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Enterol 250 mg, gélules : lactose monohydraté. Pour la liste complète des excipients, voir rubrique 6.1 du RCP. FORME PHARMACEUTIQUE Enterol 250 mg, poudre pour suspension buvable : Poudre pour suspension buvable. Enterol 250 mg, gélules : Gélule. DONNEES CLINIQUES **Indications thérapeutiques** • Prévention de la diarrhée associée à l'antibiothérapie à large spectre chez des sujets prédisposés à développer une diarrhée à Clostridium difficile ou rechute de diarrhée à Clostridium difficile. • Traitement des diarrhées aiguës chez les enfants jusqu'à 12 ans, en complément de la réhydratation orale. **Posologie et mode d'administration** Posologie : Adulte : 2 à 4 gélules ou 2 à 4 sachets-doses par jour, en 2 prises. Population pédiatrique Enfant : 2 gélules ou 2 sachets-doses par jour, en 2 prises. Mode d'administration : Gélules : avaler avec un peu d'eau. Sachets-doses : diluer la poudre dans un verre d'eau. 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Mises en garde et précautions particulières d'emploi). • Allergie aux levures, spécialement *Saccharomyces boulardii* CNCM I-745 Effets indésirables : Les effets indésirables sont classés ci-dessous par système-organe et par fréquence comme définies ci-après : très fréquents (≥ 1/10), fréquents (≥ 1/100, < 1/10), peu fréquents (≥ 1/1.000, < 1/100), rares (≥ 1/10.000, < 1/1.000), très rares (< 1/10.000), fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classes de systèmes d'organes Fréquence Infections et infestations Très rares : Fongémie chez des patients porteurs d'un cathéter veineux central, et chez des patients dans un état critique ou immunodéficients (voir rubrique 4.4 du RCP), mycose à *Saccharomyces boulardii* CNCM I-745. Fréquence indéterminée : Sepsis chez les patients de réanimation ou immunodéprimés (voir rubrique 4.4 du RCP) Affections du système immunitaire Très rare : choc anaphylactique. 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Belgique - Agence fédérale des médicaments et des produits de santé Division Vigilance - Avenue Galilée 5/03 - B-1210 Bruxelles Site internet: www notifieruneffetindesirable.be - e-mail: adr@afmps.be Luxembourg/Luxemburg - Direction de la Santé – Division de la Pharmacie et des Médicaments - 20, rue de Bitbourg - L-1273 Luxembourg-Hamm Site internet: www.guichet.lu/pharmacovigilance e-mail: pharmacovigilance@ms.etat.lu TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE BIOCODEX Benelux NV/SA - Boulevard de l'Humanité 292 - 1190 Bruxelles - Belgique - Tél : 0032(0)23704790 NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE Enterol 250 mg, poudre pour suspension buvable : BE269026, LUX 2011041132. Enterol 250 mg, gélules en flacon en verre : BE269035, LUX 2011041131. Enterol 250 mg, gélules en plaquette: BE397896, LUX 2011041131 MODE DE DELIVRANCE Délivrance libre DATE DE MISE A JOUR DU TEXTE Mise à jour : 04/2023 - Approbation : 09/2023

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125 JAAR
NUTRICIA ONDERZOEK

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Voor de baby **verandert er niets** want onze **samenstelling blijft hetzelfde**.

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Referenties: 1. Havlicekova Z, et al. Nutr J. 2016;15:28. **2.** Carnielli VP, et al. Am J Clin Nutr. 1995;61:1037–42. **3.** Kennedy K, et al. Am J Clin Nutr. 1999;70.5:920-927. **4.** Billeaud C, et al. Eur J Clin Nutr. 1990;44(8):577–83. **5.** Tolia V, et al. JPGN. 1992;15(3):297-301. **6.** Moro G, et al. JPGN. 2002;34(3):291-295. **7.** Knol J, et al. JPGN.2005;40(1):36-42. **8.** Kanabar D, et al. J Hum Nutr Diet. 2001;14:359–63. **9.** Saviano F, et al, Acta Pediatr Suppl. 2003;91(441):86-90. **10.** Vandenplas Y, et al. Eur J Pediatr. 1994;153 : 419-423. **11.** Borelli O, et al. Ital J Gastroenterol Hepatol. 1997;29(3): 237-242. **12.** Rodriguez-Herrera A, et al. Nutrients 2019;11(7): 1530. **13.** Tounian P, et al. Pediatric Gastroenterology, Hepatology & Nutrition. 2020:23(6):511. **14.** Varasteh S, et al. JPGN. 2019;68(S1):N-P-016:1049. **15.** M. Goethals, Danone Research.

Editorial

STRENGTH LIES IN UNITY !

This spring issue, the first of 2025, marks an important step in the life of our journal and in that of the Belgian paediatric associations. New year, new colours, new layout... those of the Belgian Academy of Paediatrics (BAoP). As announced and presented many months ago, BAoP is the result of the merger of the Belgische Vereniging voor Kindergeneeskunde/Société Belge de Pédiatrie (BVK/SBP), the Groupement Belge des Pédiatres de langue Française (GBPF) and the Vlaamse Vereniging voor Kindergeneeskunde (VVK). We look back with gratitude and much appreciation on what they have achieved and how they paved the way for the current BAoP.

The status and missions of the BAoP are extensively described in its website (www.baop.be). Its main goal is to represent and promote the interests of children and paediatricians at regional and national levels in Belgium and internationally. In close cooperation with all child-centred organisations, it aims to inform and influence the political arena to advocate for children and youngsters. It will also serve as an umbrella of all regional and Belgian scientific and professional paediatric organisations as well as all universities to improve standards in training, service and research in Belgium as well as in Europe. Several Task Forces have been identified to support these ambitious missions.

Bringing together and even merging several groups is a great challenge, a source of opportunity and a means of increasing the impact and sustainability of actions. It can also be a source of drift or dangers that need to be approached with great care. We see examples of this every day, not only in the sector of health, but also in the world of business, politics and diplomacy. As a small country in the heart of Europe, Belgium has always taken this into account. With many nuances, sometimes with creativity and relativity, we have tried to apply our national motto: Eendracht maakt macht - L'union fait la force - Einigkeit macht stark. This has guided the internal organisation of our country, but also its role and influence in the construction of the European Union and in our implication in major international bodies.

Our history and the times we are currently living in show us that change, the development of alliances and the merger process can also be frightening. Fears related in particular to the involvement of all, to the balance between the rights and duties of members, and to respect for diversity and singularity. It is therefore necessary to support these movements with great care. Without mentioning them by name, we would like to take the opportunity of this editorial to thank all those who, over many months, have devoted so much time and energy to defining, refining and communicating the BAoP project. In all fields, it is recognised that the strength of a group is proportional to the sense of belonging that each of its members feels. This feeling is itself nourished by the involvement and responsibility of each individual. We hope that this will be the case for our academy and, as Editors-in-Chief, we would like to reaffirm the desire of the Belgian Journal of Paediatrics (BJP) to be a key tool of communication for the BAoP. We are keen to continue sharing clinical observations and the results of scientific studies carried out by paediatricians from Belgium and from abroad. We want to strengthen our involvement in the training of young colleagues by encouraging them to write scientific articles. In this regard, we are delighted to publish in the current issue the message of Prof Stephane Moniotte at the opening ceremony of the 53rd Annual Paediatric congress. A supplementary issue is also published with the abstracts that were presented in Mons on March 13 and 14 2025. We also take this opportunity to thank the entire organising team for the quality and success of this conference.

The mission of the BJP is only possible thanks to the support of the training supervisors and the constructive review of experienced paediatricians. Once again, we would like to thank these reviewers who improve the quality of our journal year after year. The names of all our reviewers for the year 2024 are listed on page xx. The BAoP aims to take advantage of resources it has gathered to better define and regularly update new recommendations for the management of diseases and clinical situations. The Belgian JP is certainly the place of choice for the dissemination of such consensus. We hope that this will further increase the interest of the Belgian and international paediatric community in our journal.

We hope you will enjoy the read of this issue and we wish you an exciting spring !

Marc Raes and Christophe Chantrain

UW VRAGEN OF COMMENTAAR
VOS QUESTIONS OU COMMENTAIRES

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OPENING CEREMONY - 53RD ANNUAL BELGIAN PAEDIATRIC CONGRESS - MARCH 13th 2025

Ladies and gentlemen, dear colleagues, and distinguished guests,

It is an honor and a privilege to welcome you all to the 53rd Annual Belgian Paediatric Congress here in the city of Mons.

This year is truly special, as we are not only coming together to exchange knowledge and discuss the latest advancements in paediatrics but also celebrating the dawn of a new era for our profession. We gather today for the first annual meeting under the banner of the Belgian Academy of Paediatrics, a very special occasion that follows the historic unification of five national and regional paediatric societies. We look back with gratitude and much appreciation on what they have achieved and how they paved the way for the current BAoP. Like the birth of a child, this process of collaboration and growth has been months—and indeed, years—in the making, and today, we witness the fruition of that effort.

Therefore, I would like to begin this opening ceremony by acknowledging the contributions of our previous past president, Dr Marc Raes whose leadership has been instrumental in shaping the structure of our scientific working group and the program of this annual meeting, with his guidance of the national and local scientific committees.

I also would like to extend a special recognition to Dr. Ann de Guchtenaere, the current President of the BAOP, who quite literally worked nights and days to make the fusion a reality. Her unwavering dedication and tireless efforts have been crucial in the successful consolidation of our Academy.

The 3 other past Presidents of our scientific and professional societies, Dr. An Bael,

Dr. Pierre Philippet and Dr. Tijl Jonckheer worked together tirelessly to strengthen the networks within our community, ensuring that the foundations of unity are now firmly established.

It is because of their visionary leadership that we have the opportunity to continue their work in a new and dynamic phase, that will drive the future of paediatrics in Belgium.

Now, as we turn our attention to this congress, we are excited to share with you an exceptional scientific program that aligns with the central theme of "Prevention and Innovations." This theme reflects our ongoing commitment to addressing both the prevention of diseases and the continuous pursuit of cutting-edge innovations that can improve the lives of children and their families. Over the course of these two days, we will delve into critical areas such as the prevention of RSV bronchiolitis, climate change and its impact on children's health, and the latest developments in paediatric cardiology, neonatology, feeding disorders, infectious diseases, and much more.

In addition to the plenary talks, the parallel sessions will offer opportunities for deeper exploration into subspecialties such as genetic screening, paediatric endocrinology, nephrology, and paediatric pulmonology. These sessions are not just designed to update your knowledge but also to stimulate dynamic discussions, interdisciplinary collaborations, and share new ideas and insights that can shape our practices going forward.

The collaboration we are witnessing here today—across various subspecialties—further reflects the heart of what we aim to accomplish through the Belgian Academy of Paediatrics: a strong, united voice that will advocate for innovation, research, and the best possible care for our children. Just as the early milestones of a child's life set the stage for future development, this congress represents an essential step in our continued professional growth, allowing us to come together, learn from each other, and ensure that we are always advancing in our collective mission to improve paediatric care across Belgium.

As we convene today, we must also address the pressing challenges facing our profession. One of the most immediate concerns is the continuous decrease in working hours of physicians and paediatricians in training, particularly in hospitals, coupled with an emphasis on work-life balance. A profound re-evaluation of how we consume medical care in paediatrics will soon be mandatory. Given that government funding will not increase to compensate for these changes, we must collectively adopt a more responsible use of medical resources. This means prioritizing essential care, enhancing efficiency, and embracing innovative strategies. In particular, AI, artificial intelligence, is becoming a true opportunity to optimize workflows, support clinical decision-making, and reduce administrative burdens. Additionally, I believe that the role of advanced practice nurses will be crucial in bridging gaps in patient care, ensuring continuity, and alleviating the pressure on physicians. By leveraging these advancements and embracing collaborative models of care, we can maintain the highest standard of paediatric healthcare despite the evolving constraints.

On the global scene, the recent election of Donald J Trump marks another turning point in the international and Belgian medical landscape. His policies have already demonstrated a significant impact on healthcare access, funding, and international collaborations. In Belgium, we cannot remain indifferent to these shifts. We must anticipate the potential consequences of altered international policies, particularly in areas of research funding, pharmaceutical regulations, and the exchange of medical expertise. Our response must be one of vigilance and adaptation, ensuring that we safeguard the progress we have made in paediatric care.

To conclude on a much lighter note, I would like to highlight a unique cultural initiative taking place throughout this meeting: a collective painting that symbolizes our unity and creativity as a medical community. I encourage all participants to contribute to this artwork at any time, making it a shared reflection of our collaboration and dedication.

I also encourage you to visit the BAOP booth, to discover the new format of the Belgian journal of paediatrics, and to visit the booths of our sponsors. Any interaction you will have means a lot to them.

We look forward to 2 days of engaging discussions, learning, and collaboration. Together, we will continue to build upon the foundation set by the leaders before us and create a future that will benefit generations to come.

Thank you, and once again, welcome to this historic congress. Let us embrace the opportunity to learn, to collaborate, and to drive the future of paediatrics forward—together.

Prof Stéphane MONIOTTE, M.D., Ph.D.
President Belgian Paediatric Congress 2025

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Bowel Function in Children with Low Anorectal Malformations after Surgical Repair

A Retrospective Single-Center Cohort Study

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Keywords

Anorectal malformation ; imperforated anus ; child ; quality of life ; rectal diseases ; surgery ; surveys and questionnaires ; rectum / abnormalities ; rectum / surgery.

Abstract

Objective

Bowel function in patients post-surgical repair of low forms of anorectal malformations (ARMs) was evaluated. This study aimed to identify predictors of functional outcomes to guide parental counseling and predict quality of life.

Methods

Patients treated for ARMs at Ghent University Hospital between 2005 and 2015 were retrospectively analyzed. Data included demographics, ARM type, diagnosis timing, operative management, and associated anomalies. Bowel function was assessed using both Rintala questionnaire filled in by parents, resulting in bowel function score (BFS), and clinical outcome (CO) evaluated by the surgeon.

Results

In total, 80 patients were analyzed, of which 59 girls (74%), with a median follow-up age of 7.7 years. Early diagnosis (within the first week of life) occurred in 61%. The most common ARM type was rectoperineal fistula (87.5%). Associated anomalies were present in 40% of patients, with 12.5% having VACTERL association. Normal BFS (≥18/20) was achieved in 47.5% of patients, with 54% having excellent CO. There was a significant correlation between BFS and CO ($p<0.001$). Rectal trimming was associated with lower BFS ($p=0.003$). Presence of a developmental disorder significantly impaired BFS ($p=0.013$). No significant differences were observed based on timing of diagnosis or surgical intervention.

Conclusion

Half of the patients achieved excellent BFS and CO at mid-long follow-up, with significant negative impact of rectal trimming during surgery and presence of a developmental disorder later in life. Literature on trimming is absent, however our data suggests significant importance on BFS. Rintala questionnaire correlated well with CO, suggesting being useful in follow-up.

Introduction

Anorectal malformations (ARMs) represent congenital anomalies affecting the anorectal region, exhibiting a spectrum of defect severity (1). During embryonic development, abnormal cloacal division may lead to the manifestation of ARMs, although the precise etiology remains unexplained (2). It occurs in approximately 1 to 5,000 live births (3). Classification systems such as the early Wingspread or Peña classifications, and commonly used Krickenbeck classification from 2005 have been developed in an attempt to categorize ARM types based on anatomical features, although their therapeutic and prognostic utility may be limited (1). The diagnosis of ARMs typically occurs postnatally at birth through careful clinical examination, however delay with diagnosis later in life is possible when children present with functional complaints such as constipation or fecal incontinence. Correct diagnosis is essential for appropriate management and favorable patient outcomes (1, 4). ARMs may occur in isolation or in association with other congenital anomalies, with the VACTERL association being the most common (3). Surgical intervention is typically required for ARM management, with posterior sagittal anorectoplasty (PSARP) remaining the gold standard for definitive repair for low forms of ARM (5, 6). The choice between single-stage definitive repair and staged procedures involving colostomy creation depends on the type and complexity of ARMs (7). The fistulous tract is generally trimmed during surgery; however, informal debate among surgeons and sparse literature question whether this segment should be retained as it may play a role in sensitivity and continence (8-10). Long-term follow-up is essential to monitor bowel function, including, soiling, fecal incontinence or constipation (11). In pediatric patients with ARMs, incontinence

can result from an inadequate sphincter mechanism or reduced bowel sensitivity. Additionally, prolonged bowel distention may decrease bowel motility, which can exacerbate tendencies towards constipation. Both mechanisms underlying incontinence may coexist, compounding their effects (7). However, prognosis in patients after ARM repair remains multifactorial, influenced by anatomical complexity, associated anomalies, and treatment approach, including timing and approach of surgery and the integrity of neural and muscular structures. For parents to be properly informed about the child's prognosis, it is essential to accurately assess the likelihood of bowel dysfunction including incontinence, soiling and/or constipation later in life. However, there's no consensus in literature regarding the demographic and clinical characteristics that may have a prognostic value.

Objective

This study aimed to evaluate bowel function after surgical repair of low forms of ARMs in a single center cohort, exploring the relation between bowel function at mid-long follow-up, and demographic, clinical, and therapeutic characteristics.

Materials and methods

Study Population

This retrospective study received approval from the Ghent University Hospital ethics committee, Ghent, Belgium (No. BE670201837662). This single center study (Ghent, University Hospital, Ghent, Belgium) included patients treated or operated on between January 2005 and December 2015 for low forms of ARM including anal stenosis, rectoperineal fistula, rectovestibular fistula, and imperforate anus without fistula.

Data Collection

The treating physicians contacted parents or legal guardians by phone to request participation, and written informed consent was obtained. Rintala questionnaires were mailed to participants and returned by post. Simultaneously, demographic and clinical data were retrospectively collected from medical records, including ARM type, timing of diagnosis, presenting symptoms, preoperative interventions, surgical details, postoperative complications, and associated anomalies. Early diagnosis was defined as within the first week of life.

Questionnaire

The Rintala questionnaire, consisting of seven questions with corresponding scores, was used to assess bowel function (12). Questions included information concerning control of defecation, stool urge, stool frequency, soiling, incontinence, constipation, and social hindrance/discomfort in the context of bowel function. Each answer on the questionnaire corresponded to a score, with a global score known as the bowel function score (BFS) based on the responses. The maximus BFS that could be obtained was 20, where a BFS of at least 18 out of 20 was considered indicative of normal bowel function (12).

Scoring of function by expert opinion

The Clinical Outcome (CO) was assessed simultaneously by the treating surgeon. Information was derived from the last medical report at follow-up in policlinics, where outcomes were categorized as excellent, good, moderate, or poor, based on criteria related to bowel movements, social limitations, and constipation severity. CO as evaluated by the treating surgeon and BFS as reported by the patient's parents was obtained independently from each other. Both were used to provide a comprehensive mid-term view of the patient's bowel function.

Statistical Analyses

Statistical analysis was performed using SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to assess the distribution of the BFS, seen as a continuous, independent variable. We analyzed the association between BFS and predefined factors with potential influence, including the timing of surgery, type of surgery (with particular attention to trimming of the anorectum), and the presence of associated sacral/spinal anomalies. Mann-Whitney U test and the Kruskal-Wallis test were conducted due to the non-parametric distribution of the data. Based on the results of the bivariate analyses and findings from the literature, several potential variables were further analyzed as predictors using multivariate analysis in the form of multiple linear regression. The correlation between BFS and CO was evaluated using the Spearman rank correlation test. All statistical tests were two-sided, with a significance level set at $p < 0.05$.

Results

Study Population

Of the 110 patients diagnosed with a low form of ARM within the study period, two were excluded due to death from unrelated causes. Consent was obtained from the parents or legal guardians of 85 patients. Ultimately, a dataset of 80 patients was analyzed

TABLE 1: Low forms of Anorectal Malformations Types.

	Rectoperineal fistula	Rectovestibular fistula	Imperforate Anus	Total n (%)
Total N (%)	70 (87,5%)	9 (11,3%)	1 (1,3%)	80 (100%)
Gender N (%)				
Girls	50 (71,4%)	9 (100%)	0 (0%)	59 (73,7%)
Boys	20 (28,6%%)	-	1 (100%)	21 (26,3%)
Trimming, N (%)				
Yes	45 (64,3%)	4 (44,4%)	0 (0%)	49 (61,2%)
No	19 (27,1%)	4 (44,4%)	1 (100%)	24 (30%)
unknown	6 (8,6%)	1 (11,2%)	0 (0%)	7 (8,8%)

TABLE 2: Associated anomalies diagnosed in patients with low Anorectal Malformations at Ghent University Hospital.

System	Total N (%)	Associated anomalies
Cardiac	22 (27,5)	Atrial septal defect; Ventricular septal defect; Tetralogy of Fallot; Persistent ductus arteriosus; Patent foramen ovale; Pulmonary valve stenosis
Renal/Urogenital	11 (13,8)	Renal dysplasia; Vesicoureteral reflux; Hemi-uterus; Neurogenic bladder; Hypospadias; Solitary/Ectopically implanted/Multicystic kidney
Cranial	11 (13,8)	Facial dysmorphia; Preauricular tag; Malformation of the auricle; Microcephaly; Microretrognathia; Constricted ear
Limb	9 (11,3)	Clubfoot; Thumb appendages; Thumb hypo-/aplasia, Radial aplasia
Spinal/vertebral	6 (7,5)	Vertebral fusion; Missing/additional vertebrae; Tethered cord
Gastro-intestinal	2 (2,5)	Esophageal atresia with tracheoesophageal fistula; malrotation of the duodenum

after excluding patients due to conservative treatment (2), treatment abroad due to complexity of surgery (associated vaginal agenesis) (1), or incomplete questionnaires (2).

Out of the 80 included patients, 59 were girls (74%). The majority of patients (80%) were born after 37 weeks gestational age. Of the 8 (10%) premature infants, the median gestational age was 35 weeks (range: 28- 36 weeks), with unavailable data on gestational age in the remaining 8 patients. Diagnosis occurred early within 48 hours after birth in 54% of neonates (43/80), with an additional 7% within 7 days of life (49/80). In the remaining 31 children where diagnosis was initially missed in the first week of life, one or more associated symptoms which led to diagnosis included obstruction (8/31), constipation (31/31), incontinence (1/31) and painful defecation (11/31).

TABLE 3: Rintala Questionnaire: Evaluation of bowel function.

