relatives. Most European countries recommend the inactivated HAV vaccine for risk groups including travelers to endemic zones [1,2].

Transmission is mainly through the fecal-oral route, most often through contamination of food or water by human infected feces. HAV is usually a benign pathology, there is no chronic form, healing is spontaneous and the disease confers a lifelong immunity. However, fulminant hepatitis and liver failure occurs in 0,1 percent of cases, most often in elderly people. Symptomatic hepatitis develops in approximately ten to thirty percent of infected children younger than six years of age, some of whom become jaundiced. In contrast, older children with HAV infection are usually symptomatic for several weeks [2,3]. Although they are less common, cases of atypical presentations including relapses of HAV are described in children [3,4].

## Case presentation

A 14-year-old girl was admitted for an acute jaundice, associated with pale stools diarrhea, dark urine, vomiting and high fever. Diffuse crampoidal abdominal pain, more intense in the right hypochondrium had been present for two weeks, accompanied by anorexia and asthenia. She does not take any medication and she visited relatives in Morocco one month ago. Her previous medical history is marked by a glucose-6-phosphate dehydrogenase (G6PD) deficiency and a congenital hepatosplenomegaly as part of a prolidase deficiency, a rare metabolic disease that can also be responsible of recurrent skin ulcers, recurrent infections and mental retardation of varying magnitude. She was vaccinated according to the Belgian schedule that doesn't include HAV vaccination.

Clinical exam revealed mild dehydration, severe jaundice, enlargement of spleen and liver already present in prior clinical exams and diffuse abdominal pain with a positive Murphy sign. No extrahepatic manifestations were found during the clinical exam. Biology showed a severe cytolysis (alanine aminotransferase (ALT) 2468UI/L [0.1-41.0], bilirubinemia 22mg/dL [0.3-1.2]) and serology revealed HAV infection (anti-HAV IgM positive). ). Abdominal ultrasound revealed an enlargement of the liver at 165 mm [68-69]. Note that on the last known ultrasound dating from 2014 the hepatomegaly was at 130 mm. Symptomatic treatment was given and she was discharged from the department one week later when cytolysis decreased moderately (ALT 122 UI/L, bilirubinemia 16mg/dL) and general status improved. She was closely followed and four weeks later she came back with a second episode of diarrhea associated with jaundice. A diagnosis of relapsing hepatitis A was made in view of the increased cytolysis (ALT 1330UI/L and bilirubinemia 19 mg/dL). Abdominal ultrasound showed an increased hepatomegaly at 145mm. Thereafter, spontaneous healing was observed, associated with a slow normalization of liver tests (Figures 1 and 2).

**Figure 1:** Evolution of bilirubinemia throughout the disease. Normal range of bilirubinemia: 0.3-1.2 mg/dL.

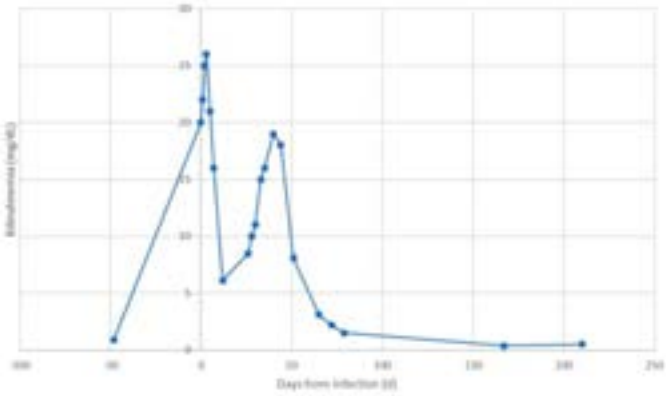
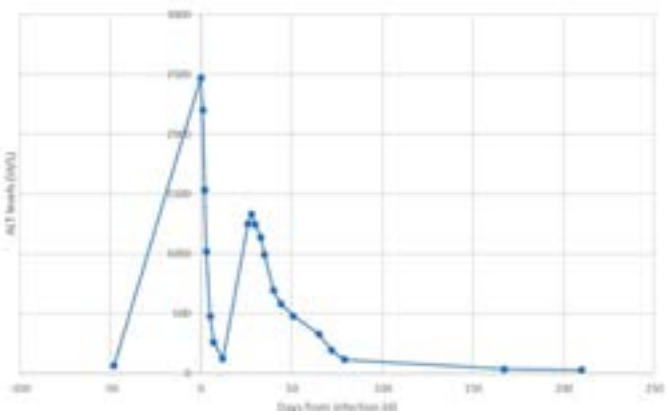


**Figure 2:** Evolution of the level of alanine aminotransferase (ALT) throughout the disease. Normal range of ALT: 0.1-41.0 UI/L.