System	Total N (%)	Associated anomalies
Factors	Score given	N (%)
Total filled in questionnaires		80 (100%)
Ability to hold back defecation		
Always	3	49 (61%)
Problems less than 1/week	2	17 (21%)
Weekly problems	1	7 (9%)
No Voluntary Control	0	7 (9%)
Feels/reports the urge to defecate		
Always	3	50 (62,5%)
Most of the time	2	18 (22,5%)
Uncertain	1	8 (10%)
Absent	0	4 (5%)
Frequency of Defecation		
Every other day - twice a day	2	64 (80%)
More often	1	9 (11%)
Less often	0	7 (9%)
Soiling		
Never	3	12 (15%)
Staining less than 1/week, no changer of underwear required	2	37 (46%)
Frequent Staining/soiling, change of underwear often required	1	19 (24%)
Daily soiling, requires protective aids	0	12 (15%)
Accidents		
Never	3	45 (56%)
Less than 1/week	2	22 (27%)
Weekly accidents, requires protective aids	1	6 (8%)
Daily, requires protective aids during day and night	0	7 (9%)
Constipation		
No Constipation	3	53 (66%)
Manageable with diet	2	8 (10%)
Manageable with laxatives	1	14 (18%)
Manageable with enemas	0	5 (6%)
Social problems		
No social problems	3	67 (84%)
Sometimes (foul odors)	2	7 (9%)
Problems causing restriction in social life	1	5 (6%)
Severe social and/or psychic problems	0	1 (1%)

Anorectal Malformation types and Associated Anomalies

Data is presented in Table 1 and Table 2. A rectoperineal fistula was present in 70 (88%) patients, a rectovestibular fistula in 9 (11%) girls, and an imperforate anus in 1 (1%) boy. A rectoperineal fistula was the most frequent type in both boys and girls: 20/21 (95%) and 50/59 (85%) respectively. Associated congenital anomalies were seen in 32 (40%) patients. A VACTERL association, defined as at least 3 out of 7 systems affected, was subsequently seen in 10 of these 32 children (12.5% out of the total population). Additionally, out of 80 patients, 13 (16%) children exhibited chromosomal anomalies.

Preoperative, Operative, and Postoperative Data

Preoperative management included dilatation in 14 (17%), irrigations in 9 (11%), and use of laxatives in 22 patients (27%). All patients underwent PSARP for definitive repair. Sixty-eight patients (85%) had single-staged repair, whereas repair after an initial colostomy creation was seen in 12 patients (15%). The median age at definitive repair was 76 (IQR 38 – 150) days, with a total range from day 1 of life to 9,3 years old. When comparing the age at definite repair for patients with single-staged repair or with colostomy creation, respectively, a median age of 61 (IQR 31 – 150) days versus 108 (IQR 73 – 156) days was seen. The fistulous tract was trimmed in 49 patients (61%) (Table 2). Postoperative complications occurred in 21 (26%) patients, including urological co-morbidities in 3 (4%), anal mucosal ectropion in 11 (14%), and wound dehiscence in 7 (9%) patients. There were 0 cases of anal stenosis.

Rintala Questionnaire

Data is presented in Table 3. All parents completed the Rintala questionnaire. The median age of patients at the time of completion of the questionnaire was 7.7 (IQR 5,6 – 10,1) years. Median BFS was 17 (range 3 - 20), with 38 out of 80 patients (47.5%) with a BFS of at least 18, which correlated with a normal bowel function.

Urge to defecate was evaluated with most children (62.5%) always feeling the urge to defecate, and 22.5% who did most of the time. However, 10% of parents were unsure about their child's awareness, and 5% reported that their child did not feel the urge to defecate.

Regarding bowel accidents, 56% of children didn't experience any, with 27.5% having infrequently bowel accidents. In 7.5% of cases weekly problems were reported. Nine percent of children needed diapers day and night due to daily accidents.

A significant number of children had some degree of soiling, with only 15% never experiencing it. Nearly half (46%) had soiling less than once a week, however, 23% soiled weekly, necessitating frequent changes of underwear. A total of 15% experienced daily soiling, requiring additional protective measures such as pads or diapers.

Most children (66%) did not suffer from constipation. Dietary measures were sufficient to manage constipation in 10% of cases, while 17.5% required laxatives. A small percentage (6%) needed more intensive interventions such as enemas.

Social problems were reported absent in almost all children (84%). The remaining children did report occasional issues, such as odor problems (9%), and 6% experiencing limitations in social interactions and activities. Only 1 child (1%) faced severe social or psychological issues.

TABLE 4: Relationship between clinical Outcome and Bowel Function Score.

Clinical Outcome	N (%)	BFS-score Median (range)	BFS ≥ 18 - N (%)	BFS < 18 - N (%)
Excellent	40 (54%)	18 (11 - 20)	27 (67,5)	13 (32,5)
Good	20 (27%)	16,5 (3 - 20)	9 (45)	11 (55)
Moderate	5 (7%)	14 (8 - 16)	0 (0)	5 (100)
Poor	9 (12%)	7 (3 - 14)	0 (0)	9 (100)
Total	74		36 (49)	38 (51)

TABLE 5: Predictors of Bowel Function Score.

		Bowel Function Score			
Variable	Total (n)	Median	IQR	Range	P-value
Gender					
Girls	59	17	14 – 19	3 - 20	0,791
Boys	21	16	14 – 19	7 - 20	
ARM-type					
Rectoperineal	70	17	14,75 – 19	3 – 20	0,166
Rectovestibular	9	15	7,5 – 18,5	4 – 19	
Gestational age					
Term	64	17	14 – 19	3 – 20	0,138
Preterm	8	14,5	8 – 17,5	3 – 20	
Timing of diagnosis					
Early (first week of life)	49	17	12,5 – 19	3 – 20	0,576
Late (after first week of life)	31	18	15 – 19	4 – 20	
Timing of surgery					
< 1 week	13	17	12,5 – 19,5	3 – 20	0,368
1 week - 4 months	41	18	14 – 19	3 – 20	
> 4 months	26	16	14,75 – 18	4 – 19	
Sacral/spinal anomalies					
Yes	6	13	7,75 – 16,75	7 – 19	0,086
No	74	17,5	14,75 – 19	3 – 20	
Development disorders					
Yes	13	11	5,5 – 18	3 – 20	0,013
No	67	17	15 – 19	3 – 20	
Trimming					
Yes	49	16	14 – 18	3 – 20	0,003
No	24	19	16,3 – 19	8 – 20	

Clinical Outcome

Data is presented in Table 4. CO was assessed by the treating surgeon, based on the last follow-up consultation, with a total of 74 assessments, as six patients had a follow-up in another center. They did complete the Rintala Questionnaire. The median age at determination of CO was 4 (IQR 3 – 5,5) years. The median time of follow-up in policlinics was 43 (IQR 32; 63) months. In total 40 (54%) patients had excellent CO, 20 (27%) had good CO, 5 (7%) had moderate CO and 9 (12%) had poor CO. CO was significantly correlated with BFS (p <0.001). Table 4 gives an overview of the correlating BFS within each clinical group, and the percentage of patients with a BFS with a normal (≥ 18/20 BFS) or abnormal (<18/20 BFS) bowel function.

Predictors of functional outcome

Data is presented in table 5. Bivariate analyses was used to assess several variables potentially influencing functional outcome. Trimming of the rectum resulted in a significant lower BFS (median BFS 16; IQR 14 - 18) compared to patients without rectum trimming (median BFS score 19; IQR 16,3 - 18) (p = 0,003).Additionally, when evaluating rectoperineal fistula only, patients with a non-trimmed approach (n = 19; median BFS 19, range 4 - 20) scored significantly better than those with a trimmed rectum (n = 45; median BFS 16; range 3 - 20) (p = 0,004). Moreover, the presence of a developmental disorder was associated with a poorer prognosis as well in terms of BFS, with a median score of 11 (IQR 5,5 – 18), in comparison without developmental disorder (median 17; IQR 15 – 17) (p = 0,013). The timing of diagnosis nor timing of intervention had any effect on BFS (p = 0,576 and p = 0.368, respectively).

The multivariate analysis confirms results of the bivariate analysis, indicating that rectum trimming (p = 0.004) and the presence of a developmental disorder (p = 0.001) having a significant effect on bowel function. Non-significant variables included spinal anomalies (p = 0.164) and the type of anorectal malformation (ARM) (p = 0.15).

Discussion

ARMs represent a frequent congenital anomaly in children where correct diagnosis, appropriate surgical management, and long-term follow-up are crucial for optimal bowel function later in life.

Timing of diagnosis and surgery

ARMs are typically identified at birth, where diagnosis depends heavily on careful clinical observation and detailed inspection of the perineal area. Early diagnosis is defined in the literature within the first 48 hours of life, or by extension the first week of life (13-15). Jonker et al. found that complex ARMs were diagnosed early in 100% of cases, while only 54% of anatomically less complex ARMs were diagnosed early (13). In this study, more than one-third were not diagnosed within one week. This may be explained as only low forms of ARM were included, mimicking normal anatomy during the postnatal period (15). Early recognition is essential, as delayed diagnosis is associated with more preoperative complications, including severe abdominal distention (69% vs. 43% in early diagnosis) and sepsis (38% vs. 21%), as represented in a prospective cohort study by Reddy et al. (14). They also reported higher mortality rates in the delayed diagnosis group (4 out of 54 neonates, compared to 0 in the early diagnosis group), all attributed to sepsis, although this was not statistically significant. When looking at mid-term follow-up they showed no significant differences, with similar results of BFS obtained in children independent of timing of diagnosis.

Timing of surgery for ARMs is widely debated. Early neonatal surgery may have positive effects due to early relief of intestinal subobstruction and earlier acquisition of a physiological defecation mechanism. The median time for definitive repair in this cohort was 76 days, ranging from the first day of life until 9 years of age. Peña et al. (7, 16), who introduced the PSARP technique in 1980, recommended definitive repair within the first two months of life. Subsequent studies have compared the timing of surgery with post-operative complications and long-term outcomes. Pelizzo et al. used the Rintala Questionnaire and found that early surgery within 3 months correlated with better colonic function scores (> 18), although not statistically significant (17). Harumatsu et al. showed significant differences in overall BFS at the age of 11 years between early (before 5 months) and late (after 5 months) surgical repair groups, with better constipation scores in the early surgery group over time (18). Other parameters like incontinence, soiling, and bowel movements showed no significant differences, and neither was scoring in younger age groups. Harumatsu et al. only included intermediate to high types of ARM, complicating direct comparisons (18).

Type of surgery

PSARP was used in all cases, reflecting a homogeneous surgical management. A colostomy was required in 15% of patients before definitive repair. In comparison, a recent large cohort study over the UK and Ireland by Long et al. reported a high number of colostomies before or during definitive repair, present in 74% of the total population, with an incidence of 37% of those with perineal fistula and 78% in those with vestibular fistula (15). The higher incidence rates were explained by local habitude (3 stage approach), need for emergency decompression and context-related factors such as prematurity or other associated anomalies. Single-stage repairs are generally associated with better prognoses compared to staged procedures (19). However, a recent systematic review by Hartford et al. compared single-stage and staged repairs, finding no evidence of differences in long-term functional outcomes regarding voluntary bowel movements, soiling, and constipation between the two approaches (20). When looking at outcome later in life, Lauriti et al. conducted a systematic review on single-stage repair in females with rectovestibular fistula, showing no association between a one-stage approach and increased fecal incontinence (21). Single-staged repair is preferable as it minimizes the morbidity of colostomy, and need for multiple procedures under general anesthesia, however does not change long-term functional outcomes.

During the PSARP technique, the distal rectum, including the ectopic anal canal or fistula tract, is generally resected or "trimmed"(16). This topic is rarely addressed in the literature and is primarily discussed informally among pediatric surgeons (e.g., at congress meetings), with no consensus on whether to retain this segment. Trimming is typically necessary in cases of stenosis or damage (e.g., rectal atresia) (8). However, a recent study by Hamrick et al. investigated a preservation approach in fourteen patients with rectal atresia and three with rectal stenosis, describing a technique to spare the anterior dentate line (8). For other forms of anorectal malformations (ARM), opinions diverge. Some surgeons argue that the distal rectum does contain a dentate line, essential for sensitivity and continence, whereas it was previously assumed that this segment was poorly developed or even absent, favoring resection (8, 9). The ectopic anal canal was often reclassified as a fistula, leading to its routine destruction without scientific justification (16). Levin is among the few authors to address this issue in the literature, emphasizing the importance of preserving all elements of the anal canal or fistula tract to optimize postoperative continence and defecation (9). Levin proposed "the cutback procedure", which preserves all anal canal elements, reporting favorable bowel function outcomes in clinical follow-up (10).

This study showed that patients without trimming of the anorectum, and preservation of the dentate line structure did have significantly better functional outcomes. BFS was significantly lower, as mentioned in both bivariate as multivariate analyses. The lack of consensus in literature on terminology and surgical techniques, combined with the absence of studies on the impact of trimming on bowel function, underscores the need for further research.

Bowel function and Clinical Outcome

Almost half of the patients in this cohort achieved a normal bowel function (BFS of at least 18), with significant correlation between the perceptions of parents and the treating surgeon. In this study, patients with a rectoperineal fistula had better outcomes (median BFS: 17 [3; 20]) compared to those with a rectovestibular fistula (median BFS: 15 [4; 19]). However, a statistically significant difference was not observed, possibly due to the small sample size in the latter group. Additionally, as both rectovestibular and rectoperineal fistulas are low forms of ARM, significant differences between these two patient groups were not expected.

Beattie et al. conducted a comparable single-center study and reported that, in contrast to presented findings, more than half of their population had poor bowel function (22). Their study included both high and low forms of ARM, with significantly worse scores regarding both incontinence and constipation, however mainly present in the high ARM group. Peña et al. reported that when bowel management was appropriately applied 90% of fecal incontinence could be overcome, even in the less favorable ARM types (23). When comparing with a recent French multicenter study by Schmitt et al., including over 350 patients post-ARM repair, constipation rate was similar (41% versus 34% in this cohort) (24). Additionally, they reported the highest incidence of constipation in the group of 12-16 years old, with almost half of the adolescents affected. In this study, bowel function was not evaluated across different age groups, however literature states that constipation improves with age, potentially due to growth and hormonal changes during puberty (18, 25).

Regarding soiling, Schmitt et al. showed a higher prevalence, with 30-35% of patients experiencing occasional soiling once a week (versus 23% in this cohort), without significant age group differences (24). They did note a lower percentage of children experiencing social problems due to soiling, with a total of 6.5%, compared to 15% in this cohort.

Developmental disorder and associated anomalies

An important influencing factor on bowel function was the presence of a developmental disorder, with clearly lower BFS obtained. Pediatricians, surgeons and general practitioners should be aware when developmental disorders are present in ARM, to actively screen and manage underlying problems regarding bowel function. Incidence of associated anomalies are reported very differently in the literature. A recent Australian study by Evan-Barns et al. reported a higher number of associated anomalies (79%) and of VACTERL association (53%) (versus respectively 40% and 12.5% in this study). However, they showed that low forms of ARMs do not necessarily correlate with a lower incidence of other anomalies, and that these children are at risk for higher morbidity, as they are less likely to receive complete screening for associated anomalies (3).

Limitations

In this cohort PSARP was carried out in all patients before 2015. Although we obtained a large cohort sample from a single center, the subgroup analyses may have lacked sufficient statistical power due to the small group sizes. To asses bowel function, the Rintala questionnaire (12) was used, which is easy to use and interpret, but evaluating and comparing bowel function remains challenging due to the lack of standardized tools. Also, data were collected retrospectively, with assessments by parents and treating surgeons at different time-points, making comparisons challenging. Interpretation of parental reports may yield bias due to overestimation of good bowel function, as data were directly linked to the treating physician. Importantly, this study focused solely on bowel function and gastrointestinal outcomes, but urogenital function, sexual and reproductive health, mental health, and social acceptance should not be overlooked and need to be evaluated in the future.

Future perspectives

Our study suggests that avoiding anorectal trimming is preferable for better functional outcomes. However, studies on this subject are absent and further research with larger sample sizes is needed to confirm these findings.

Conclusion

This study focused on a homogenous group of low ARM cases treated with PSARP, showing that almost 50% achieved normal bowel function scores, with no gastrointestinal issues at a median follow-up age of 7.7 years. A worse bowel function seems to be present after anorectal trimming, suggesting it to be avoided during surgery when feasible. The timing of surgery remains debated, with a preference for early repair. The presence of a developmental disorder showed significant impairment of bowel function, and should be taken into consideration in follow-up and counseling. The Rintala questionnaire is useful at follow-up, additional to the clinical outcome evaluated by the treating surgeon. Long-term follow-up strategies should be adapted to monitor quality of life and adequately counsel patients and their parents.

The authors declare that they have no conflicts of interest.

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En savoir plus ?

Possible Pitfalls in Adolescent Medicine in Flanders: A Qualitative Approach

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Keywords

Adolescent medicine ; patient rights ; medical decision making ; proactive consideration ; parental caregiving ; quality of care.

Abstract

Objective:

Adolescent healthcare consists of a triadic relationship involving the physician, adolescent patient, and parents. In Belgium an adolescent patient can have a high degree of autonomy based on a maturity assessment by the physician. This qualitative study assesses the perspectives of general practitioners and families with adolescent children on the rights of adolescent patients.

Methods:

The research methodology employed focus group discussions with ten general practitioners and semi-structured interviews with twelve families recruited via social media. Physicians practiced in Flanders, and families included adolescents aged 14 to 17 years and their parents without a medical background. Interviews were conducted online, with data analysis guided by the Qualitative Analysis Guide of Leuven (QUAGOL).

Results:

The analysis revealed some of the specific challenges in daily clinical practice. The identified pitfalls include an insufficient awareness of the details of patient rights among both physicians and families, the passive role of adolescents, the effect of parenting styles and the loss of intricate knowledge of the family context in group medical practices.

Conclusion:

These challenges underscore the complexity of this triadic relationship. A deliberate and mindful approach, characterized by effective communication and active engagement of all stakeholders is needed to guarantee high quality adolescent healthcare provision.

Introduction

In the contemporary medical landscape, characterized by a departure from the paternalistic model, the significance of effective communication and establishment of a sound physician-patient relationship in delivering high-quality healthcare has garnered increasing attention (1). When dealing with adolescent patients, a multifaceted three-party relationship emerges (patient-physician-parents) that inherently embodies complexities (2). Within this triadic system, the central figure is the adolescent patient, whose cognitive faculties and decision-making skills are in a state of ongoing development and evolution. Notably, teenagers exhibit a greater propensity to make imprudent decisions in 'hot' circumstances characterized by heightened emotions, peer influence, and engagement of social cognition (3). This poses a challenge to physicians who must find an equilibrium between the needs and capacities of the adolescent and the role of the parents (4). Safeguarding the rights of all individuals and ensuring the exercise of autonomy within the boundaries of cognitive and competence levels are central tenets of medical ethics and pertain to adolescent patients (2, 5).

In Belgium, Article 12 §2 of Chapter 4 of the Patients' Rights Act tasks the physician with evaluating whether the adolescent possesses sufficient "maturity" to act autonomously (6). This level of maturity determines the level of parental involvement and the consideration of adolescent opinion (7). When an adolescent is deemed sufficiently mature, he or she can exercise the patient rights autonomously and -if they request it- exclude any parental involvement. This assertion of autonomy primarily pertains to two crucial patient rights: consent and confidentiality. Confidentiality concerns the professional secrecy and trust within the healthcare relationship. Consent, within the realm of patient law, encompasses the patient's right to participate and make self-determined choices (8).

In contrast to Belgium other countries have chosen for an age-based approach. In the Netherlands, full autonomous decision-making is granted to minors at the age of 16, in Italy only at the age of 18 (9). This seems more standardized but is less adaptable

to individual growth trajectories and prevents adolescents to seek individual medical care at younger ages (10). The Belgian system is person- and context-dependent and relies on the physician's judgment. Nonetheless, every adolescent, every physician and every relationship is unique. And the legal context does not provide concrete guidelines to the physician to make this assessment (11). The decision to grant medical autonomy to an adolescent is influenced by the specific medical problem, the maturity of the adolescent, the willingness of the parent(s) to cede control and the leadership role of the physician (1).

The central question that arises during clinical practise is this: what are the barriers and facilitators to good adolescent healthcare in general practice in Belgium? In this study we explore this question using a qualitative research methodology.

Methods

Data were obtained through structured interviews with general practitioners and families. The primary focus was to identify successful practices as well as obstacles within general medical settings, along with the reasons behind such challenges. Furthermore, the interviews aimed to delve into how these obstacles were addressed and what changes should be considered.

General practitioners were recruited via email and various social channels, primarily through the collaborative network of UZ Leuven and the Academic centre for Primary Care (ACHG) inviting Dutch-speaking physicians practicing in Flanders. Exclusion criteria were not present in the study. Families were approached through Facebook via an open invitation to participate in a voluntary study. The invitation stated that we intended to recruit parents of children between the ages of 14 and 17, while the parents could not be employed in the medical field.

Participants received study information and provided informed consent. At the start they were informed of their option to withdraw from the study at any time. The interviews were conducted via Microsoft Teams and lasted approximately one hour for general practitioners, with an average duration of 35 minutes for families.

Interviews with general practitioners followed an interview template, designed on a literature review and refined through exploratory talks with three general practitioners covering a range of different concepts. Subsequently, seven general practitioners participated in three focus groups, with one individual interview due to scheduling limitations. Focus groups encouraged dynamic discussions, diverse perspectives, and deeper insights through interaction. The process followed the "Start-Stop-Continue-Adjust" principle, integrating feedback from previous discussions to refine and enhance the interviews. Based on these findings, a semi-structured interview protocol was developed and validated for the participating families. Twelve families were included in the interviews, comprising ten parents and twelve adolescents. Each adolescent was interviewed together with a parent. The questions encompassed a range of topics, with some specifically directed at either the parent or the adolescent and several case scenarios. As a concluding query, participants were asked to reflect on their experiences with current practices at the general practitioner's office and whether the interview process might influence their future interactions with medical personnel. After ten interviews data saturation seemed to be achieved as the two subsequent interviews failed to reveal any new elements. This indicated that the sample size was sufficient to capture the full range of perspectives pertinent to the study.

Each interview was audio-recorded and later transcribed anonymously. Participant names were replaced with randomly assigned numbers based on their interview role (e.g., parent, child, general practitioner). The Qualitative Analysis Guide of Leuven was employed as the analytical framework (12). The iterative coding process ensured that initial codes were generated from recurring concepts and patterns. Conceptual narratives were then developed to encapsulate the emerging themes and to interpret the underlying meanings within the participants' accounts. The coding framework was discussed and validated in successive reflective

FIGURE 1: Schematic overview of the triad, the actors, and the interactions.

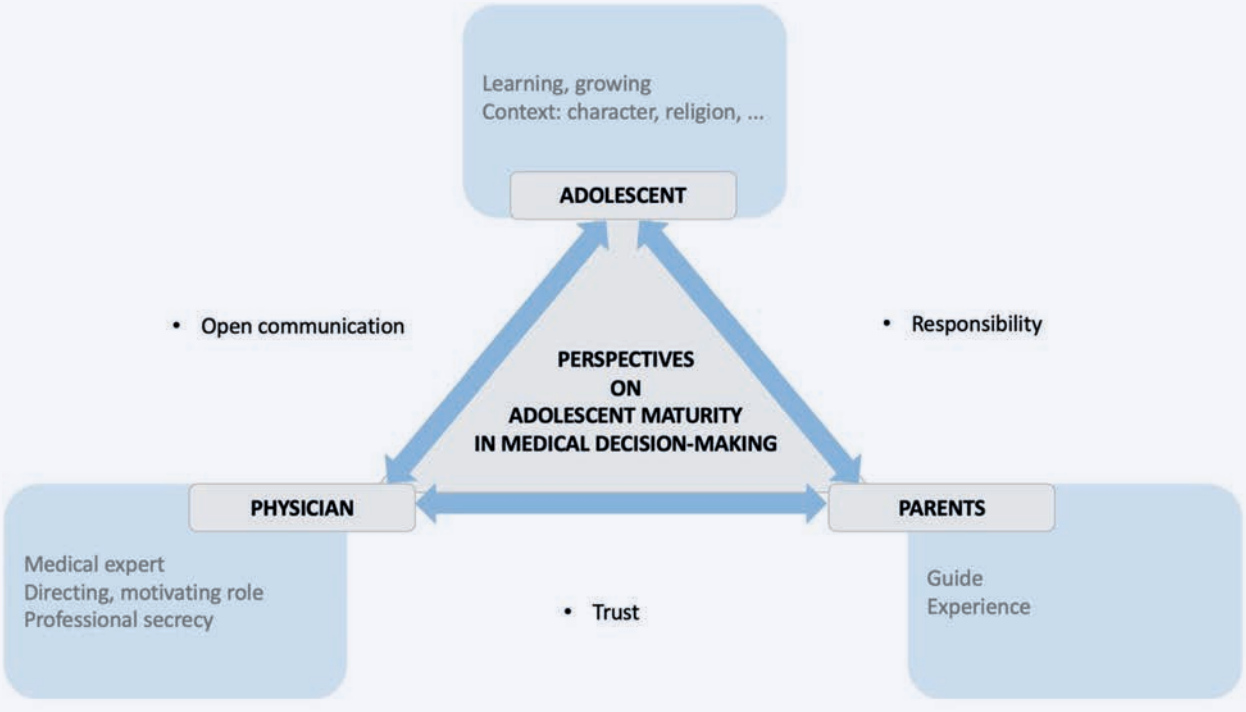

TABLE 1: Selection of quotes capturing the essence of various opinions.

RESULT, SECTION 1	Parent 2: I find that she approaches life very sensibly, wisely, and pragmatically. Since she was small, I have always let her answer questions like: what's your name, how old are you...? But when they ask about insurance, she also looks at me, and I can say, 'that's for us, X.' Those are the things I respond to.
	GP 1: When it comes to motivation, there can be two sides to it: sometimes it's actually good that parents are present when they are pulling in the same direction as a doctor (uh), and then it's sometimes good that they are there to convince the young people.
	GP 3: The logical versus the affective... And the art is then to turn it into a positive story, like "I am going to help you."... We are emotional beings. It is a very valid point that logic is usually 'not the way to go.'
	GP 4: Or I call and say, I'll schedule an appointment for them at the hospital or with a psychologist to make sure they go there and that it's not postponed indefinitely... And next time, I try to ask: "Have you called? Were you able to make that appointment?"
CHALLENGE 1	Child 5: Yes, I do find that important. Because I didn't know that at all, and it's crucial to know that not everything is automatically shared with my parents when you ask.
	Parent 10: I do think it's important, "child 12", that if that happens, I would feel comfortable if you asked us to step outside because you want to say something personal to the doctor, and you can express yourself at that moment. We don't necessarily have to be there. The most important thing is that you get help at that moment.
	GP 1: I think it's crucial that the young person trusts their general practitioner and knows that what I come here to discuss remains confidential: If I want it not to reach my parents' ears, then it stays confidential, because otherwise, you'll never see them at your door again.
	GP 1: I think the advice from the medical board is that young people from the age of 14 can assess whether parents should be informed or not. If you don't respect that, well, then the therapeutic relationship with your patient has exploded from the start.
	GP 8: No. You have to point it out in advance. Because they assume that it's an open book where everything is discussed during coffee.
CHALLENGE 2	Child 8: Yes, I find that important. That a doctor involves me in the conversation. And doesn't talk over my head with my parents. The doctor should address you directly, so you don't feel unnecessary.
	Child 8: I don't think many peers worry about this. They just go with the flow and ask the doctor if they don't want something to be said.
	GP 2: Young patients with a chronic condition are generally a bit more mature than those who haven't experienced much.
	Parent 1: They also visit the doctor so infrequently; they are simply not aware of it yet. I do think we need to educate them better about it. When I see their peers, especially those with mental health issues, they need much more guidance and autonomy. But here, it's just a common cold or an injury.
	Child 11: I would be more afraid to ask to speak to the doctor alone.
	Parent 7: I do find that important. Because I mean, in a few years, in three years, he'll be of age, then he has to do it on his own. So, he should already practice and do it now, under guidance. I think it's important to instill that in your upbringing. That a treatment needs to be followed up, and you shouldn't wait too long to go to the doctor and so on.
	GP 10: Naming that we do hear them and that they really do have something to say. I think we already do that, but do we always do it equally well and consciously? That's what these things are always good for, to reflect more on such matters.
	Child 12: Doctor Tom, for example, always talks to mom, and then she [mom] looks at me and says: what do you think? ... and then mom says: it's for you, so be sure to listen.
	Parent 1: What was crucial for "child 1": the doctor who treated him became a real role model for him. He plays hockey himself, has had knee problems himself. And then they talked about hockey, about knees, about selection...
	Parent 7: Would it make a difference for you if the doctor indicates that he also wants your opinion? Child 9: Yes, because if he doesn't say that, then I wouldn't think of doing it myself.
	GP 8: You could also work proactively, for example, by already displaying in your waiting room or on your website that it's perfectly possible for young adults to come for consultation alone.
	GP 10: Actually, it's important to make children aware of medical confidentiality as well. I say that in the context of when there is already a problem. But maybe we should tell them at a time when there is no problem yet.
	Parent 10: I think a patient should know that they can always turn to a doctor. That you can trust them. That young people know that. That could be a topic of discussion in education. If they are already getting a life perspective, throw that in there too... So it's crucial that this sentence is spoken. Especially for people who are less outspoken. And for young people who already have 2 glass ceilings to break through. I think it would help if that is consciously included at the beginning of a conversation.

CHALLENGE 3	Parent 7: I'll send "child 9" to the doctor alone sometime... Yes, when they are small, you automatically make decisions for them. But as they grow older, begin to understand their bodies better, you have the pitfalls of taking over because you're used to it, and the doctor tells you what to do. But making it explicit would be better for all parties.
	Parent 5: I think the doctor is better positioned to guide that. The parent won't have the reflex to go sit in the waiting room themselves.
	GP 8: But you can't make a patient or a parent run faster than they can. What I mean is: if those parents are convinced that the weight loss is due to exercising, then the question is: are they deluding themselves, or are they not aware that they are deluding themselves?
	GP 4: In cases of eating disorders, those are difficult consultations because the girl doesn't want to see the problem, and the mother wants us to solve it every time... Often, it's also a conflict with the mother, right. You can hardly say that when she is sitting there.
	GP 8: Yes, every family also has its own dynamics. And you have to try to read that dynamic a bit... And actually, to see past that somewhat dominating relationship between parent and child. But certainly, also to question it. To find out from those parents what the perspectives of mom and dad are. And what has happened in the past... We should certainly not limit ourselves as general practitioners only to somatic complaints and somatic treatments.
	Parent 8: And I was there just for show. Actually, I was happy about that; as he himself was the one who was worried.
	GP 9: On the other hand, I think in follow-up, especially for mental health issues, it's also important, if the child trusts or wants it, to try to involve the parents as well. If they don't want that, it's difficult to do. But otherwise, there is also a tendency to lose track of your patient somewhere.
	Child 10: From school, you have to call your parents, and then our mom would certainly say, "I'll come over, and then we'll go to the doctor together." Because I find that not yet suitable for me to do alone. Not that I can't do it, but I don't feel so great about doing it alone yet. It's still nice to have someone with you who is informed.
	Child 6: I'd prefer it in the waiting room. But it would be better if the doctor suggests it themselves... I would like the general practitioner to do that for me if he realizes that I want to discuss something separately. Because I don't think everyone dares to say that, especially when the parent is present.
	Parent 1: That seems nice to me, for both me and the children and the doctor because you can establish a connection at that moment and delve deeper. I think it can be nice for the child to speak freely but still be comfortable knowing that it will be discussed with us afterward. That the child doesn't have to bear the responsibility of decisions yet.
	GP 3: ...the dominant role of the doctor is important and expected...
CHALLENGE 4	GP 8: Perceptions and patterns of illness can be hereditary, but they are also transferable in a social context. For example, a child born to non-working parents is very likely not to work. Similarly, if parents consult for the slightest ailment, their children, when they have children of their own, are likely to consult for minor ailments as well. This is a form of health education. ...What I also regret in the entire field of general practice is the reduction of home visits. I know that home visits are very time- consuming. But a home visit is something very special. You actually enter somewhere as an outsider. You come in through the back, through the kitchen to the living room. That creates an image of the general course of affairs within that family.
	Parent 10: Usually, I call the general practitioner afterward. If I have any questions, I can just call I think that's also because the general practitioner knows us well and knows how things work here.
	GP 4: Not just alone, but I have little say in that. Patients book appointments online.
	GP 8: I have a younger colleague, and I have the habit of framing most patients, placing them in a larger context. And I always try to say: just because I say it, doesn't mean it's true. You should always rely on your own intuition.
	GP 5: In our group practice, we have determined that 16-year-olds may potentially come in alone, and all colleagues follow this practice. If younger children come, we still see them, but we say, next time your parents should definitely be present.
	GP 9: Yes, I think it's indeed difficult to assess that, so that's why I would quickly try to save some time or maybe discuss it with my supervisor, to see if they know something about that background.

meetings, ensuring inter-coder consistency and interpretative rigor. The final narrative underwent evaluation by a methodological expert before being used to draft the final written text.

Results

In our study, 10 physicians, 10 parents, and 12 adolescents participated from February to August 2023. Notably, 92% of the parents taking part were mothers. Among families and general practitioners, one-third lived in urban areas and half worked in city practices, respectively. Additionally, 70% of doctors worked in group practices, and 33% of children had a medical history, with 2 experiencing frequent illness. All participants were representative of the mainstream population of Flanders. All participants were native to the country, with no reported migration backgrounds, and they identified with the predominant cultural and religious norms typical of the national context.

The analysis of the interviews shows that the current healthcare system generally operates efficiently. Trust, responsibility, and

open communication are fundamental pillars in this context. These elements collectively lay the foundation for establishing a balance among the three key stakeholders, thereby fostering an environment in which the adolescent can develop their maturity and assume their own role in the care process. When considering the legislation in the Netherlands, which employs an age limit as a criterion, it becomes apparent that there is limited enthusiasm for this approach. Both general practitioners and adolescents express the view that actively involving a parent, even from the age of 16, does not impede the autonomy of the adolescent; instead, it can be of significant added value. This perspective holds true not only at a practical level but also in terms of building trust. The personalized approach and motivational support that parents provide clearly work in favour of the physician, as was also evident in the interviews. Dealing with the adolescent brain or behaviour is a conscious effort for many. This involves a strong emphasis on actively building trust and motivating the adolescent, achieved through logical and affective approaches, a preference for outcome-oriented work, the reduction of intervention duration, and an active follow-up. During the research, several bottlenecks were identified that complicate daily practice (depicted in figure 1).

Challenge 1: Poor knowledge of the legal framework

From the discussions and active exploration of knowledge of the Patient Rights Act, a lack of awareness in all parties about this regulation emerged, which manifested as uncertainty and making assumptions. Particularly, an adolescent with doubts about medical confidentiality may not be inclined to seek medical care. Furthermore, when doctors and parents hold different expectations regarding these rights, inadequate communication may foster future frustrations and uncertainties. During a medical consultation, transparency regarding the applicable laws can be the solution. It is important that doctors explicitly address the legislation to which they adhere for both parents and adolescents. Physicians also hope to be endorsed by the Order of Physicians when needed. Parents may appreciate a physician choosing to speak to the adolescent separately, as long as the reasoning behind the choice and acknowledgment of the ongoing role of the parent are provided. If desired, and with the adolescent's consent, relevant information can be shared with the parent to ensure the continuity of care. Several physicians and families supported a deliberate discussion of this issue, both within the family and in consultation with the general practitioner.

TABLE 2: Interview script: focus discussion with general practitioners.

STOP	• What habits or actions do we repeatedly engage in that aren't effective? • What should we stop doing?
START	• What are we currently not doing but should be? • What would be the most valuable action to begin with?
CONTINUE	• What is working well? • What should we continue doing?
ADJUST	• What should we keep doing but in a different way? • What adjustments would be most beneficial?

Challenge 2: Passive role of the adolescent

Most adolescents did not feel actively involved in medical matters, especially if they are not chronically ill and do not have frequent interactions with a general practitioner. In the presence of a parent, they tend to take on a more passive role, potentially losing awareness of the relevance of their own opinions, and the opportunity for engagement remains underutilized. This primarily widens the gap between the general practitioner and the adolescent, resulting in hesitancy to discuss matters with the physician. This barrier hinders progress toward adulthood and can even impede the transition to independence when reaching the age of 18. The successful approach, as repeatedly emphasized by the participants, involves an active strategy where the adolescent is directly addressed and engaged. Effective involvement of the adolescent includes personal addressing and finding common ground. Even small gestures, such as a thoughtful opening addressed to the adolescents, contribute to the value placed on their opinions, which can significantly enhance the treatment process. Physicians and parents observed that there should be proactive consideration of this involvement, even in the absence of an immediate need. Waiting for problems to arise before involving the adolescent is not optimal. Initiating dialogue with the adolescent while considering potential future challenges can facilitate their personal development and create opportunities.

Challenge 3: Parenting Style

A potential problem for parents is their prominent presence during consultations, where parents often default to their automatic reflexes. Parents consider it unnatural to release their child, when this is coupled with the potential difficulty for the adolescent to request a private conversation with the doctor it can result in the continued hierarchic position of the parent. In certain situations, it can have a negative impact on the disease process, such as in the case of an eating disorder where a parent plays a causal role. As some participants emphasize, each family has its own dynamics, and it is essential to consider and address the hierarchic relationship between parent and child separately. This allows the general practitioner to assess the situation and identify the interests of each involved party. However, it is important to not rush the separation, as adolescents also emphasize the value of the presence of a parent, ranging from practical assistance to moral support. The key is to find a balance between being present and giving space in parenting, especially in the follow-up of care or mental health issues. As mentioned previously, not every adolescent will explicitly indicate the desire for time alone with the physician. Here, the value of the physician's guiding role following a critical analysis is evident. Many parents and adolescents expect this role, provided there is good communication and a recognition of the parent's role.

Challenge 4: Loss of a broader perspective on the family

General practitioners often consider it a significant advantage to know the entire family, witness the adolescent's growth, and take the necessary time to understand the adolescent and the context. However, this broad view of the entire family can be at risk due to the emergence of group practices, increasing waiting times, reduced home visits, and the overall complexity of care in urban areas. In many group practices, efforts are made to address this

TABLE 3: Interview script: semi-structured interviews with families.

Basic information	*Directed to the child:* How old are you? How many siblings do you have? Are you the youngest, middle, or oldest child? Where do you live? *Directed to the parent*: Do you work in healthcare?
General autonomy of the adolescent	*Directed to child and parent*: At what age does an adolescent take full responsibility for their schoolwork? At what age are you allowed to choose your own hobbies and extracurricular activities? At what age is an adolescent allowed to attend certain activities independently, such as school or after-school programs? Do you agree on what time the child should be home after school, extracurricular activities, or going out? How are these agreements made between adolescents and parents? At what age is an adolescent allowed to go on vacation without their parents? At what age does a child start managing their own budget? *Directed to the child*: Do you have a student job? If so, at what age did you start?
Medical behavior of adolescent and parent/ guardian	*Directed to child and parent*: How frequent is the adolescent ill? How regularly do you visit a family doctor? Do you go to same GP? Does conflict arise about medical decisions, such as whether to visit the GP alone or not? *Directed to the child*: Are you currently receiving treatment for anything? If so, did you have a say in choosing that treatment? Who made the final decision? As an adolescent, how comfortable do you feel discussing your health with your parents? D*irected to the parent*: As parents, how comfortable do you feel discussing your health with the adolescent?
Medical autonomy	*Directed to the child*: Scenario 1: You come back home from school, your parents are at work and you feel very ill (heavy cough, fever). A. You call the doctor yourself and try to make an appointment. B. You call your parent asking to contact the doctor. You go to the doctor yourself. C. You call your parent for advice. You go to the doctor together. D. You wait until your parents are home to have them call the doctor. Scenario 2: You come back home from school, your parents are traveling and you feel very ill. You are staying with friends/ family A. You call the doctor yourself and try to make an appointment. B. You ask your parents/family to contact the doctor. You go to the doctor yourself. C. You ask your family for advice. You go to the doctor together. D. You wait until your parents are home to have them call the doctor Scenario 3: You are currently at the doctor's office with your parent. You have a medical question and would rather get advice from a doctor before talking to your parents. What do you do? A. You ask the question anyway, in front of your parent/guardian. B. You don't ask the question, because your parent/guardian is present. C. You don't ask the doctor if the conversation can continue without your parent/guardian present, because you are afraid the doctor will say something to your parent/guardian. D. You ask the doctor if the conversation can continue without your parent/guardian present. Scenario 4: You have a sports accident and a treatment plan is drawn up at the doctor's office in consultation with your parents. However, you disagree. What do you do? A. You remain silent during the consultation and follow the treatment plan. B. You remain silent during the consultation, but do not follow the treatment plan C. You remain silent during the consultation, but you tell your parents at home that you disagree D. You show during the consultation that you disagree, choose a plan that is more convenient for you together with parent/doctor, and follow this treatment plan
Knowledge of medical laws	*Directed to the child, the parent may step in if the child is in doub*t: Are you aware of the medical laws? How important is it to you that these laws exist? How consciously do you deal with them? *Directed to the paren*t: As a parent, how do you view the level of autonomy your child assumes/how they handle it? What role do you think parents should have in making medical decisions? How do you deal with this? In what ways do you try to get the adolescent to take on that role (how do you involve him)? Are there any specific challenges or concerns you experience as a parent in balancing that medical autonomy with your parental involvement? *Directed to child and paren*t: Do you feel that the adolescent is involved by the health care provider, for example, the doctor or nurse? What role should the caregiver take in the child's care?
Conclusion	After this conversation, do you notice a difference between child autonomy at the general level and at the medical level? If that's the case, what do you think causes this? Why does it happen? Will you handle autonomy or participation differently after this conversation?

challenge through briefings in which the family situation is outlined. One practice even emphasized the preference to have adolescents under 16 years old attend their first appointment with a parent. A thorough knowledge of the broader family context by the physician sheds light on the situation and prevents uncertainties.

Discussion

This study explored the perceptions of adolescents, parents, and physicians regarding the current legal framework of medical decision making and the representation of minors (specifically adolescents). Key themes such as trust, responsibility, and open communication (previously identified in studies by Donck et al, 2023 and Song et al, 2019), also emerged in this research (11, 13). However, we provide a more in-depth analysis of these topics by interviewing all involved parties. Overall, the results indicate that the current system adequately addresses the needs and capacities of adolescents. Physicians demonstrate an understanding of adolescent cognitive, emotional, and social maturation, aligning with prior research (3). Nevertheless, potential challenges within daily clinical practice were identified. This research reveals a lack of knowledge about regulations and doubts about their application, consistent with previous studies (14, 15). There is consensus on the importance of confidentiality for adolescents as it contributes to their sense of security (13). While the advantages of confidentiality with healthcare providers are evident, there is disagreement and therefore uncertainty regarding the sharing of information with parents (8, 16, 17). Particularly given the lack of knowledge among adolescents and parents about the rules or uncertainty about the parent's expectations (18, 19).

Adolescents should not only feel safe but also heard during a consultation. A recurring theme is that adolescents sometimes feel inhibited to speak or address certain topics, despite the fundamental trust in their doctor (20, 21). While previous research is scarce, our study indicates that actively acknowledging or questioning this hesitancy can be an effective strategy. Furthermore, some parents emphasized the importance of a positive role model, as previously investigated by Miller et al. Adolescents find this role model in a parent, sibling, or even in their doctor. Identifying common ground and thus motivating the adolescent can certainly contribute to better communication (22). In this context, the importance of proactive care is stressed. It makes little sense to wait until problems arise when adolescents can learn early on to discuss concerns with a doctor and feel that their perspective is valued (13). Promoting this awareness and creating an environment that encourages open communication contributes to a healthy relationship between the adolescent and the doctor.

Another variable in an adolescent's life is the presence of a parent and their parenting style. Research indicates that a parent's caregiving has positive effects on a child's mental health (17, 23). Detaching a child from a parent too early is rarely the best way forward and consensus on the age at which an adolescent can be seen alone lies between 16-18 years (13). The complexity of parent-child dynamics is also present in healthcare settings. Our interviews reinforced this complexity: while children generally felt more at ease for the online interviews in the presence of their parents, they could also be more reserved in answering certain questions, though this probably varies with individual personalities. The advantage of joint interviews was that we could observe the parent-child dynamic directly and observed a deeper reflection on the part of the participants due to their interpersonal exchanges... However, the boundary between parental caregiving and controlling is not always clear and can have adverse effects (24, 25). Within our existing legal framework, there exists a grey area where empathetic engagement from the part of the physician can assist in determining the most suitable approach for each unique situation.

To better understand this dynamic, considering the broader family context and the child's situation can be a contributing element. While general practitioners feel strongly about this, it could become a skill they risk losing due to the decline in home visits and the expansion of group practices, where family members are occasionally seen by other doctors (26). As one of the participants put it: "Illness experiences and disease patterns are heritably transferable but are also transferable in a social context." The home environment and parental medical behaviour significantly impact the adolescent's well-being and should not be overlooked (27, 28).

This study has several limitations. Firstly, the sample size is relatively small as is often the case in qualitative research, which could restrict diversity in responses or experiences, which can limit the richness of the data. We maintained group sizes consistent with adequate sampling, involving 10 general practitioners, 12 children, and 10 parents (29). Additionally, there is potential for selection bias, as only one father participated and 70% of the general practitioners worked in group practices. The parents and general practitioners who agreed to participate may have had different perspectives than those who declined. Furthermore, the use of case-based surveys presents some limitations, such as the subjective interpretation of the case by the participant and the limited generalizability of the research results to other situations or cases. Yet, quantitative research provides participants with the opportunity to critically reflect on the case without direct influence from the researcher (30). Finally, important to note is that we did not actively account for variables such as educational levels, religious beliefs, and cultural differences. For future studies, addressing these limitations will be crucial and provide opportunities for further research. Aspects such as culture and socioeconomic status deserve more attention to achieve a more accurate reflection of our diverse society.

To conclude, a brief self-reflection: The same person conducted all the interviews and prepared the transcripts. This ensured consistency in data collection and allowed for the comparison of non-verbal cues and contextual factors. However, it also implied a risk of subjectivity and bias due to the researcher's personal expectations, a potential decline in quality due to the high workload of transcriptions and interviews, and limited variation in questioning and follow-up prompts.

Conclusion

We chose a qualitative research approach to deeply explore adolescents attending medical appointments alone or with their parents, as well as general practitioners' decisions regarding parental presence. While enriching, previous studies extensively cover this topic. Focusing on specific areas of improvement enhances the relevance of our research, highlighting the complexity of interactions among physicians, parents, and adolescents. A deliberate approach, clear communication, and active involvement of all parties are crucial for maintaining a balanced healthcare system. This prompts further investigation into potential solutions: Can promoting communication increase knowledge about laws? Does actively encouraging and expecting adolescent involvement improve their understanding of their role in medical contexts? Can physicians, through empathy, discern between caregiving and controlling parental roles? Can discussing the entire context enhance the quality of care for adolescents?

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

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Meer weten?