## Discussion

A few clinical presentations of HAV are well described in literature. Among them is the asymptomatic or subclinical infection, most often seen in children under the age of five. The most typical presentation is characterized by a clinical triad including jaundice, light-colored stools and dark-colored urine, associated with elevated transaminases at more than twenty-times the normal rate. Apart from the well-known classical forms there are atypical manifestations of the disease such as prolonged cholestasis, relapsing hepatitis A, characterized by reappearance, within six months after the first episode, of the clinical, biochemical and viral markers of the disease and fulminant hepatitis. Finally, HAV infection may also trigger autoimmune type I hepatitis in genetically susceptible individuals [3–7].

A few studies showed that the different atypical presentations of HAV were found in children usually older than seven years of age having higher serum bilirubin values compared to children with a typical course of the pathology [6].

In this case, the patient also suffers from G6PD deficiency which has been reported to be associated with a more severe form of acute HAV as well as with extra-hepatic manifestations of the disease such as hemolysis and renal failure [5,8]. In addition, she suffers from a prolidase deficiency which may be responsible for, among other things, hepatomegaly with elevated liver enzymes and splenomegaly, which partly explains the clinical picture of our patient.

A study showed that children with chronic liver disease are susceptible to hepatitis A virus infection and that they tend to present a more severe form or even fulminant hepatitis. It is suggested that these children receive hepatitis A inactivated vaccine 9we studied the prevalence of anti-HAV in 60 children and adolescents with chronic liver disease, aged between 1 and 16 years, from the Unit of Pediatric Hepatology of the Hospital de Clínicas de Porto Alegre. The total anti-HAV was determined by a commercially available competitive ELISA method (Abbott.

Relapses of hepatitis A are well described and are called biphasic form of the disease although sometimes it can be polyphasic. They occur in 5-10 percent of cases of HAV. Most often, a first acute episode occurs lasting for three to five weeks followed by complete remission associated with normalized levels of aminotransferases. The period of remission lasts between one and three months followed by a relapse of the infection characterized by aminotransferase levels higher than 1000 IU/L and a persistence of anti-HAV IgM positivity throughout the entire course of the disease. The relapse is typically less severe than the initial episode. The total duration of the disease can vary between sixteen and forty weeks; the healing is complete and spontaneous, as it was the case for our patient [3,4,10]. Although a few studies show that the use of steroids during the relapse is associated with a remarkable improvement in terms of symptoms and biochemical markers, it does not seem to alter the course nor the duration of the disease. It is suggested that steroids should be used in severe, symptomatic cases of relapsing hepatitis A, although further studies are needed to determine the use of steroids as a part of treatment [3].

## Conclusion

Different clinical presentations of HAV infection exists in children from asymptomatic to fulminant hepatitis. We faced a case of relapsing HAV infection. After remission, a relapse of the infection is characterized by reappearance of clinical, biochemical and viral markers of the disease. HAV infection in children is usually benign and an auto-limited disease but the clinical presentation of relapsing hepatitis can be tricky. It is crucial to keep those atypical presentations in mind as it can avoid unnecessary invasive procedures such as liver biopsy. A close follow-up of patients suffering from those atypical presentations until full recovery should be sufficient as the healing is spontaneous.