Evaluating the Real-World Applicability of Healthcare Transition. A Qualitative Study Across Disciplines

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Keywords
Transition ; cross-discipline ; adolescents ; young adults.

Abstract

Purpose
Increasing prevalence and improved survival of children with a chronic disease necessitate effective transition programs for adolescents transferring to adult care services. Despite established benefits, real-world implementation of these programs varies across medical disciplines. This study aimed to elucidate the multifactorial nature of transition implementation and the underlying variations across disciplines from the perspectives of healthcare providers.

Methods
We conducted a qualitative Grounded Theory study using the Gioia method to explore real-world applicability factors of transition by in-depth interviews. Pediatricians and adult care physicians (N=18), representing diverse medical disciplines (i.e., cardiology, pneumology, gastro-enterology and hepatology, nephrology and rheumatology, oncology and hematology, neurology, endocrinology, and urology) were recruited using a theoretical sampling strategy.

Results
We identified a wide range of challenges of implementation, with variation across medical disciplines, resulting in four theoretical domains influencing the applicability of transition programs: healthcare service characteristics, personal factors, adjustability, and continuity. A cross-discipline key barrier for a comprehensive transition program was the absence of a coordinating treating physician for patients with complex health needs.

Conclusion
Current generic guidelines and programs for transition are not as applicable as they are presented. Variations in implementation are fundamentally rooted in basic healthcare principles and differ significantly across medical disciplines. The differences in characteristics of the patient population, medical departments, and the complexity of the care patients require are substantial barriers difficult to overcome. Feasibility and effectiveness-implementation hybrid design studies should be performed.

Implications
To improve transition, strategies should primarily focus on enhancing the domains of healthcare continuity.

Introduction

Improvements in screening, diagnosis, and treatment are leading to more children with chronic diseases transferring to adult care services each year, a trend observed across all medical disciplines (1, 2). Patients at transfer age (defined between 16-25 years) face distinct age-specific, clinical, and psychosocial challenges. To address these evolving needs effectively, structured and personalized transition programs are recommended (3–8). Transition is defined as the gradual and planned process by which patients are prepared to take charge of their medical management when transferring from pediatric to adult services. Transfer is a part of the transition process whereby the patient is being treated by the new adult-oriented team (9). Numerous programs have

been developed and have demonstrated their benefits, particularly in addressing psychosocial needs (4,5,10,11).

Adolescents and young adults with chronic diseases share some similar needs across medical disciplines, leading to common elements in transition programs (9,12–14) and the development of generic guidelines and models (6,9,12,13,15,16). Key components often include assessment of transfer readiness, patient education, and interdisciplinary planning of a transition trajectory (13). However, the real-world applications of such programs and guidelines vary strongly across medical disciplines, even within a single healthcare setting (15,17,18).

This discrepancy reflects a multifactorial interplay that hinder the prioritization of transitional care and requires more empirical data concerning generalizability of these guidelines. Hence, the objective of this study was to elucidate the multifactorial nature of transition implementation and the underlying variations affecting it. By examining the perceptions of healthcare providers across disciplines, we hope to gain insights into how transition programs could be adapted and tailored for better adoption and effectiveness. Unlike studies that compare contrasting pediatric and adult care perspectives, our research integrates perspectives from both departments, offering a discipline-specific view on transition.

Methods

Research design

A qualitative Grounded Theory approach was chosen, given the paradox of the extensive literature on transition and the poor real-life application of guidelines, prompting the question: why do many physicians discuss transition yet only a few actively integrate it into their practices? We contend that the inductive nature of Grounded Theory research is ideally suited to examine this paradox. Grounded Theory is an inductive research approach that develops theories from systematically analyzed qualitative data (19).

We applied the Gioia method, which focuses on developing new concepts in areas lacking a consensus theory by providing a structured coding framework to enhance transparency and rigor in theory development (20). Recognizing that existing recommendations are often grounded in poor-quality data, the Gioia method views organizational phenomena as shaped by individuals with real-life expertise and experience, capable of sharing their thoughts and actions (13, 20).

We conducted semi-structured interviews with physicians, maintaining a close connection to their experiences during data interpretation. Our qualitative process adhered to the Consolidated Criteria for Reporting Qualitative Research (COREQ) (21).

Setting and participants

Physicians were recruited at Ghent University Hospital between December 2022 and October 2023. To be eligible, they had to be involved in patient care within pediatric or adult departments, including gastroenterology and hepatology, cardiology, pneumology, endocrinology, hematology-oncology, rheumatology, nephrology, neurology and metabolic disorders, and urology. Notably, experience or expertise in caring for adolescents or young adults was not a prerequisite, allowing diversity in perspectives on transition.

Recruitment

We employed a theoretical sampling strategy, allowing us to adapt as our theoretical framework evolved and we achieved theoretical saturation. Diversity in experiences, expertise, and opinions on transition among participants was taken into account (22). This approach allowed us to identify key patterns and core experiences crucial for the development of our theory (22). To identify potential participants, we consulted department heads to discuss candidates. Subsequently, we contacted those to confirm their interest. Upon obtaining written informed consent, interviews were scheduled, which took place at our hospital or via video-call. Additionally, we ensured within each medical discipline participation from both pediatric and adult healthcare physicians.

Data collection

Three researchers, trained in qualitative research, conducted the interviews using an interview guide and follow-up questions. The guide addressed the following topics chronologically: [1] physician's experience with transition and the current practices within their discipline; [2] perceived positive and negative aspects of current practices; [3] the desired situation of practices; [4] the current (discipline-specific) barriers and facilitators; and [5] the application and applicability of existing guidelines (13). The interviewers concluded with a summarized statement, offering an opportunity to correct or add information. The interview guide was developed by experts in qualitative research and transition, and was piloted. Co-authors not involved in the initial data collection or prior analyses reviewed the interview guide to ensure it covered the full scope of relevant themes, was free from bias, and contributed to the validity and reliability of the tool. Throughout the iterative process of data collection and analysis, adjustments could be made to explore specific areas more in depth; small modifications were deemed necessary. All interviews were audio-recorded and transcribed verbatim manually. Translation followed after coding.

Data analysis

Two authors, a policy advisor on transition and a pediatrician in training, both trained in qualitative research, independently analyzed the data through several steps: line-by-line in vivo coding; comparison of codes and grouping into first-order concepts; axial coding and grouping concepts into second-order themes, with code revision, refining, and rephrasing every 4 interviews; and theoretical coding involving multiple discussions to identify underlying categories at a higher abstraction.

All participants had experience with transitional care, so data-analysis did not make a distinction in between groups.

TABLE 1: Participant characteristics

Number of participants (n)	**18**
Mean age (years; range)	48,5 years (33-58)
Sex	Male: 11, Female: 7
Pediatricians / adult care physicians (n)	9 /9
Number of participants per discipline (n):	
Cardiology	3
Pneumology	2
Gastro-enterology and Hepatology	2
Nephrology and Rheumatology	2
Oncology and Hematology	3
Neurology	2
Endocrinology	2
Urology	2
Number of disciplines with a formal, implemented, and standardized transition program	2

TABLE 2a: Code Tree | Aggregate dimension 1: **Healthcare service characteristics**

Third order themes	Second order themes	First order concepts
Characteristics of pediatric vs. adult care	Vertical organization of adult care	Difficult transition due to sub-specialization of physicians (1)
	Differences in medical care	Differences in medical care need effective communication (2)
		Policy disparities between pediatric and adult services (3)
		Managing significant policy differences requires careful and gradual consideration (4)
		Different treatment options in adult services (5)
	Differences between regional and tertiary care settings	Pediatrician's preference for a holistic approach in regional hospitals (6)
	Practical organization challenges between departments	Reduced accessibility of adults services (7)
		Varied organization and patient flow at adult outpatient clinics (8)
Guidelines	Absence of local pathways or guidelines	Absence of age thresholds hinders effective transfer (9)
		Lack of a well-defined transition approach (10)
		Challenges arise due to vague age limits for transition agreements (11)
	Presence of local pathways or guidelines	Implementation of guidelines or care pathways support the execution of transition plans (12)
	Presence of non-implementable guidelines	Challenges in applying an existing transition vision locally (13)
		Theoretical frameworks from other contexts are not applicable (14)
Organizational challenges due to schedules	Efficiency	Challenges in efficiently scheduling joint consultations (15)
		Inefficiencies observed during multidisciplinary staff meetings (16)
	Compatibility of schedules	Challenges in scheduling multidisciplinary meetings (17)
		Late communication about a transfer impacts overall scheduling (18)
		Compatibility of schedules for joint consultations (19)
		Flexibility is needed for successful scheduling of joint consultations (20)
		Challenges related to schedule meetings or consultations in regional hospitals (21)
	Administrative support	Identified lack of administrative support for scheduling consultations and meetings (22)
		Administrative support is a facilitator for scheduling (23)
Organizational challenges due to location	Physical distance between pediatric and adult healthcare services	Facilitation of transition through the presence of shared physical locations (24)
		Absence of a fixed location for joint consultations acting as a barrier (25)
		Physical separation as a barrier to effective transition (26)
Personnel power and support	Institutional support	The necessity for hospital-wide support to assist staff (27)
		Coordination requirements between various care pathways, especially in transition scenarios (28)
		Importance of having a central point of contact for planning transition in complex cases (29)
	Specific support in adult services	Importance of a nurse specialist in facilitating transition (30)
		Need for nursing support to prevent drop-out during and after transition (31)
		Limitations in psychosocial support within adult services (32)
	Specific support in pediatric services	Earlier start of transition due to the presence of a nurse (33)
		Association between absence of standardized practices and personnel shortage in pediatric services (34)
		Limited preparation of transition due to time constraints (35)
	Support tailored to the specific needs of both pediatric and adult services	A too limited number of patients to consistently schedule joint consultations (36)
		Recognition of the importance of existing nursing support in facilitating transition (37)
		Need for a coordinating person during transition (38)
		More physicians (personnel power) has a positive impact on the execution of transition (39)
		Absence of paramedical personnel due to the remuneration issues (40)
		Recognition of a total absence of support or framework (41)
		Absence of paramedical personnel specifically for certain patient populations (42)
		Acknowledgement of the positive impact of structured reimbursement on ensuring a smooth transition process (43)
Financial remuneration and funding	Limited remuneration for performance	Absence of remuneration of multidisciplinary meetings (44)
		Absence of remuneration of consultations with nurse specialists (45)
	Other financing options for pediatric vs. adult services	Variations in funding availability for paramedical services in pediatric and adult healthcare (46)

2 of the researchers who conducted the interviews did not participate in this analysis, since the data obtained additionally was used for a separate analysis which they conducted independently. Nvivo Pro 11 software was used. Data saturation, defined as the point where no new second-order themes emerged, was achieved after 13 interviews.

Ethical considerations

The study obtained approval from the ethics committee of Ghent University Hospital (registration number: B6702022000427), and all participants provided written informed consent.

Results

Participant characteristics

Eighteen physicians, split evenly between pediatricians and adult care physicians participated in our study (Table 1). The interviews had an average length of 37 minutes, ranging from 22 to 102 minutes. Six out of eight disciplines lacked a formal, standardized transition program or policy applied to a majority of their patient population. Given that transition encompasses more than coordinating transfer, most practices were deemed insufficient to qualify as transition programs.

Causes of variation in implementation

We identified four aggregate dimensions: [1] healthcare service characteristics, [2] personal and relational factors, [3] adjustability, and [4] continuity (Table 2 a,b,c,d).

1. Healthcare service characteristics

Physicians linked the variation in feasibility and features of transition programs to various healthcare service characteristics, encompassing disparities between pediatric and adult healthcare settings, the availability of local protocols, organizational challenges, staffing constraints, and remuneration models. These elements can either facilitate or hinder the implementation of transition programs.

Characteristics of pediatric versus adult care services

Healthcare structures, practices, and resources differ significantly between adult and pediatric settings. Particularly disciplines managing patients with cognitive disabilities or complex medical, social, and psychological needs perceived this difference as a major transition challenge.

A key observation is the silo-type organization in some adult departments, characterized by a greater number of highly specialized sub-disciplines than in pediatric care, hindering transfer. Physicians also pointed to disparities in medical care

TABLE 2b: Aggregate dimension 2: **Personal and relational factors**

Third order themes	Second order themes	First order concepts
Collaboration between pediatric and adult physicians	Transition practices arising from structure	Transition improves through mutual agreements (47)
		Recurring staff meetings between pediatric and adult healthcare providers (48)
		Collaboration growing from medical necessity (49)
	Transition practices evolve from personal relationships between healthcare providers	Pediatrician's trust and confidence in physicians from adult services (50)
		Improved collaboration among physicians (51)
		Presence of a constructive relationship between physicians (52)
Beliefs	Resistance to support joint consultations	Resistance to participate in joint consultations by pediatric healthcare providers (53)
		Resistance to participate in joint consultations by physicians on adult healthcare services (54)
		Resistance due to prolonged joint consultations (55)
	Awareness	Delayed initiation of transition due to a lack of awareness (56)
		Pediatrician's belief in self-sufficiency to care for patients, hindering transition (57)
		Departmental awareness among adult physicians (58)
		Recognition of the significance of psychosocial care (59)
		Joint awareness in both services (60)
	Enthusiasm to participate and contribute to transition	Initiative of the pediatrician plays a crucial role in scheduling joint consultations (61)
		The need for someone to take initiative for successful transitions (62)
		Imperative to establish a shared vision by pediatric and adult healthcare providers (63)
		Challenge for pediatricians in relinquishing control (64)
		Successful transition facilitated by the interest of adult physicians (65)
Knowledge and training	Knowledge specific to paramedics	Insufficient knowledge of paramedical staff for accurate cognitive assessments (66)
		Lack of disease-specific knowledge among paramedical staff (67)
	Medical knowledge	Gaps in knowledge about the scale of the patient population (68)
		Lack of knowledge among physicians (69)
		Insufficient knowledge in pathology among healthcare providers (70)
		Positive aspect of the presence of medical knowledge (71)
	Lack of holistic vision/knowledge	Adult physicians lacking a holistic perspective (72)
		Insufficient knowledge about age-specific needs (73)
	Barrier to knowledge building	Lack of transfer experiences hinders knowledge development in adult physicians (74)

TABLE 2c: Aggregate dimension 3: **Adjustability**

Third order themes	Second order themes	First order concepts
Differentiation between patient populations	Heterogeneity in the pathology of patient populations	Lack of standardization due to the diverse pathology within patient populations (75)
	Differentiation based on psychosocial needs	Certain patient groups exhibit lesser requirements for psychosocial support or transition (76)
	Differentiation based on the complexity of care	Insufficient time for discussing advanced care planning (77)
	Differentiation based on the complexity of care	Need for multidisciplinary discussions associated with complexity of care (78)
		Reduced necessity for briefing other physicians in straightforward pathology cases (79)
		Increased need for joint consultations in case of more complex pathologies (80)
		Enhanced collaboration between pediatric and adult services when dealing with intricate and complicated cases (81)
	Differentiation based on the cognitive abilities	Parents serve as co-patients in cases involving cognitive disabilities (82)
		Specific transition challenges for patients with cognitive disabilities (83)
Complex care	Challenges in organizing multidisciplinary care	The involvement of multiple disciplines requires a structured plan for effective care coordination (84)
		Multipathology introduces complexities in determining appropriate transfer timings (85)
		Different paces of transition between disciplines hinders coordinated transfer (86)
		Uncertainties regarding the assignment of responsibilities in complex care cases (87)
		A designated main physician to provide continuity and coordination in complex care transitions (88)
	Role of parents	Parents play an integral part in the care and transition of patients with complex medical conditions (89)

TABLE 2d: Aggregate dimension 4: **Continuity**

Third order themes	Second order themes	First order concepts
Continuity in care	Partner on the adult side	Patient stop in regional hospital (90)
		Complex psychosocial contexts hinder the transfer to regional hospitals (91)
		Challenges when transitioning to other community care institutions due to limited capacity (92)
		Lack of a healthcare providers with the necessary competences (93)
	Unanticipated transfer	Unexpected health issues may lead to unplanned transfers (94)
	Continuity of healthcare providers	Patients receive ongoing care from the same team (95)
		Simultaneous follow-up by both pediatric and adult care providers (96)
		Persistence of psychosocial support, even after the transfer (97)
	Intermediary or facilitator	The necessity for a person to accompany patients throughout the transition process (98)
Continuity in information	Standardized and integrated communication	Insufficient flow of information to the adult physicians during transfer (99)
		Briefings on patient transfer can be conducted on the go (100)
		Absence of feedback after transition (101)
		Improved information transfer during joint consultations (102)
	Challenging communication	Challenges in finding opportunities for briefings on sensitive psychosocial information (103)
		Absence of briefings to regional physicians hampers continuity of information (104)
		Inadequate communication between referring parties negatively impacts transition (105)
	Record/file	Absence of comprehensive psychosocial records (106)
		Incomplete medical record hinders transfer of information (107)
		Complete medical record contribute to successful transitions (108)

and infrastructure between adult and pediatric settings, ranging from available treatment options to different healthcare policies, as negatively impacting transition. One physician remarked, "*We don't have the infrastructure and time to perform bone marrow aspirations under anesthesia (…) As a result, these procedures need to be conform to our standards.*"

Guidelines

Complex and unrealistic guidelines hindered establishing a protocol in practice, "*We've had a protocol on paper for the past few years that is theoretically sound, but its real-world application has been hindered by the complexity to involve and engage a large number of stakeholders.*". For disciplines without a formal protocol, the transition process often became an arbitrary event.

Despite recognizing the importance of transition, many physicians expressed concerns about the feasibility of applying currently existing theoretical models in daily practice.

Personnel power and support

According to some, a key to successful transition is placing the right staff at essential positions. The availability of hospital-wide support that extends beyond specific disciplines and ensures the coordination of transition programs is perceived to be crucial for multidisciplinary transitions. Additionally, the perceived need for psychosocial support and adequate staffing was emphasized by physicians, though it varied across different disciplines. "*Having a hospital-wide framework in place, especially for resources like social workers, would streamline the process. Relying on each single discipline for funding could not be feasible due to limited patient numbers in some specialties.*"

Various adult care physicians reported challenges in maintaining staff engagement post-transfer due to time constraints. The impact of this challenge was reported to be greatly dependend on the availability of lump sum financing in their discipline, enhancing continuity of multidisciplinary care and transition support. Disciplines with a larger share of patients eligible for this financing, seemed better equipped for transition. A physician reported, *"In our discipline, transition is particularly effective for certain patient groups, specifically those covered under lump sum financing"*. This financing model also addresses the remuneration gap for nursing and multidisciplinary consultations, particularly affecting disciplines with staffing shortages. It was unclear whether this coverage was also used to support transition for patient groups from the same discipline but not covered by the lump sum financing.

2. Personal and relational factors

Collaboration between pediatric and adult physicians

Collaborations between pediatric and adult care physicians were perceived to be crucial for the development and implementation of transition programs. Regular meetings were reported as facilitating, transforming medical necessity into organizational protocols. Moreover, mutual respect and trust was considered to significantly impact transition effectiveness. In the interviews, strong collaborative and interpersonal relationships among physicians were often associated with smoother transitions. *"Engaging in the transition consultations with the pediatrician was a straightforward decision, given our existing collaboration in research, which paved the way for a seamless transition*".

Beliefs

The interviews made it apparent that developing a transition program requires committed individuals. Notably, none of the participants were opposed to transition. However, there appeared to be substantial differences in perspectives about the scope of transition and who should coordinate it.

Three main subthemes emerged as key factors in shaping perspectives on transition:

- Awareness, comprising the initiation and perceived need for transition in physicians. A pediatrician noted, "*I believe that it (referring to lacking a transition program) is, to some extent, an issue of mindset. We feel like 'we can manage this on our own'.*"
- Eagerness to engage and support the transition process, comprising the need for dedicated individuals. *"It's clear that both groups value transition (referring to pediatricians and adult care physicians). Moreover, it was striking that during a workshop on transition, adult care physicians outnumbered pediatricians, indicating adult care physicians are indeed willing to participate."* (pediatrician).
- Resistance to joint consultations, for multiple reasons as noted in Table 2. *"I find it is a waste of time. I wouldn't opt for a joint consultation. It just doesn't fit with the way I need to structure my day."* (Adult care physician).

Knowledge and training

While many pediatricians and adult care physicians did not consider lack of expertise an issue, certain pediatric specialties, particularly those treating metabolic conditions, struggled with transfer due to a lack of knowledgeable healthcare providers, this being enhanced by transfer delays and therefore the impossibility to gain knowledge. Moreover, the absence of data on patient groups, like their size, limited adult care physicians' ability to evaluate the need and feasibility of establishing a transition program.

"If a substantial number of patients or significant potential is identified, organizing transfer consultations could be feasible. (…) However, the actual number of patients over 16 years in pediatric care remains unclear but is likely higher than we assume."

3. Adjustability

Differentiation between patient populations

Physicians noted that while routine conditions might not require extensive transition protocols, rare or complex conditions demand a more in-depth collaboration and a patient-tailored approach, especially for patients with severe intellectual disabilities. A pediatrician stated, *"Compared to other disciplines, we care for a significant number of patients with intellectual disabilities. For these individuals, standard transition protocols do not suffice due to the distinct needs and abilities of these patients.".*

Complex care

The prevalence of patients with complex care needs seemed to vary between disciplines, with those treating more complex conditions facing greater transition challenges. An adult care physician noted, *"In complex cases, the question arises: to whom should the patient be transferred? Which condition is considered primary, and which physician should take the lead in coordination?"*.

4. Continuity

Despite the emphasis on transition, participants consistently highlighted the actual transfer as a significant challenge, impacting both the transition process and continuity of care.

Continuity of care

In certain patient populations, pediatric care involved a team-based approach where adult care physicians participated early on, often in staff meetings. When such a collaboration is absent, physicians suggested appointing a liaison to facilitate the transition process. Another significant issue identified by adult care physicians was the abrupt and unplanned transfer of patients.

Continuity of information

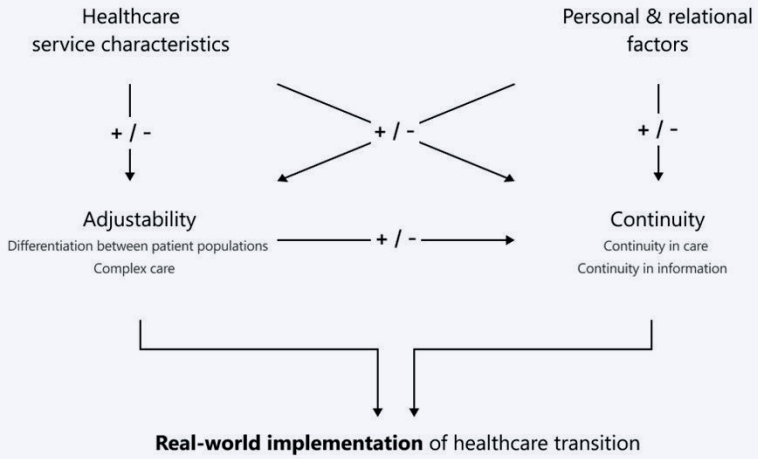
Establishing a standardized approach for sharing patient information was considered crucial to ensure continuity of care. While some disciplines use structured forms, others depend on joint

consultations, meetings, or letters. The challenge lies in sharing comprehensive and sensitive information efficiently. Especially the transfer from a pediatrician to a physician in another service posed a substantial risk for information loss. An adult care physician noted, *"A structured transfer document is crucial for an effective follow-up post-transfer. Manually shifting through comprehensive health records is both inefficient and time-consuming. In its absence, the burden of a transfer on healthcare providers would become overwhelming."*.

A grounded theory on the feasibility of a transition program

This article aims to enhance the understanding of the concept, causes of variation, and feasibility of implementing a transition program across different disciplines. It presents the following summarized propositions based on the theoretical foundations (Figure 1):

FIGURE 1: A theory on the applicability of transition programs. '+/-' indicates a positive or adverse impact



Proposition 1:

The structure and characteristics of healthcare services vary across different departments and patient groups, leading to disparities in how effectively these disciplines can implement and adapt transition programs.

Proposition 2:

Personal and professional relationships generally evolve gradually over time, driven by medical necessity. Lack of established collaboration and differences in scope on transition hinders efficient communication and the seamless execution of transition.

Proposition 3:

Maintaining continuity of care and information is multifaceted, influenced by factors such as service characteristics, system adjustability, and interpersonal dynamics, all of which contribute to varying implementation.

Proposition 4:

The main challenge in deploying transition programs lies in ensuring continuity of care, particularly during the actual transfer phase, to prevent disruptions and support patient-centered transition pathways

Discussion

This study examined physicians' perspectives on transition across disciplines to elucidate the multifactorial nature of implementation and underlying variations. To our knowledge, this study is the first to pose a theory on these variations, identifying four theoretical domains: [1] healthcare service characteristics, [2] personal and relational factors, [3] adjustability, and [4] continuity. Despite the study's focus on transition, predominantly challenges related to the actual transfer were highlighted.

Our findings indicate that the barriers faced during transition are fundamentally rooted in basic healthcare principles, particularly in the concept of healthcare continuity. Healthcare continuity can be defined as the degree to which patients experience a series of healthcare events as coherent, connected over time, and aligned with their needs, typically comprising **relational**, **informational**, and **management** aspects (23). Interestingly, the causes of variation we identified, contributing to the theoretical domain 'continuity', correspond directly to these aspects (proposition 3).

Relational continuity, the concept of patients consistently receiving care from the same provider or team, is central to our theory's second proposition (23). We identified several synergistic factors contributing to variations in relational continuity: [1] poor collaborations, making it challenging to find adult care physicians for patient transfer; [2] limited opportunities to build relationships and expertise; [3] loss or lack of coordinated multidisciplinary care due to remuneration issues; and [4] a high turn-over of physicians, whether or not in training, to perform outpatient clinic activities. A cross-discipline, treating and coordinating physician for complex cases could streamline transition paths but also centralize data, thereby providing a single point of contact for the patient (24).

Informational continuity involves the comprehensive transfer of patient information across care episodes, both between patients and providers and among providers themselves (23). Despite all participants having access to the same electronic health record system, noticeable variations in information continuity were observed. Pediatricians pointed out the difficulties in sharing sensitive information that cannot always be documented, while adult care physicians noted the absence of complete and transparent patient health records (25). More effective information exchange could be achieved through population-tailored transfer documents or during meetings and joint consultations (12). Conversely, multidisciplinary transfers or transfers that occur without an established collaboration between pediatric and adult care physicians – such as those to non-academic healthcare providers or to other academic hospitals – often experience significant loss of information (26). Thus, achieving informational continuity necessitates established collaboration among all stakeholders to ensure stakeholder-empowerment and a well-informed transfer.

Management continuity, which ensures a consistent yet adaptive approach to health management and adherence to standard care practices and policies, was a key challenge (23). Participants agreed that adult care should not simply be the appendix of pediatric practices and vice versa, and recognized the lack of resources to adopt pediatric protocols in adult settings (cf. proposition 1) (27). Yet, disparities in policies, for instance in managing procedural fear and pain, lead to patients resisting the transfer (28). Associations with funding models could be observed as a primary cause of variations in healthcare management continuity. Lump sum funding across pediatric and adult departments allows for continuity and adjustability in various domains of healthcare, including psychosocial support and standard care practices, whereas its absence can result in the loss of coordinated care post-transfer (29). For complex conditions, management continuity is achievable through cross-disciplinary and cross-departmental collaboration, coordination, and resource sharing, underscoring the importance

of funding models that promote these kinds of collaborations and introduces quality assurances (23).

All disciplines highlighted the particular challenges of transferring patients living with rare diseases impacting all three continuity domains: [1] relational, due to the lack of experienced and knowledgeable adult care providers; [2] informational, stemming from limited collaborations between healthcare providers or from uncertain prognosis or delayed diagnosis; and [3] management, due to the absence of coordinated practices, protocols, and adequate funding models (30).

Although this is a single-center study, our findings hold relevance for others as we developed a theoretical framework through the abstraction of causes of variation, rather than solely on department-specific challenges. Furthermore, the Belgian healthcare service system is characterized by its universal coverage and equitable access, with the government playing a significant role in regulation and funding. Consequently, introducing additional barriers to a healthcare system, like challenges in access to health insurance, is likely to exacerbate the findings that were observed in the Belgian healthcare system. Our theory can serve as a tool for healthcare providers and hospital services to reflect on their context-specific challenges to implement transition.

Feedback on current literature

This study highlights a significant knowledge gap in the field of transition, particularly in addressing real-world transfer challenges and adapting services to meet the diverse needs of patients within a healthcare setting. While models like "GOT Transition" and "Ready, Steady, Go" propose a generic approach to transition, our findings indicate that the primary challenges to implementing transition are fundamentally but differently rooted in the design of healthcare systems and services (6,9,12,16). Consequently, these one-size-fits-all models currently remain unattainable ideals for various patient populations. As current transition frameworks are mainly developed in experimental contexts, they do not fully account for real-world implementation challenges. Future research should thus develop and evaluate interventions in real-world contexts, targeting healthcare continuity's three key domains to enable the implementation of transition programs. It should also involve a broader range of stakeholders in designing transition services beyond patients, parents, and physicians, and investigate conditions that affect transition program effectiveness in real-world settings using a multidisciplinary and multiprofessional setup.

Strengths and limitations

This research's strength lies in engaging pediatric and adult care physicians from all relevant disciplines. Our adoption of a theoretical sampling strategy enabled the selection of physicians with varied perspectives on transition. By consulting department heads for participant recommendations instead of relying on our acquaintances, we reduced selection bias.

A key limitation of this study is the focus on physicians, while transitional care is inherently interprofessional. Including perspectives from nurses, social workers, and care coordinators in future research could provide a more comprehensive view on implementation challenges and multidisciplinary collaboration.

Further, the study is conducted in the specific setting of a tertiary hospital with a transition coordinator already in place, so one must be cautious when translating these results to other situations. Also, owing to confidentiality and privacy issues, we were not allowed to link specific challenges to disciplines.

In conclusion, challenges to implementing transition are fundamentally and differently rooted across healthcare services and disciplines. The causes of variation in transition are diverse, primarily related to the actual process of transfer, and more specifically, to the concept of healthcare continuity. Current generic guidelines and programs are not as applicable as they are presented. Our study underscores the need for implementation-effectiveness studies in broader, real-life contexts; including a diverse range of stakeholders to comprehensively evaluate interventions along the transfer journey of patients, assessing their value both to the patient and the healthcare system.

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

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Mieux boire. Mieux vivre.

How to Provide the Best Care for Young People with Gender Dysphoria

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Keywords
Gender dysphoria ; puberty.

Abstract
In a recent report pediatrician Hilary Cass (UK) makes recommendations on high standard care for children and young adolescents experiencing gender dysphoria; care, that meets their needs, is safe, holistic and effective. This report fuels the polarized debate on the moment that throughout the Western world, there has been a very significant increase of children with gender dysphoria. This group is characterized by a predominance of natal girls with late onset gender dysphoria who have frequently additional mental health problems. These children are often treated in gender clinics according to the Dutch Protocol which implies administration of puberty blockers, administration of cross-sex hormones, followed by surgical procedures, including genital reassignment.

In this manuscript we describe concerns about the scientific basis of the Dutch Protocol. The argument that gender-affirming care improves the well-being of transgender and reduces suicide risks is not supported by sufficient empirical support. Two systematic reviews have shown that the evidence for the benefits of hormone interventions on the mental health of minors is very weak while the use of pubertal suppression seems to be a one way ticket towards transition: more than 95% of those who started puberty suppression continue with gender-affirming treatment. Although the effectiveness of puberty blockers is not endorsed by evidence there are significant risks, such as infertility, lifelong drug dependence, reduced bone density, reduced sexual function. The authors of this manuscript plaid for a first-line intervention that is supportive, non-judgmental and based on exploratory psychotherapy by an independent psychotherapist outside a gender clinic.

Introduction

Recently, significant attention has been directed towards improving care for children with gender issues. The final report by dr Hilary Cass (the Cass Interim Report resulted in the closure of the UK's largest gender clinic in 2022) plays a crucial role in these discussions. It is essential to critically examine this report in the Belgian context.

The term 'transgender' refers to a person whose sex assigned at birth (usually based on external genitalia) does not correspond with their gender identity (the gender that a person feels to belong to). People who are transgender may experience gender dysphoria, implying a strong sense of dissatisfaction with one's sex assigned at birth, often corresponding with higher rates of depression, anxiety and suicidal ideation (1).

There are few areas of healthcare where professionals are so afraid to openly discuss their views. Polarization and suppression of debate however do not help the young people facing these problems nor their parents or caregivers. In the long run, this polarization will inhibit the critical research needed to find the best approach for these young people.

Evolution in cohort characteristics

Throughout the Western world, there has been a very significant increase of children with gender dysphoria. In the UK, the number of referrals grew from a few dozen in 2009 to 5000 in 2021 (2). The same phenomenon has been observed in many other countries, including Sweden and Spain, where applications have augmented exponentially since 2014. Whereas previously mainly natal boys reported with gender dysphoria in childhood ('childhood onset' or 'early onset'), today 2 to 3 times more natal girls are reported. These girls report later ('adolescent onset' or 'late onset'), often during puberty and often with additional psychological problems (2). Among referrals there is a greater complexity of presentation with high levels of neurodiversity and/or co-occurring mental health issues and a higher prevalence than in the general population of adverse childhood experiences and looked after children. Also in Belgium, the demand for gender dysphoria treatment is increasing, resulting in longer waiting lists, and there are plans to expand the current pediatric gender clinics (Ghent and Liège)

The Dutch Protocol

In these gender clinics, children and adolescents are frequently treated according to the Dutch Protocol, which was first described in two studies by the VU Amsterdam (3, 4). The Standards of Care of the World Professional Association for Transgender Health (WPATH), serving as the primary guideline in most Western countries, largely adopts this protocol (5).

The *Dutch protocol* includes three phases of medical transition following psychological assessment: (i) administration of puberty blockers, usually from the onset of puberty, (ii) administration of cross-sex hormones, followed by (iii) surgical procedures, including breast removal (from age 16) and genital reassignment (from age 18).

With both the sharp increase in the number of patients undergoing medical transition and its changing population, concerns about the scientific basis of the *Dutch Protocol* have increased. Treatment according to this protocol is based on research involving a very small number of patients. All these patients reported gender dysphoria which developed in childhood, usually without known psychiatric problems (6). The studies were conducted without a control group and with a short follow-up. Methodological objections have already been raised and more and more scientists consider this basis far too narrow to be considered *evidence-based* (7-9).

This is reflected in a changing approach to the problem in many countries: where the *Dutch protocol* was initially emulated, other choices are now being made. The United Kingdom, Finland, Sweden and Denmark are reforming their transgender care with respect to its pharmacological and surgical interventions (2, 10-13). The administration of puberty blockers is highly restricted e.g. to the original target group of the Dutch Protocol, namely children with childhood-onset gender dysphoria persisting into puberty. Additionally, such administration only takes place in study settings. For adolescents, the first-line intervention consists of the treatment of (additional) psychological problems and exploratory psychotherapy. In fact, on average this group is characterized by many more additional mental health problems or personality disorders, such as autism (2, 14, 15). It is possible that their identification as a trans person is partly due to the impact of social media and peer influence, and regret is more common after medical transition (15-20). Studies should first clarify the extent to which gender dysphoria resolves spontaneously in adolescents not displaying gender incongruent behavior in childhood (15).

In countries, such as France, Norway, Australia and New Zealand, professional organizations and health institutes advocate the same caution with an emphasis on psychological care (21-23). Research in the Netherlands and the UK shows that more than 95% of those who start puberty inhibition continue with gender-affirming treatments (24, 25). However, when adolescents with gender dysphoria go through the natural changes of puberty, only a small 15% will continue to experience gender dysphoria. There are 11 known prospective studies in which a total of 385 children with gender dysphoria went through puberty without hormone treatment (26-36). From this group, 329 (85.5%) had come to terms with their birth sex by the end of puberty (they are known as desisters). In contrast, 56 (14.5%) suffered from persistent gender dysphoria *(persisters),* with a variation ranging from 2% to 27% between studies. These figures indicate that both the early life period (from prenatal development to age three) and puberty are crucial for gender development, with puberty playing a pivotal role in its completion. The importance of sex hormones in gender differentiation, with respect to stimulating both sexual interest and activity and the development of other gender-specific traits, is confirmed by other studies (37-40). A qualitative study of Steensma et al. shows that twists during puberty such as physical changes (e.g. breast development), changing interests, friendships, first crushes, emerging sexuality and budding fantasies are determinants in this regard. Steensma additionally found a high percentage of homosexuals among these individuals with gender dysphoria, as shown in older prospective quantitative studies (41). The reprograming of the brain during puberty is hormonally determined rather than age dependent (42-44). The differentiating effect of pubertal hormones on the brain is also confirmed by MRI studies (45-49).

Scientific concerns

In Belgium, there's an ongoing debate, but no steps have yet been taken to adapt the policy. Moreover, triptorelin (Decapeptyl®), a puberty-inhibiting hormone equivalent, has recently become freely available in Belgium, but, although on medical prescription, without any specific prior examination or certification. This situation necessitates a thorough discussion of the arguments both for and against this practice. An important reason for administering puberty blockers to children with gender dysphoria is to prevent the development of secondary sexual characteristics (e.g. voice change, hair growth, breast development), thereby improving the external outcome of a later medical transition. Furthermore, advocates argue that gender-affirming care improves the well-being of transgender and gender-diverse people and reduces suicide risks. However, there is insufficient empirical support for this argument. Hitherto, two systematic reviews have shown that the evidence for the benefits of hormone interventions on the mental health of minors is very weak (2, 50). Neither is there scientific evidence that hormone interventions are an effective way of preventing suicide. Furthermore the claim that puberty inhibition is a pause button that puts puberty 'on hold', allowing time for 'further exploration' is not supported by evidence. Instead, the use of pubertal suppression seems to be a one way ticket towards transition. In the Netherlands, for example, 96.5% of those who started puberty suppression continue with gender-affirming treatment (24). Also in Belgium, most children who start puberty blockers go on to transition. It is possible that young people have stopped exploring other options, viewing pubertal suppression as the initial step in their transition (51-53). The British pediatrician Hillary Cass suggests that there is a real possibility that puberty blockers may be 'locking' adolescents into a medical trajectory by stopping normal psychosocial and psychosexual development at puberty (2).

Apart from the merely hypothetical and empirically unconfirmed advantages, there are significant risks associated with the use of puberty blockers, such as infertility, lifelong drug dependence, reduced bone density, reduced sexual function, more difficult genital surgery due to underdeveloped genitals, and distress due to regret (2, 7, 8, 54).

In summary, the situation is critical: an exponentially increasing number of minors are considering medical transition, despite the lack of compelling evidence that it will improve their lives.

The concern *about this questionable treatment does not imply that healthcare providers should not treat these patients*. Gender dysphoria is accompanied by, or is part of, psychological suffering and emotional distress. For this reason, an increasing number of European countries and international professional organizations recommend care based on several key principles (10-12, 23):

- Care is focused on the individual needs of the patient
- Care is supportive, ethical and non-judgmental
- A comprehensive multidisciplinary assessment is essential, fully exploring the patient's gender identity, together with both the personal and family context and history in which it has developed. In adolescence, specific clarification is needed whether or not a particular gender identity crisis is a

temporary expression of an underlying treatable psychiatric comorbidity that is not uncommon at this developmental age.

- In order to maximize positive mental health outcomes ongoing psychosocial support should be offered to adolescents and their families.
- Especially in case of 'late onset' gender dysphoria, psychotherapeutic treatment with an independent psychotherapist outside a gender clinic is preferable.
- Instead of focusing on whether or not gender should be changed, one should provide room for experimentation within the (temporary) gender-fluid context.
- If after very thorough consideration and in specific situations hormonal intervention is deemed necessary, it should be administered in a research setting.
- In order to move towards an evidence-based care model, sufficient resources for both scientific research and appropriate care are needed.

These principles should encourage governments, medical associations and treatment teams to align their policies, recommendations or actions with the best available evidence.

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The authors have published an article on the same topic in the Tijdschrift voor Geneeskunde en Gezondheidszorg (TvGG 2024;80:431-436) and are publishing this more detailed version in the Belg. J. Paediatrics with permission of the editors of the TvGG.

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

who will?

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

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

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

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

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GSK

Poverty Increases Inequality from an Early Age

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Keywords
Poverty ; inequality ; adverse childhood experiences ; health ; child advocacy ; child.

A growing problem in families with children

In 2024, 11.5% of the Belgian population lived below the poverty line — a slight decrease compared to 2023 (12.3%) and 2019 (14.8%). This decrease is mainly among the elderly, partly due to the indexation of pensions (Figure 1) (1).

It is striking, however, that *poverty is rising among families with children*, especially among *single-parent families* (2). Today, *one in five children in Belgium* lives in poverty or social exclusion (1).

Poverty as an Adverse Childhood Experience (ACE)

Growing up in poverty is one of the *Adverse Childhood Experiences (ACEs)* and has far-reaching consequences (Figure 2). Poverty increases *inequality of opportunity and health inequalities* from an early age and *has an intergenerational effect* (2, 3).

Children living in poverty are more likely to experience (4):

- Social exclusion and isolation
- Uncertainty about the future
- Emotional burden due to the worries of parents
- Reduced access to healthcare
- Greater risk of learning difficulties and school dropout
- Developmental and attachment problems
- Psychological complaints such as fear, shame or sadness
- Unhealthy lifestyle and delayed medical care

Unequal access to care and opportunities

The *European Child Guarantee* states that 53% of Belgian children do not have access to childcare and 3% lack medical care (5, 6). On top of that, 28% to 48% of parents postpone medical care for their child due to financial problems (7).

Due to *health inequalities and limited health literacy*, families in poverty are often labelled as 'not therapy-adherent' — when in fact this is a result of structural barriers.

The *WHO* emphasizes in its definition of health determinants that *it is the living environment that determines health* — and that it is wrong to hold individuals responsible for their health status.

The harsh reality of poverty and health

Children in families with a *preferential reimbursement* in health insurance have:

- 60% more likely to be admitted to hospital
- An average of 32% longer hospitalisation

For families with a chronically ill child, the financial impact is even heavier. These children are more at risk of poverty, and children in poverty are in turn more at risk of chronic diseases — a vicious circle that is difficult to break, especially if the situation is prolonged.

In addition, families in poverty are more likely to live in unhealthy neighbourhoods, with exposure to moisture, mould, air and noise pollution (8). Poverty acts as a *persistent negative catalyst* of health problems and social inequality. The impact affects education, development, living environment, social relationships and mental well-being.

The role of paediatricians: identifying and acting

Poverty often remains an *invisible problem*. Many families *hide their situation out of shame or mistrust*, which makes it difficult for caregivers to respond in a timely manner.

Nevertheless, identifying poverty is a crucial task of every paediatrician, regardless of specialization. During every moment of contact, there is a unique opportunity to discuss poverty — from a relationship of trust and with attention to the broader context of the family.

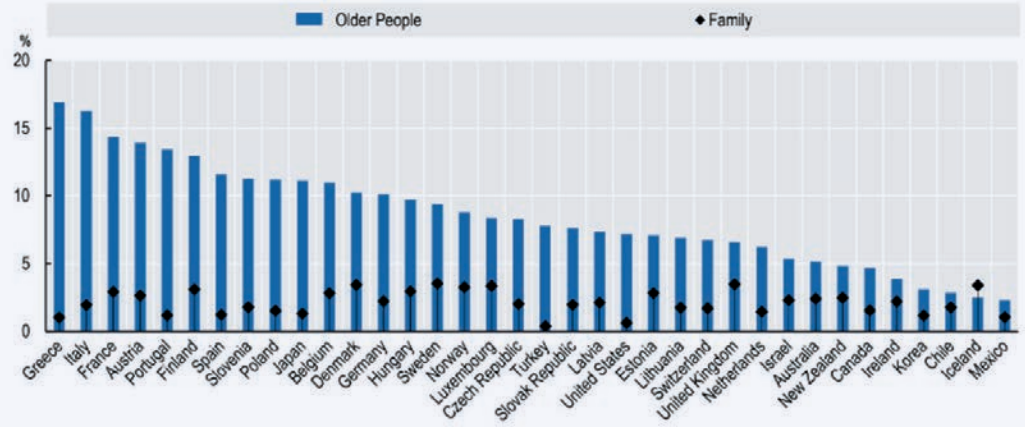
From medical care to social involvement

Although we, as paediatricians, agree that child poverty is *unacceptable*, it often remains a *blind spot in daily work*. If we really want to make a difference, we have to leave the medical island and take up our role in the broader social landscape.

An effective approach to child poverty requires (9):

- *Multidisciplinary collaboration*, both within the hospital and in primary care.
- *Transmural care pathways* that actively engage families.
- *A safe, accessible and trusting climate* in which families feel heard and supported.

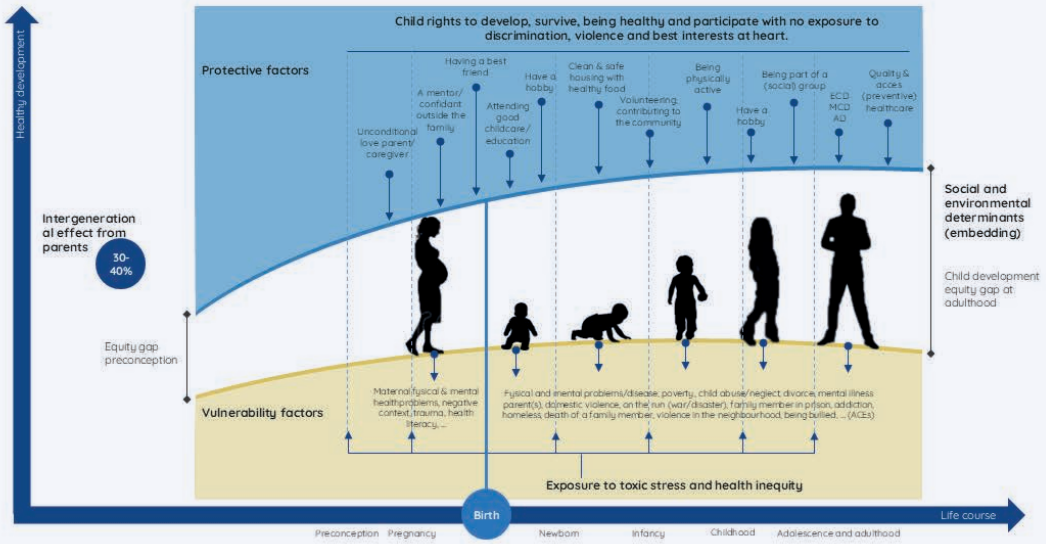
FIGURE1: Public social expenditure on Older People and Family as percentage of GDP, 2017.