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# Towards new therapies for bronchopulmonary dysplasia

PhD thesis presented on 9th of October 2019 at KULeuven, Leuven, Belgium

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## Introduction

Fifty years ago, Northway was the first to describe fibrotic changes in the lungs of preterm infants who could only be kept alive with aggressive mechanical ventilation and supraphysiological oxygen administration [1]. He referred to this disease as bronchopulmonary dysplasia (BPD). Even though advances in perinatal medicine have increased the survival of ever more premature infants, these developments were unable to reduce the incidence of long-term respiratory morbidity. At present 45% of survivors of extremely preterm birth (<28 weeks of gestation) still develop BPD [2]. The most recent consensus definition is based on the need for supplementary oxygen or respiratory support on 36 weeks postmenstrual age [3]. Despite doubts regarding the predictive value of any of these definitions, BPD continues to be associated with disabling consequences throughout life. It is linked with respiratory morbidity (lung function abnormalities, increased episodes of wheezing and frequent hospital admissions), pulmonary hypertension (which is associated with a mortality rate up to 38% [4,5]), and even abnormal neurological development [6,7]. Also from a health economics perspective, BPD remains an important problem [8]. As the current clinical care fails to prevent BPD, the development of effective preventive and therapeutic strategies remains imperative.

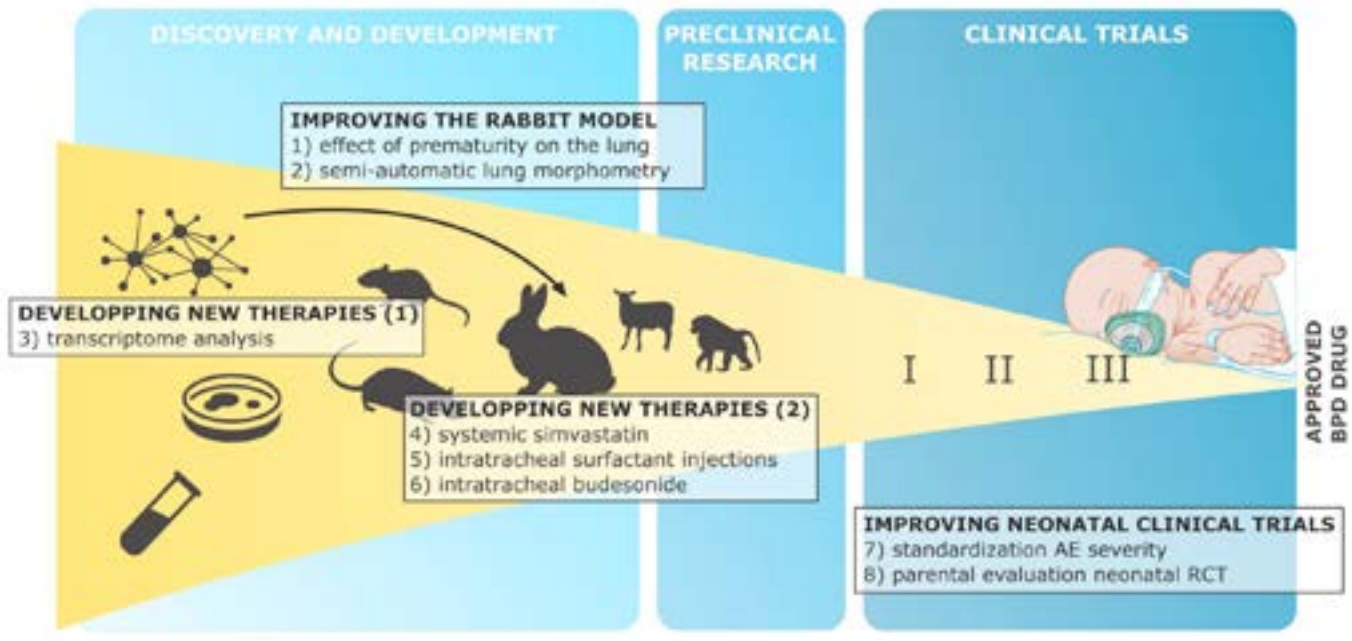
The objective of this thesis was to advance the search for novel therapeutic strategies for BPD. We aimed to develop and improve the methods for preclinical and clinical research on BPD, and use these methods to search for novel therapeutic strategies (Figure 1).

## Improving models and methods for explorative and preclinical research on BPD

Despite advances in (3D) cell culture methods [9,10], there are currently no in vitro models mimicking the complexity of a developing lung. BPD research thus relies mainly on animal models. It is not easy to develop an ideal animal model that incorporates the morphological, functional and vascular manifestations of BPD and at the same time provides a good representation of the human pathophysiology. Neonatology is a constantly changing field and this affects the utility of the different animal models. Where aggressive iatrogenic insults (high $FiO_2$ and mechanical ventilation) were the cornerstones of the so called "old BPD", this may no longer hold true for the BPD that neonatologists currently encounter[11]. Modern BPD remains a multifactorial disease, but the consistent common denominator in the whole disease spectrum is extreme prematurity. We therefore think that there is a major translational advantage in using preterm animals to study BPD.

In a first study we demonstrated that preterm rabbits born at a gestational age of 28 days have functionally and structurally immature lungs at birth. Furthermore, prematurity -in the absence of hyperoxia- was enough to cause a lung developmental arrest in preterm pups on day 7, in comparison to term pups of the same postconceptional age [12]. We noted functional defects, while structural defects were more subtle (catch-up development of alveolar structures, but decreased total alveolar surface due to smaller lung size). To our knowledge, we are the first to report on the pulmonary effect of 'pure' prematurity in an animal

**Figure 1:** Thesis overview. Position of the different studies along the drug development pathway.



model, in contrast to many papers focusing solely on the effects of hyperoxia and mechanical ventilation. A precocious transition from intrauterine life to room air, representing a supra-physiological exposure to oxygen for the fetal lung [10,13], or a precocious weaning from maternal and placental growth factors could explain these findings. We hypothesize that identifying the factors and pathways that perturb normal lung development after preterm birth, might lead to novel treatments for BPD. Our findings demonstrate the importance of prematurity in the pathogenesis of BPD, and support the use of a preterm animal model. In the rest of our work we used a rabbit model that combines prematurity and hyperoxia.

A single perfect animal model for BPD does not exist. Small animal models using term mice and rat pups are particularly suited for basic explorative research on pathways involved in specific aspects of the disease (e.g. hyperoxia or mechanical ventilation), because of the availability of state of the art molecular techniques. On the other hand larger animal models such as preterm primates and lambs provide a good platform for the translational study of innovative therapeutic strategies in a setting similar to the neonatal intensive care unit. Practical and ethical constraints however limit extensive use, so only the most promising therapies can be tested out in these models. In our work we focused on the preterm rabbit model. This elegantly sits between the small and large animals and can be used for both explorative and translational research, as it is the smallest model that combines structural and functional prematurity. The use of the appropriate animal model for each research question will benefit the development of novel therapeutic strategies for BPD [14].

Overall, in all animal models, BPD researchers could do more efforts to avoid bias in their experiments. As stated in the introduction, a systematic review of animal research in BPD demonstrated that aspects like randomization, blinding, allocation concealment or prior calculation of sample size were only occasionally applied in the reviewed articles [15]. One of the primary read-outs in BPD research is the mean linear intercept of the airspaces (Lma), together with several other parameters of alveolar morphometry. Few researchers however use an unbiased stereological approach to obtain these measures [16,17], as this is very time consuming. Furthermore, we showed high inter-observer variability after manual counting. In a second study we developed and validated a computerized method to facilitate the assessment of alveolar morphometry that is compatible with a stereological approach (manuscript in preparation). This semi-automatic method was markedly faster than manual counting, and provided highly reproducible results. The use of this method could improve the quality of morphometric results in BPD research.

## Developing novel therapies for BPD in the preterm rabbit model

New systems-biology based approaches offer opportunities to identify novel targets for the treatment of BPD [18]. In a third study, we performed transcriptome analysis on lung tissue of a relevant animal model [19]. By using mRNA-seq we identified 2217 genes that were significantly up- or down-regulated in whole lungs of preterm rabbit pups exposed to hyperoxia, in comparison to those of preterm pups exposed to normoxia. We used several strategies in the Ingenuity Pathway Analysis software to filter out relevant therapeutic targets from this vast amount of information. Several interesting molecules such as CCL2, IL8 and DKK1 were highly upregulated, while CYP1A1 was downregulated. Secondly, we arranged the dysregulated genes in functional networks. We identified gene networks involved in inflammation (up), lung development (down), vascular development (down) and reactive oxygen species metabolism (up) to be contributing to the lung phenotype of preterm rabbits exposed to hyperoxia. Finally, we combined our mRNA-seq results with published data on interactions between molecules in an upstream regulator analysis [20]. We hypothesized that an altered activity of several master switch molecules such as NFE2L2, NF-κB and KLF-2 would be involved in the observed dysregulations in gene expression. Molecules identified as upstream regulators could be interesting targets for drug development.