Note: Data refer to cash and services expenditure.
Source: OECD, Social Expenditure Database (SOCX, www.oecd.org/els/social/expenditure).

StatLink https://doi.org/10.1787/888934038818

FIGURE 2: Child rights to develop, survive, being healthy and participate with no exposure to discrimination, violence and best interests at heart.



Adapted from: Sustainable Development Goals measuring protective and risk factors for child wellbeing across life

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High-grade Compression of the Internal Carotid Artery in a 4-Year-Old Child with a Retropharyngeal Abscess. Case Report

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Keywords
Retropharyngeal abscess ; ICA compression ; internal carotid artery ; case report.

Abstract
For pediatricians and otolaryngologists, retropharyngeal abscesses in children are not uncommon. Most pediatric patients make a complete recovery without complications with the use of broad-spectrum antibiotics, often supplemented by surgical incision and drainage.

We report an unusual complication of retropharyngeal abscess in a 4-year-old girl, namely high-grade compression of the internal carotid artery and compression of the internal jugular vein. The patient was treated conservatively with intravenous broad-spectrum antibiotics. No vascular or neurological complications occurred. A review of current knowledge and treatment approaches will be discussed.

Introduction

A retropharyngeal abscess is a collection of pus in the space behind the pharynx and in front of the prevertebral fascia. It primarily affects children, often after an upper respiratory tract infection. Most children make a full recovery with the use of broad-spectrum antibiotics, often supplemented by surgical drainage. However, complications can occur, including airway compromise, jugular vein thrombosis, mediastinitis, sepsis, esophageal perforation, and carotid aneurysm or rupture. Major vascular complications are rare.

We report a high-grade external compression of the internal carotid artery by a retropharyngeal abscess in a 4-year-old child. A review of current knowledge and management approaches is provided.

Case

A 4-year-old girl presented to the emergency department with a 3-day history of high fever, neck pain and anorexia. She had a pronounced adenopathy in the left cervical region with reduced neck mobility. Furthermore she had a hyperemic pharynx, a strawberry tongue and a scarlatiniform rash on the thorax. Laboratory analysis revealed a bacterial blood count with leukocytosis 18.58x10³/µL (5.00-10.60x10³/µL), C-reactive protein (CRP) 230.0 mg/L (<10 mg/L) and sedimentation rate 120 mm/h (<11 mm/h). Ultrasound revealed bilateral reactive lymphadenopathy.

She was admitted to the hospital and started on intravenous (IV) ceftriaxone (105 mg/kg/day in 1 dose). Figure 1 presents a timeline detailing the treatment and key steps during the admission.

FIGURE 1: Timeline detailing the treatment and key steps during the admission.

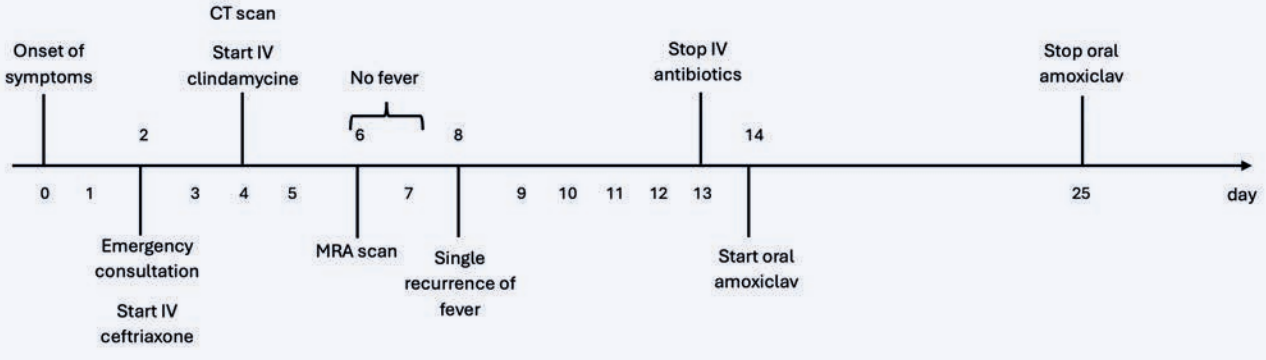


FIGURE 2:
CT scan revealed a hypodense, irregularly marginated abscess collection in the left retropharyngeal space at the level of the nasopharynx. The abscess compresses both the ICA and the IJV (orange arrows).during the admission.

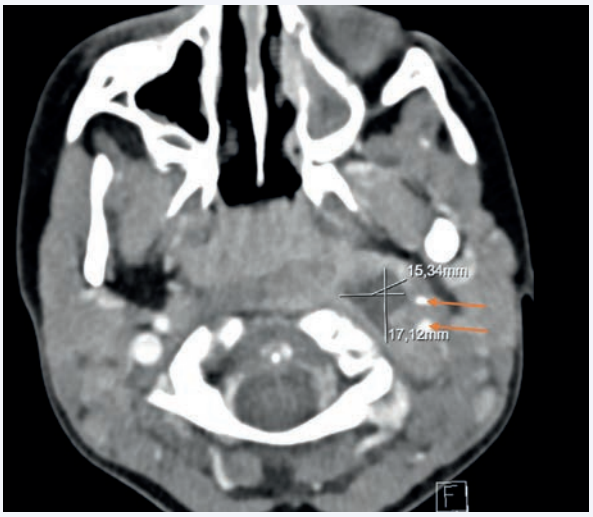


FIGURE 3:
CT scan shows a high-grade collapse of the left ICA (orange arrow) secondary to the mass effect of a RPA (green arrow).

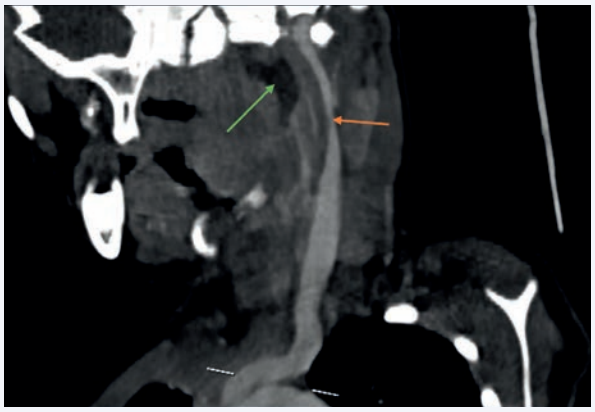
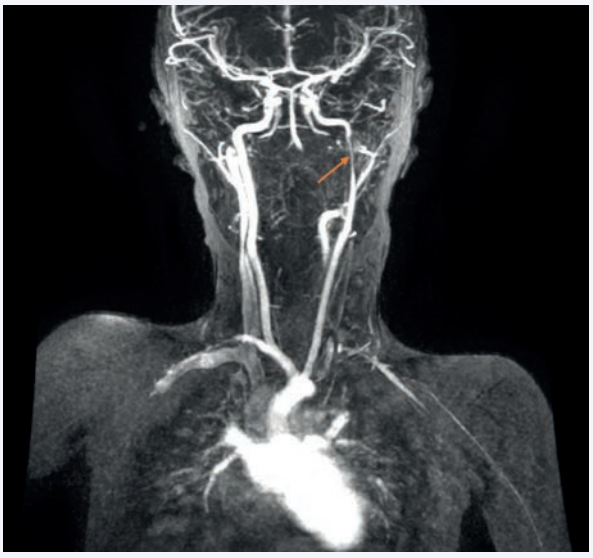


FIGURE 4:
MRA, conducted 2 days post-CT-scan, shows the ICA compression (orange arrow). Additionally, the normal morphology and patency of other blood vessels is visualized.



Two days after starting IV ceftriaxone, a computed tomography (CT) scan with contrast was performed because of persistent pyrexia, which revealed a hypodense, irregularly marginated abscess collection in the left retropharyngeal space at the level of the nasopharynx, exerting a moderate mass effect. The abscess measured approximately 15 x 17 x 27 mm and extended to the base of the skull (Figure 2). Imaging also showed high-grade compression of the left internal carotid artery (ICA) and compression of the left internal jugular vein (IJV), with no evidence of an intraluminal thrombus (Figure 3). Given the diagnosis of an abscess and the presence of a bacterial blood count, IV clindamycin (50 mg/kg/day in 4 doses) was associated 2 days after starting IV ceftriaxone to cover the patient against bacterial toxins. Coagulation screening showed no abnormalities. Clinically, the patient had no neurological deficits or additional complaints. Given the anatomically challenging location of the abscess, the absence of neurological impairment, the decrease in inflammatory markers, and the patient's stable clinical condition, the decision was made to continue IV antibiotic therapy (ceftriaxone + clindamycin) without proceeding with surgical drainage. Due to the arterial nature of the compressed blood vessel, anticoagulant therapy was not administered.

In order to obtain a better visualization of the cervical and intracranial vasculature, magnetic resonance angiography (MRA) was performed. The scan, performed two days after the CT scan, demonstrated an external compression of the ICA (Figure 4). In addition, the scan showed further reduction of the abscess (12 x 11 x 22 mm), normal morphology and patency of other blood vessels, and no evidence of ischemia. Intravenous antibiotic therapy was continued.

The fever resolved after six days, 3 days after the start of IV ceftriaxone. Clinically, she appeared generally well, although cervical adenopathy and reduced neck mobility persisted. Her white blood cell count and CRP also decreased.

On day five of treatment, eight days after the onset of the symptoms, there was a recurrence of fever. No significant clinical changes were noted and there was no indication of an intercurrent viral infection. Serial blood counts showed a continued decrease in inflammatory markers. The treatment regimen remained unchanged, and no subsequent febrile episodes were recorded.

After completing a 12-day course of IV ceftriaxone and a 10-day course of clindamycin, the patient was discharged with mild persistent cervical adenopathy. Amoxiclav (50/6,25 mg/kg/day in 3 doses) was administered orally for an additional twelve days.

At the end-of-treatment follow-up, the swelling and cervical adenopathy had completely resolved. After 2.5 months, a repeat MRA of the cervical vessels showed complete re-expansion of the ICA and complete resolution of the abscess

Written informed consent for the use of this case in this report was obtained from the patient's parents.

Discussion

Retropharyngeal abscesses (RPAs) are not uncommon in pediatric patients. In most cases, abscess formation follows an upper respiratory tract infection, leading to suppurative adenitis of the retropharyngeal lymph nodes and subsequent abscess formation. This process occurs mainly in children under the age of five years due to the involution of these lymph nodes starting at four to five years of age (1,2). Although abscess formation is often preceded by an upper respiratory tract infection, trauma involving inoculation at the level of the posterior pharynx or dental disease can also serve as an entry point for retropharyngeal infection leading to abscess formation (1). Timely diagnosis and treatment is important, but can be difficult in children, especially in nonverbal children, because of insidious onset. RPA should be included in the differential diagnosis of a child

presenting with fever, with or without torticollis and decreased oral intake. Complications are more common when there is a delay in diagnosis and treatment. Two separate studies found that, among deep neck abscesses, the risk of complications was highest for RPAs (3,4). Several complications have been described, including airway compromise, jugular vein thrombosis, mediastinitis, sepsis, esophageal perforation, and carotid aneurysm or rupture (1,4).

Serious vascular complications secondary to RPA are uncommon. Arterial complications, which were more common before the advent of antibiotics, are even less common than venous complications (5). To our knowledge, only a single case report about an ICA occlusion has been published, defined radiologically defined loss of signal in the ICA, secondary to a RPA (6). In contrast, several studies have demonstrated that vascular narrowing with partial patency (which is unambiguously defined) is a prevalent radiographic finding associated with RPAs (5,7,8). Its significance is controversial. Hudgins et al. found ICA narrowing (range 1-5mm) in 13 children with RPA, without complications, or neurological symptoms (8). Caroll et al. identified carotid or jugular narrowing in 93 of 208 patients with deep neck abscess, without neurological complications. Three patients had jugular vein thrombosis, one possibly an artifact (5). Derinkuyu et al. observed ICA narrowing in 5 children with parapharyngeal-lateral RPA. One patient had mild lower extremity weakness that resolved with heparin treatment; otherwise, there were no complications (7). Hudgins and Caroll consider ICA narrowing to be benign and not requiring intervention due to its common and usually uneventful course (5,8). Derinkuyu emphasizes the importance of recognizing this common finding to prevent progression and fatal complications (7).

As with the significance of ICA narrowing, the treatment of RPA is controversial, especially concerning the role and timing of surgical intervention. To our knowledge, there are no established guidelines for the treatment of RPA. Most studies advocate an initial trial of intravenous antibiotics alone, while others argue that surgical drainage should be included as part of the treatment (2). Increasing attention is being given to the role of corticosteroids in treatment as they may reduce the need for surgical drainage, shorten hospital stays, and decrease hospitalization costs (9).

Guidelines for the treatment of ICA compression secondary to RPA are also currently lacking. Current recommendations for acute ischemic stroke in children recommend the administration of unfractionated heparin, low-molecular-weight heparin, or aspirin until dissection and cardioembolic causes are ruled out. If these causes are excluded, the guidelines recommend continuing aspirin therapy for at least two years (10). In our patient, there was no stroke, only an asymptomatic ICA compression, and no evidence of dissection or a cardioembolic source, so anticoagulation was not initiated.

In our perception, external compression of the ICA should not be considered a trivial finding. The importance of recognizing and managing ICA compression lies in the potential risk of ischemic events. These events do not always occur with ICA compression because many individuals have an intact circle of Willis or develop collateral circulation from another intracranial source or from the external carotid artery to the ICA. In children, leptomeningeal collaterals are particularly well developed (8). In this context, we do not believe that it is necessary to treat all patients with anticoagulation. However, if neurological symptoms or dysfunction are present, further evaluation of cerebral perfusion should be performed and intervention or medication may be warranted.

Conclusion

In summary, we present a case of high-grade internal carotid artery compression secondary to a retropharyngeal abscess. The patient was treated with broad-spectrum antibiotics and had no neurological or vascular complications.

The clinical significance of internal carotid artery compression due to retropharyngeal abscess remains uncertain, and there are no established guidelines for its management. We believe that internal carotid artery compression should not be considered trivial because of to the potential risk of ischemic events.

Further research into the recognition of and therapeutic approaches to arterial compression due to retropharyngeal abscesses would be of value, although the low incidence of such cases poses a challenge to a comprehensive study.

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

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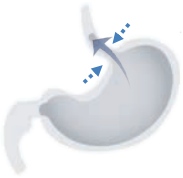

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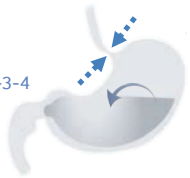

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Dit document is voorbehouden voor gezondheidsspecialisten. Belangrijke informatie voor (para)medici: de Wereldgezondheidsorganisatie (WHO) heeft aanbevolen om zwangere vrouwen en moeders van zuigelingen te informeren over de voordelen en de superioriteit van borstvoeding. In het bijzonder dat borstvoeding de beste voeding is en de beste bescherming tegen ziektes biedt. Moeders moeten ook begeleid worden met de voorbereiding op en de verderzetting van borstvoeding, met de nadruk op het belang van de kwaliteit van hun eigen voeding tijdens de zwangerschap en na de geboorte. Onnodige introductie van gedeeltelijke flesvoeding of andere voedingsmiddelen of dranken zou ontmoedigd moeten worden omdat het een negatieve invloed op borstvoeding kan hebben. Bovendien moeten moeders gewaarschuwd worden dat zij niet terug kunnen komen op hun beslissing om geen borstvoeding meer te geven. Voordat een moeder besluit om flesvoeding te geven, zou ze geadviseerd moeten worden over de sociale en financiële gevolgen van haar beslissing, bijvoorbeeld als een baby exclusief flesvoeding krijgt, dan is meer dan 450 gram per week nodig, dus de familiale omstandigheden en de kosten moeten in overweging worden genomen. Moeders moeten eraan herinnerd worden dat borstvoeding niet alleen de beste voeding, maar ook de meest economische voeding is. Wanneer toch wordt besloten om flesvoeding te geven is het belangrijk om de juiste instructies mee te geven omtrent het gebruik van deze voeding en erop te wijzen dat ongekookt water, niet gesteriliseerde zuigflessen of een onjuiste bereiding de baby ziek kan maken. **Met vriendelijke groeten, Nestlé Babyvoeding.** V.U : Kartien Desmedt, Nestlé Belgilux SA/NV, rue de Birminghamstraat 221-1070 Bruxelles/Brussels, BCE/KBO 0402.231.383. PID3598 Maart 2025

Triple A Syndrome Presenting as Hypoglycemic Convulsions in a 3-Year-Old Boy: A Case Report

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Keywords
Triple A syndrome ; alacrima ; achalasia ; ACTH-resistant adrenal insufficiency ; Addison crisis.

Abstract
Triple A syndrome, characterized by the triad of alacrima, achalasia, and adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, is a rare and often underreported condition. We present the case of a 3-year-old boy who presented with hypoglycemic seizures unresponsive to glucose boluses. A detailed history revealed congenital alacrima. Suspicion of triple A syndrome led to the initiation of hydrocortisone therapy, which resulted in rapid resolution of symptoms and confirmed the diagnosis. Early recognition of this multisystemic genetic disorder is crucial, as delay in diagnosis can be life-threatening.

Introduction

Triple A syndrome, also known as Allgrove autosomal recessive syndrome, includes the classic triad of alacrima, achalasia and adrenocorticotropic hormone-resistant adrenal insufficiency (1). It is a rare and underreported syndrome, due to its diversity in clinical presentation, with an estimated prevalence of 1/1000000. In addition to the classic triad, a wide variety of symptoms can be associated, including neurological symptoms, dermatological problems and dental caries. The onset of symptoms may not be simultaneous. Alacrima is known to be the first symptom and is often present from birth but is not always immediately recognized. Also, not all cases present with the classic triad, complicating the diagnosis. Achalasia or adrenal crisis is often the presenting symptom.

As Triple A syndrome is a rare disease, the literature is limited and consists mostly of case reports. In this article a clinical case of Triple A syndrome is discussed, followed by a review of the literature.

Case

A 3-year-old boy presented to the emergency department of a regional hospital with symptoms of fever, vomiting, and a tonic-clonic seizure lasting more than 30 minutes. On arrival, the child was somnolent and only responsive to pain stimuli. His capillary glucose was 45 mg/dL (normal range 70-100 mg/dL), for which a glucose bolus was promptly administered. Laboratory tests revealed mild hyponatremia (132 mmol/L; normal range 135-145 mmol/L) and a moderately elevated C-reactive protein (CRP) (45 mg/L, normal range 0-5 mg/L). A brain CT scan and lumbar puncture ruled out central nervous system pathology. After initial treatment with antiepileptic medication, the child was admitted to the intensive care unit with the hypothesis of severe dehydration due to gastroenteritis and an intravenous rehydration was started.

Despite adequate rehydration and glucose supplementation, the boy's clinical status remained unchanged and hypoglycemia persisted, prompting his transfer to our center. On arrival, the blood glucose level was 54 mg/dL with a CRP of 89 mg/L, and a sodium level of 135 mmol/L. During the patient's history-taking, his mother mentioned the absence of tear production since birth, for which he had been prescribed artificial tears by an ophthalmologist. In addition, the mother reported feeding difficulties, such as gagging and dysphagia during meals.

With the differential diagnosis of Triple A syndrome in mind, an acute adrenal crisis was suspected. The patient was treated with a stress dose of intravenous hydrocortisone (2 mg/kg), followed by a stress regimen (50 mg/m²/day in four divided doses). Ceftriaxone was also administered to cover possible infectious causes. The child's symptoms resolved within hours of receiving hydrocortisone, and he was discharged three days later with oral hydrocortisone replacement therapy.

Further investigations confirmed elevated ACTH levels of 393 ng/L (normal range 7.2–63.3 ng/L) and low cortisol levels of 3.3 µg/dL (normal range 3.7–19.4 µg/dL), consistent with adrenal insufficiency. Combined with the presence of alacrima and feeding difficulties, a diagnosis of Triple A syndrome was confirmed. The patient was referred for endocrinological follow-up. Genetic testing revealed a mutation in the *AAAS* gene (c.1331+1G>A), confirming the diagnosis of triple A syndrome.

Discussion

Triple A syndrome, also known as Allgrove syndrome, is a rare autosomal recessive disorder first identified by Allgrove et al. in 1978 (1). Due to limited literature and frequent misdiagnoses,

the exact prevalence remains unclear but is estimated at approximately 1 in 1,000,000 (2-4). The syndrome is characterized by a classic triad of adrenocorticotropic hormone (ACTH)-resistant adrenal insufficiency, alacrima, and achalasia. These features are pathognomonic for Triple A syndrome, though other symptoms such as autonomic dysfunction, neurological abnormalities, xerostomia, dental caries, hyperkeratosis (thickened skin), microcephaly (small head), gait disturbances, and delayed puberty can be present (2, 4-6). The clinical symptoms, time of onset and progression of the disease are highly variable, leading to the proposal of the term "4A syndrome" to include additional autonomic dysfunctions (2, 4, 7). Alternative syndromes similar to Triple A, such as AAMR (alacrima, achalasia with mental retardation), do not involve adrenal impairment (7).

Genetics and Pathophysiology

Triple A syndrome is caused by mutations in the *AAAS* gene located on chromosome 12q13, which encodes the nuclear pore protein ALADIN (2, 4, 5, 8). ALADIN plays a vital role in nucleocytoplasmic transport, essential for cellular function. The *AAAS* gene is widely expressed in various human tissues, contributing to the diverse symptomatology of the syndrome (4). High expression levels of the gene are particularly found in the adrenal glands, gastrointestinal tract, and brain (5, 9). Mutations in the *AAAS* gene are spread across all 16 exons, with the c.1331+1G>A mutation being the most common worldwide (5). Over 40 mutations have been documented, and no clear genotype-phenotype correlation has been established (2, 4, 5, 8). There is no gender difference in prevalence, and the phenotypic spectrum can vary significantly even among individuals with identical mutations. Thus, DNA studies are not particularly effective in predicting phenotype or prognosis (4).

Clinical Presentation

Triple A syndrome is often diagnosed in early childhood, although adult-onset cases have been reported (4). Pediatric cases usually present with alacrima or adrenal insufficiency, whereas late-onset cases may initially present with neurological symptoms (4, 5). Antenatal history is typically unremarkable, but consanguinity has been reported in 50% of cases (4). Clinical features may not appear simultaneously, with approximately one-third of patients presenting with only two symptoms and 10% presenting with only one (2)

Alacrima

Alacrima is often the earliest and most consistent finding in Triple A syndrome, though it may be overlooked due to its mild clinical significance (5, 6). Present in all patients, it often becomes evident later during diagnostic evaluations (6). This finding is attributed to parasympathetic dysfunction of the autonomic nervous system (2, 4, 10). Alacrima is rarely isolated and should prompt consideration of a congenital disorder such as Triple A syndrome, particularly when accompanied by other autonomic dysfunctions (2, 4, 7). Untreated, it can lead to serious complications like keratopathy and corneal ulceration (5).