Simvastatin for instance is a drug that is known to induce KLF-2. If we expanded the upstream regulator analysis to exogenous molecules, simvastatin itself was predicted to reverse the dysregulation of other dysregulated downstream molecules (CCL2, IL8, VEGF-A, …). We hypothesized that simvastatin, a cholesterol lowering drug but with pleiotropic effect, could be repurposed for BPD-like lung disease. In a fourth study we assessed the efficacy of simvastatin in the preterm rabbit model [21]. A daily enteral dose of 5mg/kg attenuated the lung functional effects of hyperoxia. Most importantly it also completely prevented arterial medial thickening, which is in line with other observations in animal models for perinatal pulmonary vascular disease [22,23]. We successfully predicted that simvastatin has beneficial effects on the lung phenotype of preterm rabbits exposed to hyperoxia. The mechanism of the observed effect of simvastatin therefore remains largely unknown. We speculate that VEGF-A and Rho-kinase [22] play a role, but more research is needed to prove this. Furthermore, we also noted an unexpected and unexplained mortality in the normoxia control group treated with simvastatin, which currently limits the translational value of our findings. Future experiments could focus on identifying the exact working mechanism to find other more targeted molecules aimed at this pathway. Alternatively, local drug delivery could be explored, preserving the local effects of simvastatin, while omitting its systemic side effects.

A second target for therapeutic interventions is inflammation (CCL2, IL8 and IL1β are examples of highly upregulated genes in lungs of preterm pups exposed to hyperoxia). This idea is anything but novel. In the nineties up to 40% of babies born before 28 weeks of gestation were treated with postnatal steroids in order to prevent lung inflammation leading to BPD [2]. Despite reduction in BPD, postnatal steroids resulted in increased rates of cerebral palsy [24,25]. More recently, local delivery of steroids for the prevention of BPD have been investigated. The most successful approach was the intratracheal administration of a mixture of surfactant and budesonide [26], yet many questions remain on the most ideal dosing regimen or formulation.

So far, research on the long term (BPD) effects of a drug added to surfactant, was only possible in larger animal models and sheep. In a fifth study, we developed a technique for intratracheal administration in preterm rabbits [27]. We confirmed the safety and feasibility of daily intratracheal injections with surfactant (as a vehicle for drug delivery). We also assured a good delivery to and distribution within the lungs by means of microPET-CT. The preterm rabbit model is a good model to study locally administered steroids, as it combines prematurity with the ability to translate clinical procedures like intratracheal delivery. More in general, this model is therefore well suited to study neonatal applications of local pulmonary drug delivery, an area that is gaining interest [28].

To prove this statement, we used this model and delivery method to assess safety and efficacy of two doses of intratracheal budesonide, mixed in surfactant in a sixth study. While other researchers [26] used a repetitive dosing regimen of 0.25mg/kg budesonide/surfactant mixes, we were able to show that a single dose of 0.25mg/kg budesonide was even more effective (manuscript in preparation). It improved compliance and inspiratory capacity, decreased septal wall thickening and decreased expression of inflammatory cytokines CCL2 and IL8. It remains unclear whether the lower efficacy of the repetitive dosing is a rabbit specific issue, but it draws attention to the toxic potential of high doses of steroids in a growing body. Based on the data from this experiment, we would suggest future clinical trials evaluate the safety and efficacy of a single dose of surfactant plus budesonide, early after birth.

## Improving methods for clinical research on BPD

Any promising innovative therapy for BPD should undergo clinical testing in human subjects, before it gets market approval. In a final group of studies that we will not discuss in detail here, we focused on improving the methods for clinical trials in newborns [29,30].

## General conclusion

This thesis did not result in the identification of “the golden bullet” to prevent or cure all BPD. However we have advanced the ongoing search for novel therapies in several ways, along different phases of the drug development pathway. We developed new methods and new hypotheses to boost future research that will help to improve the respiratory outcome of survivors of extremely preterm birth.

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# Statins for children with familial hypercholesteremia: effective and safe in the short term, long-term safety remains unknown

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## Question

Are statins effective and safe to treat children with familial hypercholesterolemia?