Achalasia

Achalasia may present at any age, with symptoms including difficulty swallowing, food aversion, and prolonged mealtimes (6). Early symptoms such as dysphagia and vomiting can precede the diagnosis by years (2, 4, 5). Rarely, achalasia can be misdiagnosed as a chronic cough (2, 4). Manometric studies are the gold standard for diagnosing achalasia, revealing aperistalsis and a hypertonic lower esophageal sphincter (11). Achalasia can lead to dental caries and premature tooth loss due to xerostomia and exposure of teeth to gastric acid, making regular dental check-ups essential (2, 5, 9).

Adrenal Insufficiency

Adrenal insufficiency is the most common presenting symptom and ranges from severe manifestations such as hypoglycemia, hypotension, and ketoacidosis to milder symptoms like hyperpigmentation and poor growth (2, 4, 6, 11). This condition is present in 85% of patients, though some may never develop it (4, 5). Adrenal function may be borderline at presentation but deteriorate over time, necessitating regular monitoring of morning cortisol and ACTH levels (5). Elevated ACTH levels with a normal cortisol response on stimulation tests suggest latent adrenal failure and require close monitoring (11). Hypoglycemia from adrenal insufficiency can result in convulsions or sudden death (6, 12). Low DHEA-S (dehydroepiandrosterone sulfate) concentrations indicate involvement of the adrenal cortex layers (2, 9). Glucocorticoid deficiency is an obvious finding in patients with Triple A syndrome, whereas mineralocorticoid deficiency is rare. This suggests that the zona glomerulosa, is partially preserved in these patients (9).

Neurological and Autonomic Symptoms

Neurological dysfunctions occur in about 85% of patients, usually presenting in adolescence or adulthood (5). Rarely, neurological symptoms may precede adrenal insufficiency (4). These symptoms include developmental delay, distal weakness, sensory-motor neuropathy, intention tremors, gait imbalance, motor neuron disease, and optic atrophy (4, 5, 9). Cognitive impairment is common but not universal (6). Neurological symptoms generally progress slowly and stabilize in adulthood. Peripheral polyneuropathy is the most prevalent neurological finding (12). Autonomic disturbances, such as postural hypotension and abnormal sweating, are seen in approximately 30% of patients (4, 5, 11). The pathophysiology of these symptoms remains unclear, with ongoing debate on whether they are a primary manifestation of the disease or secondary to glucocorticoid deficiency affecting neurological development (4).

Management and Treatment

Patients with Triple A syndrome need to be medically monitored as adrenal insufficiency may not be present at diagnosis but can develop over time. Alacrima is a clinical sign of autonomic dysfunction and should always be investigated.

Treatment of adrenal insufficiency primarily involves oral hydrocortisone, with dosage adjustments during stress or illness (2, 4). Intravenous hydrocortisone may be used if oral administration is not feasible. Chronic steroid use can lead to central obesity, weight gain, and elevated hemoglobin A1c levels (5). Some studies suggest that systematic treatment may not always be necessary if glucocorticoid secretion remains borderline, but regular follow-up is crucial (10). Glucocorticoid supplementation does not significantly affect neurological symptoms, but physical therapy may improve endurance and balance (5).

Although there are no guidelines for the surveillance of patients with Triple A syndrome, it seems evident that regular follow-up is necessary. One study suggested that patients with adrenal insufficiency should be monitored every 3 months, whereas patients with borderline or no adrenal insufficiency should be monitored every 6 months or sooner if symptoms are present (5). Therefore, parents should be made aware of the possibility of developing symptoms related to adrenal insufficiency and consult promptly if those symptoms appear.

Lubricant eye drops are recommended to manage dryness and prevent ophthalmic complications associated with alacrima, with annual ophthalmological evaluations advised (2, 4, 6). Treatment for achalasia varies based on severity, from lifestyle changes to more invasive procedures such as balloon dilatation, nifedipine, or surgical myotomy (2, 6). Managing severe achalasia is essential for controlling hypoglycemia and supporting growth and development (5). DHEA supplementation may be necessary for patients with low adrenal androgen levels affecting libido and sexual function (2).

Conclusion

Triple A syndrome is a rare and potentially life-threatening condition (4, 12). It is characterized by a triad of symptoms: alacrima, achalasia and adrenal insufficiency. Although not all present simultaneously. Low glucose levels that do not normalize after an IV correction should alert the clinician to question the initial diagnosis. The importance of a thorough anamnesis in patients with an unclear medical condition should also be emphasized, as demonstrated in this case. Treatment of triple A syndrome depends on the symptoms and may include chronic hydrocortisone therapy and artificial tears. Early diagnosis of this syndrome prevents unnecessary investigations and inappropriate treatment (11).

None of the authors has a conflict of interest related to this article.

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

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

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

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

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Acute Late-onset Pyruvate Dehydrogenase Deficiency with Specific Diagnostic Clues

Report of Five New Patients

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Keywords

Pyruvate dehydrogenase complex deficiency ; mitochondrial disorder ; ataxia ; ketogenic diet.

Abstract

The aim of this article was to explore acute late-onset pyruvate dehydrogenase complex (PDHc) deficiency, a mitochondrial disorder affecting energy metabolism. Five new cases are reported, and clinical features, genetic pathogenic variants and therapeutic strategies are described. Patients presented with intermittent episodes of ataxia and weakness. The diagnosis was based on biochemical studies and confirmed by molecular genetic analysis, which revealed pathogenic variants in the *PDHA1* gene. Treatment consisted of a ketogenic diet and vitamin supplementation, which led to a reduction in symptoms. This study highlighted the diversity of PDHc deficiency, the relevance of genetic analysis and the efficacy of personalised treatments such as ketogenic diets.

Introduction

Pyruvate dehydrogenase complex (PDHc) is an essential enzyme complex involved in mitochondrial energy metabolism, which catalyses pyruvate to acetyl-CoA and acts as a gateway to carbohydrate metabolism in mitochondria. This complex comprises three catalytic enzymes: E1 or pyruvate dehydrogenase, E2 or dihydrolipoamide transacetylase, and E3 or dihydrolipoyl dehydrogenase, along with an additional protein E3BP or E3 binding protein, formerly designated as protein X, as well as two regulatory enzymes, including pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase (1,2). PDHc deficiency impairs mitochondrial pyruvate oxidation. As a result, pyruvate is inefficiently metabolized and does not reach the tricarboxylic acid cycle, resulting in increased lactate production and reduced adenosine triphosphate production by the mitochondrial respiratory chain (3).

The clinical presentation is heterogeneous, with four phenotypes reported in patients with a pathogenic variant of the *PDHA1* gene (1,4,5), as follows:

- a neonatal-onset encephalopathy with lactic acidosis, facial dysmorphism, and brain malformations (corpus callosum, cortex, or both), mainly affecting female patients;
- an early infantile form with chronic and progressive neurological deterioration;
- an infantile form with the clinical and radiological features of Leigh syndrome and mild systemic acidosis;
- a childhood intermittent-relapsing or milder later-onset form with acute and transient weakness and ataxia episodes, possibly associated with high lactic acid and pyruvate levels in the blood, or peripheral neuropathy.

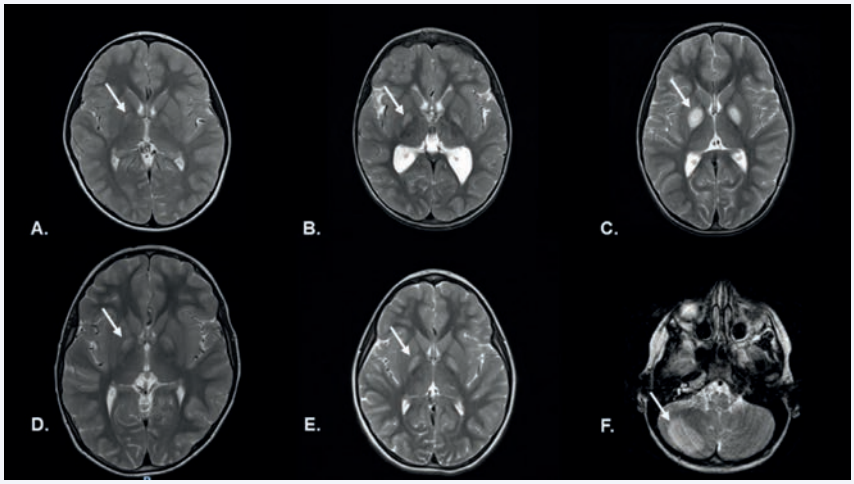
The late-onset acute form manifests as recurrent ataxia episodes and neuropathy. The first episodes can be misdiagnosed as cerebellitis or Guillain Barré syndrome (4,6).

High lactate and pyruvate levels associated with a low lactate/pyruvate ratio (<10-15) in blood and cerebrospinal fluid (CSF) are consistent indicators of PDHc deficiency. However, in milder forms, clinical and biochemical features can normalize, yet with persistent neuroradiological and electrophysiological abnormalities (5). Several genes are implicated in PDHc deficiency: the *PDHA1* (76%-85%), *PDHX* (7-11%), *PDHB* (4-9%), *DLD* (1-6%), *DLAT* (1-4%), *PDP1,* and PDK3 (each <1%) [2]. The *PDHA1* gene is located on chromosome Xp22.12. Thus, most PDHc deficiency cases are X-linked disorders. Considering the X-linked *PDHA1* gene, no known genotype-phenotype correlations were so far reported among the different pathogenic variants. Variations in severity are anticipated in female patients, given the different patterns of X-linked inactivation. However, this variability can also be observed in male patients, where it remains unexplained (7).

The ketogenetic diet is used to treat PDHc deficiency, aiming to induce ketosis, which provides an alternative source of acetyl-CoA. Thiamine is similarly used, but with limited efficacy. Thiamine responsiveness has been correlated with certain missense variants, particularly those found in exon 3 or the thiamine pyrophosphate binding site of the E1-alpha subunit (*PDHA1*), which are most receptive to treatment.

Certain treatments, such as dichloroacetate (DCA) and phenylbutyrate, function as PDHc activators. They inhibit pyruvate

FIGURE 1: Brain magnetic resonance imaging of axial T2-weighted images. A. Patient #1 at the age of five; B. Patient #2 at the age of six; C. Patient #3 at the age of six; D. Patient #4 at the age of seven; E. Patient #5 at the age of nine exhibiting bilateral and symmetric high signals of the internal part of the globi pallidi. F: Patient #5 at the age of nine presenting with a large unilateral right hemispheric cerebellar lesion.



dehydrogenase kinase 1 (PDK1), the primary inhibitor of PDHc. These therapeutic approaches are currently being investigated (NCT02616484) (8).

Methods

The aim of this paper was to report the case of five patients with acute late-onset PDHc deficiency who have been followed up over the past 10 years. Informed consent was obtained from the patients or their legal guardians.

Clinical reports

Patient #1 was a 13-year-old boy, born at term to unrelated parents. Psychomotor development was normal. At 22 months of age, he experienced intermittent ataxia and global weakness with undetectable deep tendon reflexes. A discrete bilateral diffusion restriction was detected in the globi pallidi on brain magnetic resonance imaging (MRI). Lactate levels were increased in cerebrospinal fluid (CSF), as were alanine and proline levels in plasma. Elevated lactate and pyruvate levels in blood along with the lactate/pyruvate ratio were indicative for a PDHc deficiency (Table 1). The diagnosis was confirmed by the identification of a heterozygous pathogenic variant NM_000284.4(*PDHA1*), c.262C>T, p.(Arg88Cys) in the E1alpha subunit. Thiamine and riboflavin supplementation and a ketogenic diet were implemented for 1 year, after which the ketogenic diet was discontinued and replaced by a limited sugar intake. Brain MRI performed 5 years later showed modest bilateral and symmetrical high signals in the globi pallidi (Figure 1A). At the age of 13 years, the patient showed normal psychomotor development, while following the regular education curriculum without difficulty. He did no longer experience episodes of ataxia or global weakness.

Patient #2 was a 7-year-old boy, born at term to unrelated parents. He began walking at 16 months old. His development of gross motor skills was marked by difficulties in running and frequent falls. At the age of four, he presented with falls, episodic ataxia, and fatigue persisting for several months. The clinical examination was normal except for absent deep tendon reflexes in the lower limbs. Nerve conduction velocity and electromyography were within the normal range. Brain MRI demonstrated symmetrical bilateral high T2 and FLAIR signals of the globi pallidi, with discrete diffusion restriction (Figure 1B). Elevated levels of lactate, pyruvate, and alanine were observed in the blood and CSF. The lactate/pyruvate ratios in plasma and CSF were indicative for a PDHc deficiency (Table 1). The diagnosis was confirmed by the identification of a hemizygous pathogenic variant NM_000284.4(*PDHA1*):c.214C>T, p.(Arg-72Cys) in the E1alpha subunit. Treatment involved a ketogenic diet supplemented with riboflavin and thiamine. Episodes of ataxia persisted during fever, prolonged effort, or periods of reduced diet compliance. The patient benefitted from physiotherapy and was enrolled in a regular education program.

Patient #3 was a 7-year-old boy, born at term to unrelated parents. At the age of five, the patient presented with fatigue and gait disturbances following a febrile influenza A infection. Clinical examination revealed generalized weakness and absent deep tendon reflexes, indicative of Guillain Barré syndrome. CSF analysis showed high lactate levels with normal protein levels, which did not align with the Guillain Barré syndrome. Further investigations confirmed elevated levels of lactate and pyruvate in blood and CSF, with a lactate/pyruvate ratio in blood indicative for a PDHc deficiency (Table 1). Brain MRI showed bilateral isolated discrete high T2 signals of the globi pallidi (Figure 1C). Diagnosis was confirmed by the identification of a hemizygous pathogenic variant NM_000284.4(*PDHA1*):c.262C>T, p.(Arg88Cys) in the E1alpha subunit. Treatment comprised thiamine and riboflavin supplementation, alongside a ketogenic diet, intensive physiotherapy, and occupational therapy. However, the patient continued to experience balance and endurance problems on the motor level. Additionally, as he faced learning difficulties, he is enrolled in a specialized education program.

Patient #4 was a 9-year-old boy, born at term to unrelated parents and the brother of patient #3. He has been undergoing physiotherapy since the age of four due to global hypotonia. At 7 years old, he presented with generalized weakness and balance disorders following a febrile episode. Given his brother's diagnosis, a genetic analysis was conducted, confirming the presence of the same pathogenic variant within *PDHA1* gene (E1alpha, c.262C>T). His alanine levels were increased in blood, while lactate levels were normal in urine, with slightly elevated pyruvate levels (Table 1). Brain MRI revealed a slight high T2 signal in the globi pallidi (Figure 1D). Treatment consisted of thiamine and riboflavin supplementation, along with a ketogenic diet. As the boy experienced learning difficulties, he was enrolled in a specialized education program.

Patient #5 was a 23-year-old woman, born at term to unrelated parents. She was hospitalized at the age of two due to speech loss and general weakness following a febrile illness. Guillain Barré syndrome was suspected based on her clinical presentation. Subsequently, the patient developed intermittent stiffness in her lower limbs leading to balance disorders, which were particularly exacerbated by factors like cold weather, walking, and sustained effort. Her neurological examination at 8 years old revealed absent deep tendon reflexes and bilateral tremors. Brain MRI showed bilateral high T2 signals in the globi pallidi (Figure 1E). The CSF lactate levels were increased (Table 1). Though a mitochondrial disease was initially suspected, the mitochondrial respiratory chain analysis on liver and muscle biopsies yielded normal

TABLE 1: General information, clinical and biological features, molecular genetics, and outcome

	Patient #1 (male)	Patient #2 (male)	Patient #3 (male)	Patient #4 (male)	Patient #5 (female)
General Information					
Origin	Armenia	Belgium	Belgium	Belgium	Belgium
Age of onset	22 M	4 Y	5 Y 2 M	7 Y 3 M	2 Y 4 M
Age at diagnosis	23 M	5 Y	5 Y 2 M	7 Y 3 M	14 Y
Actual age	13 Y 3 M	7 Y 10 M	7 Y 6 M	9 Y 1 M	23 Y
Neurological features					
Triggers	-	sustained physical effort	fever	fever	fever, sustained physical effort
First symptoms	falls	ataxia, falls	ataxia, falls, weakness	weakness, ataxia	weakness, ataxia, falls
Early development	nl	motor delay	speech delay	speech delay	nl
Ataxia	paroxysmal	paroxysmal	+	paroxysmal	paroxysmal
Deep tendon reflexes	absent	absent	absent	absent	absent
Dystonia	-	paroxysmal	-	-	paroxysmal
Endurance	nl	weak	weak	nl	weak
Hemiplegia/paresis	-	-	-	-	Paroxysmal
Brain MRI					
Cerebellar hyperintensity	-	-	-	-	+
Globus pallidus involvement	+	+	+	+	+
Biochemical features					
Blood					
Lactic acid (0.4 -1.8mmol/L)	7.9	2.8	3.2	ND	1.58
Pyruvate (0.03-0.10mmol/L)	0.55	0.2	ND	ND	0,19
Lactic acid/pyruvate (<15)	14,4	14.2	ND	ND	/
Alanine (144-314µmol/L)	1120	644	954	326	622
Proline (53-201µmol/L)	367	364	349	160	318
CSF					
Lactic acid (1.1-1.7mmol/L)	4.6	9.06	6.59	ND	3.2
Pyruvate	ND	0.91	0.66	ND	ND
Lactic acid/Pyruvate (<15)	ND	10	10	ND	ND
Alanine (12-34 µmol/L)	ND	92	ND	ND	43
Urines					
Lactic acid (<50mmol/mol creatine)	2546	1247	2821	<50	205
Pyruvate (<20mmol/mol creatine)	ND	151	619	33	25
Treatment					
Thiamine (B1)	+	+	+	+	+
Ketogenic Diet	limited sugar intake	modified Atkins diet	modified Atkins diet	modified Atkins diet	modified Atkins diet
Outcome					
Motor skills	Normal	Weak endurance	Weak endurance	Normal	Normal
Relapse	-	+	+	-	+
Rehabilitation	-	Physiotherapy	Speech therapy, Physiotherapy	Speech therapy, Physiotherapy	Physiotherapy
Education	Regular school	Regular school	Specialized school	Specialized school	Non-university graduate education

Y: years; M: months; NI: normal; ND: not done; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid

results. At 9 years old, she experienced further balance issues and generalized weakness. Brain MRI demonstrated a large cerebellar lesion in addition to known lesions in the globi pallidi (Figure 1F). Thiamine and riboflavin treatment was initiated as was physical therapy. By the age of 13 years, metabolic investigations revealed elevated alanine levels in blood, in association with high lactate and pyruvate levels in urine (Table 1). Genetic analysis identified a heterozygous pathogenic variant NM_000284.4(*PDHA1*):c787C>G, p.(Arg263Gly) in the E1alpha subunit. A ketogenic diet was implemented but discontinued after 4 years. While the patient continued to experience intermittent muscle cramps, she was able to pursue a non-university graduate course.

Discussion

PDHc deficiency exhibits a heterogeneous presentation manifesting across a spectrum of clinical phenotypes. One such phenotype is the childhood intermittent-relapsing or milder later-onset form with acute and transient episodes. We have described the findings from five patients whose initial symptoms first appeared between the age of 22 months and 7 years and 3 months of age, triggered by fever or prolonged physical effort. Neurological manifestations mainly comprised ataxia, falls, generalized weakness, and absent deep tendon reflexes (Table 1).

In all patients, the brain MRI displayed high T2 signals of the internal part of the globi pallidi. Several inborn metabolism errors can induce basal ganglion lesions (9). Globi pallidi involvement has been linked with respiratory chain disorders, mitochondrial short-chain enoyl-CoA hydratase 1 deficiency (ECHS1D), cerebrotendinous xanthomatosis, methylmalonic aciduria, succinic semialdehyde dehydrogenase deficiency, urea cycle disorders, and metal storage disorders, such as Wilson disease, hypermanganesemia, and certain neurodegeneration forms with cerebral iron accumulation (NBIA), due to mutations in genes like WD repeat domain 45 *(WDR45)*, pantothenate kinase 2 *(PANK2)* and phospholipase A2 group VI *(PLA2G6)*.

All patients exhibited elevated lactate levels in blood or CSF when analyses were done. Additionally, four of the five patients displayed increased urinary lactate levels. The lactate/pyruvate ratios, which were examined in either CSF or plasma in three of the patients, were indicative for a PDHc deficiency. Other biological indicators consisted of increased alanine and proline levels (Table 1). Outside of acute episodes, the analyses performed in patients #4 and #5 were likely normal. PDHc deficiencies induce conversion of pyruvate into alanine and lactate rather than into acetyl-coA, the latter being essential for complete carbohydrate oxidation via the Krebs cycle. An increase in plasma proline is observed given the inhibition of proline oxidase, the first enzyme in the proline degradation pathway, in context of acquired and genetic lactic acidosis. The primary laboratory test for detecting PDHc deficiency involves measuring lactate and pyruvate levels in both blood and CSF. It is crucial to analyse lactate level in CSF in cases where Guillain Barré syndrome or acute ataxia is suspected without a clear diagnosis. Additionally, quantitative analysis of urinary organic acids and amino acids in both blood and CSF may facilitate the diagnosis.

The clinical diagnosis was confirmed by molecular genetic analysis, revealing a pathogenic variant in the E1α subunit of the *PDHA1* gene in all five patients. Three of them were found to be hemizygous for the pathogenic variant NM_000284.4*(PDHA1)*:c.262C>T, p.(Arg88Cys). The other alterations included a heterozygous pathogenic variant NM_000284.4*(PDHA1)*:c.214C>T, p.(Arg72Cys) and a heterozygous NM_000284.4(*PDHA1)*:c787C>G, p.(Arg263Gly). Notably, all variants identified in our patients were previously published in the literature.

Patient management relied on implementing a ketogenic diet, which effectively alleviated symptoms. In addition, vitamins, mainly thiamine and riboflavin, were prescribed. These vitamins are given to enhance the mitochondrial function (10). The effect of thiamine has been reported in some patients with PDH deficiency, with a reduction in blood lactate and apparent clinical improvement (9). The role of riboflavin is less reported and may be questionable. The ketogenic diet reduced the symptoms of all patients, with relapses in patient #2 due to a reduced diet compliance and in patient #5 following diet cessation. Oxidation of fatty acids and ketone bodies like acetoacetate and 3-hydroxybutyrate provided alternative acetyl-CoA sources. This diet has been associated with favourable outcomes in some patients, as manifested by a better prognosis (9,11). Their evolution was characterized by participation in regular education programs and in a special program for two patients, with or without paramedical support, such as speech therapy and physiotherapy.

In conclusion, we have herein presented five patients with pyruvate dehydrogenase deficiency exhibiting a childhood intermittent-relapsing or milder later-onset form characterized by acute and transient episodes of weakness and ataxia. Symptoms were intermittent and related to triggers, such as fever and sustained effort. A predominant biological indicator consisted of increased CSF lactate levels. Brain MRI showed high T2 signals in the globi pallidi. Molecular genetic analyses identified pathogenic variants in the *PDHA1* gene. Treatment with ketogenic diet led to symptom reduction. As aforementioned, sampling and imaging must be performed during acute episodes in order to avoid false negatives and delay management (5).