## Context

Familial hypercholesterolemia is a common inherited metabolic disease in which the blood choles-terol level is high. It is an autosomal dominant disorder in which heterozygotes, so-called carriers, are affected and homozygotes have severe disease. The average worldwide prevalence of heterozygous familial hypercholesterolemia is at least 1 per 500, but according to more recent data could be closer to 1 per 250. Coronary atherosclerosis and its clinical complications often occur at an earlier age than usual, especially in men.

Lifelong therapies, started in childhood, are therefore needed to reduce the risk of vascular disease. In children with the disease, diet has been the cornerstone of treatment. The addition of lipid-lowering medication has provided significant improvement in treatment, but anion exchange resins, such as cholestyramine and colestipol, are poorly tolerated due to their unpleasant taste and treatment plans are not followed. Statins seem to be safe and well-tolerated in children, but their long-term safety in this age group remains unknown. This Cochrane review therefore assessed the efficacy and safety of statins.

## Criteria for study selection

The Cochrane review included studies comparing statins to placebo or diet alone in children and adolescents up to 18 years old. The participants had to be diagnosed with heterozygous familial hy-percholesterolemia based on genetic testing or clinical criteria (level of serum total cholesterol is higher than age-adjusted upper limit and at least one parent has hypercholesterolemia). The main outcomes of interest were change in carotid intima-media thickness, change in serum LDL cholester-ol-level and change in measures of growth and maturation, e.g. age of puberty onset.

## Summary of the results

The review identified nine randomised controlled trials with a total of 1177 participants. The studies compared different statin treatments with placebo. Both the intervention and follow-up was rather short and ranged from six weeks to two years with a median of 24 weeks.

Statins reduced the mean LDL cholesterol concentration at all time points (6 studies, 669 partici-pants, high-certainty evidence). The mean change in serum LDL cholesterol level in the placebo groups ranged from a 5% increase to a 4% decrease , whereas in the statin groups the LDL cholesterol decreased with a mean of 32% (95%CI*: 35% lower to 29% lower). Despite some concerns regarding risk of bias and heterogeneity across studies, the review authors consider this to be high-certainty evidence given the effect size. The effect of statins on puberty was measured by the change in Tanner stage. There may be little or no difference between treatment with statins or placebo on this measure of growth and maturation (placebo: 636 per 1000 vs statins: 604 per 1000 (95%CI 489 to 750); 1 study, 211 participants, low-certainty evidence). There may be little or no difference in liver func-tion, measured as proportion of participants with changed aspartate aminotransferase or alanine aminotransferase levels (7 studies, up to 924 participants, low-certainty evidence). Statins may also make little or no difference on myopathy, measured as change in serum creatine kinase (6 studies, up to 669 participants, low-certainty evidence), or adverse events (control: 399 per 1000 vs statins: 402 per 1000 (95%CI 323-502); 2 studies, 276 participants, moderate-certainty evidence). One study on simvastatin showed that it may slightly improve flow-mediated dilatation of the brachial artery (1 study, 50 participants, low-certainty evidence). One study showed that pravastatin may induce a regression of the carotid intima-media thickness at 2 years (1 study, 211 participants; low-certainty evidence). No studies reported on rhabdomyolysis or death due to rhabdomyolysis, quality of life or compliance with the treatment.

## Conclusion

Statins are an effective lipid-lowering therapy in children with familial hypercholesterolemia. Statin treatment seems to be safe in the short term but longer-term safety still remains unknown.

## Implications for practice

Children receiving statins for familial hypercholesterolemia should be carefully monitored by their paediatrician.

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# 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 Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) - EU/1/12/812/001 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 | Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen [d] |
| **Adolescenten (11 jaar of ouder) en volwassenen*** | | | |

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **CONTRAINDICATIES** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **BIJZONDERE WAARSCHUWINGEN EN VOORZORGEN BIJ GEBRUIK** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfunctie. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door ***Neisseria meningitidis*** groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. **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, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen Zeer vaak: misselijkheid 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** 03/2019 (v09) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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

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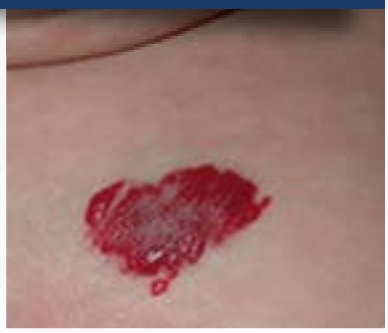

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