Conflict of interest. The authors have no conflict of interest to declare that are relevant to the content of this article

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Human Herpesvirus 6 (HHV-6) in the Cerebrospinal Fluid of a Newborn: Active Infection or Chromosomal Integration?

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Keywords
Human herpes virus-6 ; iciHHV-6 ; neonatal sepsis.

Abstract
This article describes a case of congenital human herpesvirus-6 (HHV-6) infection in a five-day-old infant initially suspected of having meningoencephalitis. Despite positive detection of HHV-6 in cerebrospinal fluid, subsequent evaluation suggested vertical transmission of integrated virus rather than acute infection. High viral loads in cerebral spinal fluid, maternal blood, and neonatal blood supported this hypothesis. Normal neurodevelopmental evaluations during the first year of life further supported the suspicion of integrated HHV-6. This case highlights the importance of differentiating active HHV-6 infection from integrated virus and advocates whole blood quantitative PCR testing to avoid unnecessary antiviral treatment in immunocompetent infants.

Introduction

Human Herpes Virus-6 (HHV-6) is a member of the Herpesviridae family. It usually causes an asymptomatic infection or a benign childhood disease named "roseola" in young children. Serious infections more commonly affect immunocompromised patients (1). After primary infection it remains latent and may reactivate later. But the HHV-6 complete genome can also be integrated into a human chromosome in somatic cells or even in germline cells (2).

Congenital HHV-6 infection can result from transplacental transmission during a primary infection or a reinfection or more commonly from vertical transmission of inherited chromosomally integrated HHV-6 (iciHHV-6) (3-5). iciHHV-6 carriers have at least one copy of the HHV-6 genome in every nucleated cell and can therefore transmit it in a mendelian way (6). The prevalence of iciHHV-6 is 0.2 to 2.5% in the general population (3, 4).

With the increased use of multiplex molecular diagnostic panels, HHV-6 can be more easily identified in cerebrospinal fluid (CSF). Understanding the clinical significance of this finding is essential to avoid unnecessary investigations or treatments.

We report a case of congenital HHV-6 infection in a newborn admitted with a suspected meningoencephalitis.

Case report

A five-day-old male newborn was admitted to our neonatal intensive care unit (NICU) for fever (maximum temperature, 38.4°C) and irritability. His heart and respiratory rates were 137 and 30 bpm respectively, his saturation was 96%, and his blood pressure was 96/70 mmHg. He had a bulging fontanel and a mottled skin. The rest of the clinical examination was unremarkable.

Pregnancy was uneventful except for an episode of *Chlamydia trachomatis* infection at 12 weeks of gestation, which was successfully treated with azithromycin. The infant was born vaginally at 38 weeks of gestational age. He had an Apgar score of 9/10/10. There were no signs of chorioamnionitis or risk factors for early onset sepsis (no maternal GBS colonization, clear amniotic fluid and rupture of membranes 4 hours prior to delivery).

On admission, he had a full sepsis workup and broad intravenous antibiotic therapy (amoxicillin, amikacin, cefotaxime). Blood tests showed a normal white blood cell count (10,530 cells/mm³; 51.2% neutrophils) and no C-reactive protein (CRP) elevation (0.6 mg/L - normal value < 5 mg/L). Cerebrospinal fluid (CSF) analysis showed a slightly elevated protein concentration (1.63 g/L; normal value <1 g/L) and white blood cell count (29 cells/mm³; normal value for age is 20-22 cells/mm³) but the lumbar puncture was traumatic (131 red blood cells/mm³). CSF glucose level was 28.3 mg/dL but concomitant glycemia was unknown. CSF multiplex polymerase chain reaction (PCR) assay (BioFire FilmArray Meningitis/Encephalitis panel) performed on CSF was positive for HHV-6 only.

Blood and CSF cultures were negative at 48 hours. Treatment with intravenous ganciclovir (6 mg/kg q12h) was started on day 5 of life due to persistent irritability and lack of a clear explanation. Antibiotics were discontinued on day 7 of life.

A brain ultrasound and a brain magnetic resonance imaging on day 10 of life showed a grade II left lateral ventricular and intraventricular sub-ependymal hemorrhage. However, the correlation between

such images, our patient's irritability, and the HHV-6 encephalitis and/or iciHHV-6 remains inconclusive. There were no other central nervous system abnormalities. An electroencephalogram on day 10 of life and auditory, visual and somatosensory evoked potentials on day 12 of life were normal. The added value of such evoked potentials is debatable. However, the daily clinical evolution of this patient was a concern, and we tend to lower the threshold for such assessment in all our patients with neurological signs. The patient recovered rapidly and remained afebrile after admission to the NICU. Intravenous ganciclovir was switched to oral valganciclovir (15 mg/kg q12h) on day 10 of life. The patient was discharged on day 13 and the treatment was discontinued after 3 weeks.

The etiological workup was completed with quantitative HHV-6 PCRs on day 7 of life (AltoStar HHV6 PCR kit). They revealed very high viral loads in CSF (106,000 copies/mL) and in maternal and neonatal whole blood samples (6,105,270 copies/mL and 4,021,580 copies/mL, respectively). This suggested an iciHHV-6 rather than an acute primary infection.

Follow-up during the first year of life was unremarkable. At 12 months of age, neurodevelopmental assessments (Amiel-Tison and Gosselin; Bailey Scales of Infant and Toddler Development-III) were normal.

Discussion

Herein we report a case of congenital HHV-6 infection in a 5-day-old infant initially suspected of meningoencephalitis. PCR performed on CSF and whole blood samples did not confirm this diagnosis but rather suggested a vertical transmission of integrated virus.

The multiplex PCR meningoencephalitis (M/E) panel can detect 6 bacteria, 7 viruses, and 1 yeast in CSF in about 1 hour and is therefore increasingly used (7). Interpretation of a positive result for HHV-6 should be made with caution, remembering that it could reflect acute infection, latency, reactivation, or asymptomatic chromosomal integration (5, 7). HHV-6 DNA can be recovered from CSF of iciHHV-6 carriers even though there is no viral replication. Indeed, every nucleated cell contains at least one copy of HHV-6 genome (normal CSF containing up to five nucleated cells/µL) (2). Viral load on whole blood can help distinguish an infection from integrated DNA (2). An HHV-6 viral load greater than 1 x 10^6 copies/mL on whole blood is described as strongly suggestive of an iciHHV-6 (1-4).In our case CSF quantitative HHV-6 PCR showed 106.000 copies/mL, which exceeds 1 viral copy/CSF leukocyte. Moreover, HHV-6 PCR on whole blood sample largely exceeded 1 x 106 copies/LI. HHV-6 PCR analysis of hair and nails could have provided a definitive answer but is not readily available. This test is not mandatory to confirm the diagnosis as quantitative whole blood PCR testing provides a high level of certainty regarding a case of iciHHV-6 (2, 5). The very high viral load in the maternal whole blood sample supports our suspicion of a vertical transmission from an iciHHV-6 carrier parent.

Previous studies have suggested that replicating virus could arise from integrated genome, leading to reactivation, particularly in immunocompromised patients (2, 6). In immunocompetent adults and young children, acute neurological symptoms ranging from seizures to fulminant brain edema have been associated with HHV-6 DNA in the CSF (1, 8). Yet, this should be interpreted with caution due to the unclear role of HHV-6 and the difficult distinction between primary infection and integration (1). Occurring in approximately 1% of births, congenital infection usually remains asymptomatic (4). However, adverse neurodevelopmental outcomes at 12 months of age have been reported in a prospective cohort study of 57 patients (9). Congenital HHV-6 infection was associated with lower Bayle Scale scores at 12 months of age (mean difference: 4.3 (95%CI: 0.4-8.1) compared to infants without congenital HHV-6 infection.

Given these conflicting data, the scarcity of guidelines and the immaturity of the neonatal immune response, we opted for an antiviral treatment with ganciclovir. HHV-6 is susceptible to ganciclovir, foscarnet, and cidofovir. Each of them has possible toxicities such as bone marrow suppression and renal insufficiency for the major ones. However, randomized control trials are lacking and data on efficacy are limited. As such, antiviral treatment is usually not recommended for immunocompetent patients (10). However, a neonate might be considered as an immunocompromised patient, justifying the initial therapeutic choice. No adverse effects have been observed in our patient.

Our understanding is that no definite conclusion can be drawn regarding the etiology of our patient's clinical manifestations. Our working hypothesis is that it is probably related to benign grade II subependymal hemorrhage without concurrent infection. However, as mentioned above, due to uncertainties regarding diagnostic, prognostic and therapeutic options in HHV-6 encephalitis, our multidisciplinary medical consensus was to continue the ganciclovir treatment as precautionary measure. The risk/benefit of such medication, including both long-term neurological development after HHV-6 exposure and antiviral side effects need further clarifications.

Conclusions

This case report highlights the need to further understand the clinical implications of iciHHV-6 and to improve the rapid differentiation between integrated virus and active primary infection. When HHV-6 is recovered from CSF, clinicians should consider the possibility of iciHHV-6, particularly in immunocompetent children without documented encephalitis. In challenging clinical situations, quantitative PCR should be performed on whole blood samples.

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Impact of RSV Immunization with Nirsevimab (Beyfortus®) on RSV-Related Hospitalizations of Pediatric Patients in a Regional Hospital in Belgium

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Keywords
Respiratory syncytial virus ; immunization ; nirsevimab ; hospitalization ; child .

Abstract
Respiratory infections caused by respiratory syncytial virus (RSV) are a significant cause of hospitalizations in young children. This study evaluates the impact of immunization with nirsevimab (Beyfortus®) on RSV-related hospitalizations and severity of outcome at Jessa Hospital, Belgium. Comparing pre- and post-immunization periods, data from the 2024–2025 RSV season show a reduction in hospitalizations, with a notable 78.7% decrease in infants under 6 months comparing to last season. Immunization resulted in reduced oxygen and Optiflow® need. Findings suggest that nirsevimab decreases hospitalizations and severity of RSV infections.

Introduction

Respiratory infections caused by respiratory syncytial virus (RSV) are the leading cause of hospitalization among young pediatric patients (1). Recently, immunizations have been developed to protect children against RSV. Nirsevimab (Beyfortus®) is a monoclonal antibody targeting the RSV F protein, developed to reduce severe RSV infection (e.g., hospitalization) in young infants. Since June 2024, this immunization is reimbursed in Belgium. Starting from October 2024, parents have been able to immunize their children against RSV, with reimbursement for all infants born after April 1, 2024, and all neonates born after October 1, 2024.

Objectives

This study aims to evaluate the impact of RSV immunization with nirsevimab on the number of hospitalizations, severity of outcome, and mortality due to RSV in children.

Methods

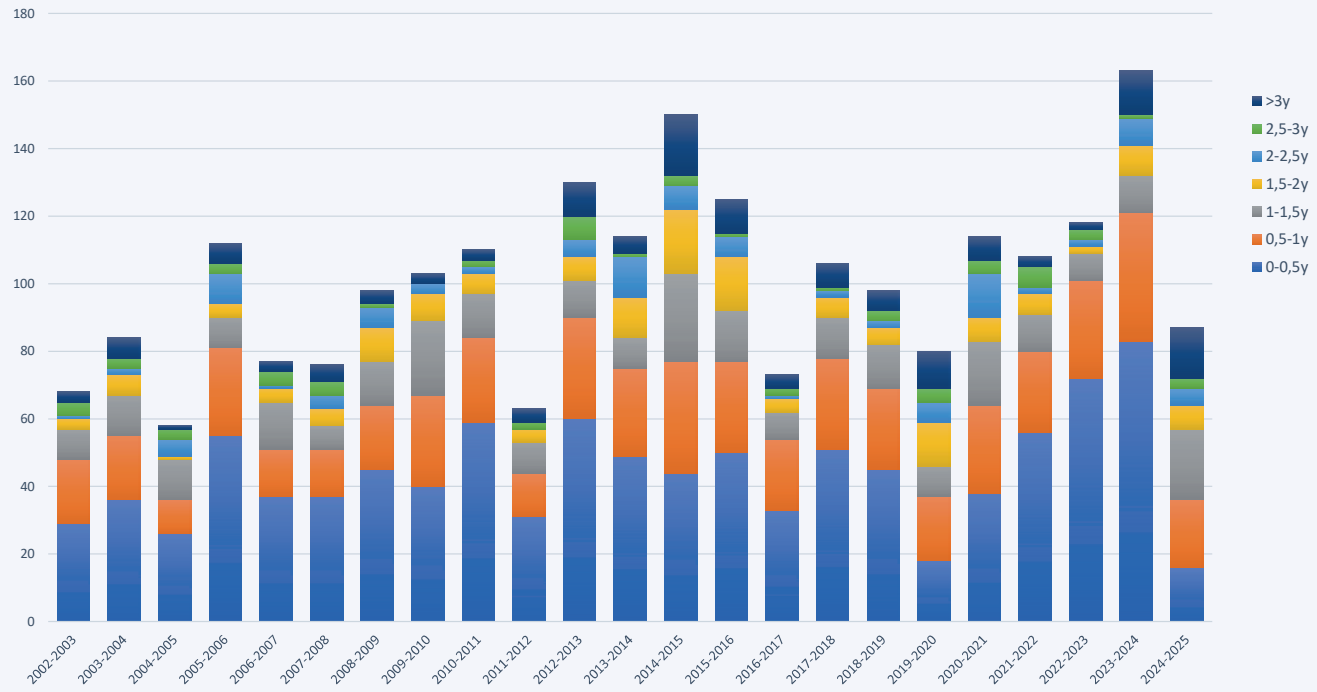
This retrospective study was conducted at Jessa Hospital in Hasselt, Belgium. Since 2002, epidemiological data on all RSV hospitalizations have been collected within this hospital. We included data up to February 2025 to compare the number of hospitalizations, morbidity and mortality rates during RSV seasons before and after the initiation of immunization with nirsevimab (Beyfortus®). All hospitalizations within the hospital were evaluated. In children with a positive RSV nasal swab, the reasons for admission, age, immunization status, and characteristics of the hospitalization (including oxygen need, Optiflow® need, intubation, or transfer to PICU (Pediatric Intensive Care Unit) were analyzed.

Results

During the RSV season 2024-2025 (October 2024 – February 2025), a total of 882 children were hospitalized at Jessa Hospital, of which 87 patients had a positive RSV nasal swab (9.8%). Among these 87 patients, 16 were younger than 6 months (18.39%), 20 were between 6 months and 1 year (22.98%), 28 were between 1 year and 2 years old (32.18%) and 23 were over 2 years old (26.43%). Out of the 87 hospitalized children, 21 were eligible for reimbursed RSV immunization, of which 8 children were effectively immunized with nirsevimab (9,19% of total RSV hospitalizations and 38.09% of children eligible for reimbursement).

Since 2002, in Jessa Hospital, we systematically collected data on the number of hospitalizations due to RSV infection. This extensive data collection allows us to compare the number of patients admitted monthly over a span of 23 years. Over the years, the average number of RSV hospitalizations has been 101,91 per season (58-160). With 87 this year, the number of hospitalizations is below the average, with a reduction of 14,63%. Looking at hospitalizations categorized by age, we see that in the 2024-2025 RSV season, 16 of the 87 children hospitalized were younger than 6 months (18.39%). This is a significant reduction in the number of children of this age compared to the 2023-2024 RSV season when 75 out of 160 patients (46.88%) and the 2022-2023 season, when 74 out of 122 patients (60.66%) were in this age group. We see a significant reduction of 78.7% of hospitalizations from children

FIGURE: RSV hospitalizations at Jessa hospital from 2002 to 2025, categorized by age.



younger than 6 months old compared to the 2023-2024 season. Figure 1 shows the number of RSV admissions by age from 2002 to 2025.

Looking at morbidity, we see that children who were immunized were significantly less ill. There was less need for oxygen therapy (3 children with nirsevimab versus 26 without immunization), less need for Optiflow® (1 child with nirsevimab versus 7 without immunization) and less need for transfer to the PICU (0 children with nirsevimab versus 2 without immunization). During this RSV season, no children were intubated, and no children died.

Conclusion

Our findings suggest that immunization with nirsevimab has a favorable impact and are consistent with real-life surveys in other countries (2). Primarily reducing the number of hospitalizations due to RSV, especially in young children less than 6 months old. Secondarily reducing the severity of RSV infections in immunized children. Larger national data analysis needs to confirm these local figures. The long-term effects and influence on RSV transmission require further investigation in upcoming seasons. Additionally, we question the potential impact of less stringent reimbursement criteria and the immunization of more children. Given the high cost of the treatment, the economic feasibility of reimbursement must also be considered. Further research and follow-up are needed to fully understand the overall impact of nirsevimab immunization.

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

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In an electronic book: Authors. Title of chapter. In: Editor AA, Editor BB, Editors. Title of book [Internet]. Place of publication: Publisher, year of publication. [cited YYYYMonDD]. Page or chapter number/. Available from: URL DOI (if available) .

Example:

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

In an electronic book: Halpen-Felsher BL, Morrell HE. Preventing and reducing tobacco use. In: Berlan ED, Bravender T, editors. Adolescent medicine today: a guide to caring for the adolescent patient [Internet]. Singapore: World Scientific Publishing Co.; 2012 [cited 2012 Nov 3]. Chapter 18. Available from: http://www.worldscientific.com/ doi/pdf/10.1142/9789814324496_0018.

More examples of other published, particularly material from internet, and unpublished material can be found in the quick Vancouver reference guide (https://guides.lib.monash.edu/ld.php?content_id=48260115) or on the website of the U.S. National Library of Medicine: https://www.nlm.nih.gov/bsd/uniform_requirements.html.

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

Disclosure of potential conflicts of interest: The corresponding author must disclose any conflicts of interest on behalf of all co-authors. Co-author enquiries should be recorded and retained by the corresponding author. The disclosure declaration must be written in a separate paragraph after the conclusion and before the references.

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

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

After acceptance

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

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

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

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Reviewers must provide a fair, honest, and unbiased assessment of the strengths and weaknesses of the manuscript. Reviewers should offer thoughtful suggestions to help authors enhance the quality of the manuscript, doing so in a respectful, constructive, and actionable manner.

Comments to the authors will be passed in full to authors. The reviewers can also provide additional confidential comments to the editors, which will not be passed to the authors.

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Instructions for invited editors

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

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

The tasks of the invited editors are:

- To make choices of topics
- To invite authors
- To supervise the manuscripts in terms of content
- To protect the expected deadline for publication
- To write an editorial introducing the chapter

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

ESSENTIELE GEGEVENS - NAAM VAN HET GENEESMIDDEL Enterol 250 mg poeder voor orale suspensie - Enterol 250 mg harde capsules. *Saccharomyces boulardii* CNCM I-745 - KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING Enterol 250 mg poeder voor orale suspensie: Elk zakje poeder voor orale suspensie bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 109 levensvatbare cellen op het ogenblik van de fabricage en 1 x 109 gelyofiliseerde levensvatbare cellen op de vervaldatum). Enterol 250 mg harde capsules: Elke harde capsule bevat 250 mg gelyofiliseerde *Saccharomyces boulardii* CNCM I-745 (hetzij minstens 6 x 109 levensvatbare cellen op het ogenblik van de fabricage en 1 x 109 gelyofiliseerde levensvatbare cellen op de vervaldatum). Hulpstof(fen) met bekend effect (zie rubriek 4.4 van de SKP): Enterol 250 mg poeder voor orale suspensie: fructose, lactosemonohydraat, sorbitol. Enterol 250 mg harde capsules: lactosemonohydraat. Voor de volledige lijst van hulpstoffen, zie rubriek 6.1 van de SKP. FARMACEUTISCHE VORM Enterol 250 mg poeder voor orale suspensie: Poeder voor orale suspensie. Enterol 250 mg harde capsules: Harde capsule. KLINISCHE GEGEVENS **Therapeutische indicaties** • Preventie van diarree bij behandeling met breedspectrumantibiotica van patiënten voorbeschikt tot het ontwikkelen van diarree door Clostridium difficile of hervallen in een diarree veroorzaakt door Clostridium difficile. • Adjuverende behandeling naast orale rehydratie van acute diarree bij kinderen tot 12 jaar. **Dosering en wijze van toediening** Dosering: Volwassenen: 2 tot 4 harde capsules of 2 tot 4 zakjes per dag, in 2 innames. Pediatrische patiënten Kinderen: 2 harde capsules of 2 zakjes per dag, in 2 innames. Wijze van toediening: • Harde capsules: de harde capsules met wat water inslikken. • Zakjes: het poeder mengen in een glas water. Te nemen voorzorgen voorafgaand aan gebruik of toediening van het geneesmiddel Vanwege een risico op besmetting via de lucht, mogen zakjes of capsules nooit worden opengemaakt in patiëntenkamers. Beroepsbeoefenaren in de gezondheidszorg moeten tijdens het hanteren en het toedienen van probiotica handschoenen dragen, waarna de handschoenen onmiddellijk moeten worden weggegooid en de handen moeten worden gewassen (zie rubriek 4.4 van de SKP). Duur van de behandeling: Preventie van een nieuwe episode of recidief van diarree door Clostridium difficile: 4 weken. Behandeling van diarree als aanvulling op orale rehydratie bij het kind: 1 week. Contra-indicaties: • Overgevoeligheid voor de werkzame stof of voor één van de in rubriek 6.1 van de SKP. •Patiënten met een centrale veneuze katheter, patiënten in kritieke toestand of immuungecompromitteerde patiënten, vanwege een risico op fungemie (zie rubriek 4.4 van de SKP).• Allergie voor gisten, vooral *Saccharomyces boulardii* CNCM I-745. Bijwerkingen: De bijwerkingen worden hieronder geklasseerd per orgaansysteem en volgens de frequentie. Die laatste wordt als volgt gedefinieerd: 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). Systeemorgaanklasse Frequentie Infecties en parasitaire aandoeningen Zeer zelden : fungemie in patiënten met een centraal veneuze katheter en in patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP), mycose door *Saccharomyces boulardii* CNCM I-745 Frequentie niet bekend : sepsis bij patiënten in kritieke toestand of immuungecompromitteerde patiënten (zie rubriek 4.4 van de SKP) Immuunsysteemaandoeningen Zeer zelden : anafylactische shock Bloedvataandoeningen Zeer zelden : anafylactische shock Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Zeer zelden : dyspneu Maagdarmstelselaandoeningen Zeer zelden : verstopping, epigastralgie, abdominaal meteorisme (epigastralgie en abdominaal meteorisme werden waargenomen in klinische studies) Huid- en onderhuidaandoeningen Zeer zelden : jeuk, exantheem, Quincke-oedeem Algemene aandoeningen en toedieningsplaatsstoornissen Zeer zelden : dorst Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijk 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 - Galileelaan 5/03 - B-1210 Brussel - Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN BIOCODEX Benelux NV/SA - Humaniteitslaan 292, 1190 Brussel - België Tel : 0032(0)23704790 NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN Enterol 250 mg poeder voor orale suspensie: BE 269026 Enterol 250 mg harde capsules in glazen flesje: BE 269035 Enterol 250 mg harde capsules in blisterverpakking: BE 397896 AFLEVERINGSWIJZE Vrije aflevering DATUM VAN HERZIENING VAN DE TEKST Herziening: 04/2023 - Goedkeuring: 09/2023

10	10,32 €	10	10,32 €	10	10,32 €
20	19,36 €	20	19,36 €	20	19,36 €
50	38,96 €				

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