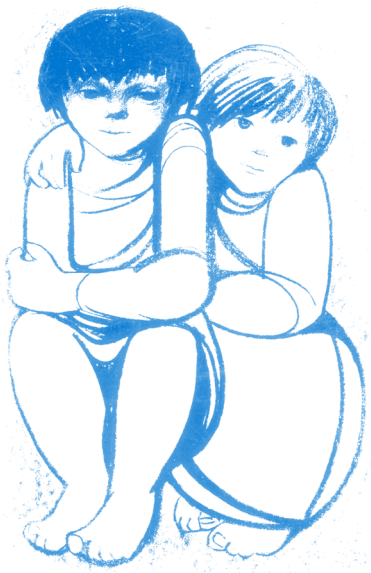
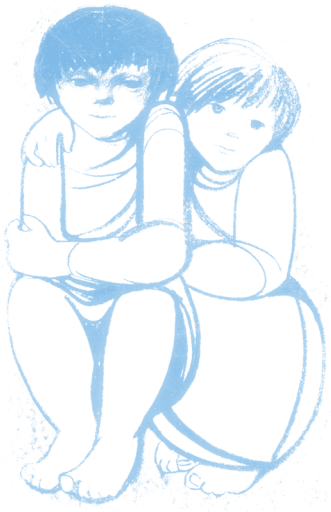
BIRTH AND GROWTH MEDICAL JOURNAL

35|1





BIRTH AND GROWTH MEDICAL JOURNAL

Year | 2026 **Volume |** 35 **Number |** 1

BIRTH AND GROWTH MEDICAL JOURNAL

Year | 2026 **Volume |** 35 **Number |** 1

Quarterly Publication, indexed and summarized by

Catálogo LATINDEX EMBASE / Excerpta Médica
REDIB
Repositório Científico da ULS de Santo António
SARC – Serviço de Alojamento de Revistas Científicas
SciELO

Graphic execution and layout

Andrea Buschbeck

Editing

Auditaccount

E-ISSN

2183-9417

Legal deposit

4346/91

Publisher

Department of Education and Training
Unidade Local de Saúde de Santo António
Largo do Prof. Abel Salazar – 4099-001 Porto
Phone: (+351) 222 077 500
Mobile Phone: (+351) 915 676 516
nascerecrescer@chporto.min-saude.pt

BIRTH AND GROWTH MEDICAL JOURNAL PRIZE
BEST ORIGINAL PAPER

The Birth and Growth Medical Journal has established an annual award for the Best Original Paper published in the journal. This initiative aims to promote and encourage high-quality research in the fields of maternal-fetal, neonatal, and pediatric health.

PROCEDURES

1. The prize is awarded to the author(s) of the best Original Article published in the Birth and Growth Medical Journal between January and December of the respective year.

2. An author may compete with more than one Original Article.

3. In the evaluation of Original Articles, the Selection Jury will consider the following criteria:
   a. Relevance and originality;
   b. Clarity and relevance of objectives, and consistency with methodology;
   c. Adequacy of methods/procedures and statistical analysis;
   d. Clear and concise presentation of results;
   e. Critical and well-reasoned discussion;
   f. Contribution to knowledge advancement, applicability, and potential impact of the findings.

4. If the article has multiple authors, the prize will be awarded to the first author.

5. No formal application is required for consideration.

6. The evaluation and classification process will be conducted by a Selection Jury appointed by the journal's Editors

7. The Jury's decisions are final and cannot be appealed.

8. The award will be announced in issue 4 of the Birth and Growth Medical Journal.

9. Any cases not covered by these regulations will be decided by the Editorial Board of the Birth and Growth Medical Journal.

summary

number35.vol.1

summary

number35.vol.1

Birth and Growth Medical Journal
2026;35(1):6-8. doi:10.25753/BirthGrowthMJ.v35.i1.47529

EDITORIAL

Art and Medicine – A Travel Throughout History and Mystery

Teresa Costa[1]

The close relationship between medicine and the arts is indisputable, whether literature, poetry, music, painting, or other forms of artistic expression. Although art and science are traditionally approached as separate fields, there is a critical interdisciplinarity between them. The creative and emotional character of art can, in some way, complement the objectivity of science, allowing for a more holistic and human vision of medicine. The practice of medicine is actually an art. Hippocrates (460 BC - 377 BC), the father of medicine reportedly said, "Wherever the art of Medicine is loved, there is also a love of Humanity." On the other hand, the father of modern medicine, William Osler, in 1919, reminds us that scientific evidence is important, but not a substitute for a humanistic approach. He said in his last speech, "The practice of medicine is a calling in which your heart will be exercised equally with your head". We must consider his message and try to reconcile the two perspectives.[1]

The relationship between art and medicine is deeply rooted in human history, reflecting a shared concern with the understanding, representation, and care of the human body. From prehistoric anatomical depictions to contemporary medical illustration, art and medicine have evolved in parallel, often influencing one another. In ancient societies, art served not only aesthetic purposes but also educational functions related to health and disease. Sculptures and paintings often reflected empirical observations of the human body, long before the formal establishment of medical science.

The first records of anatomical study drawings date back to the 3rd century BC, produced by Herophilus and Erasistratus, two Greek physicians from the Greek School of Medicine in Alexandria. Later, in the 2nd century AD, the Roman physician Galen dedicated himself to the study and representation of anatomy, contributing to the knowledge in the medical field.[2]

On the other hand, ancient Egypt represents one of the earliest and most sophisticated examples of the integration of art and medicine, as it is documented in papyri such as the *Edwin Smith Papyrus* and the *Ebers Papyrus*. Wall paintings, reliefs, and sculptures frequently depicted physicians, medical instruments, and healing rituals. The precision observed in Egyptian artistic works, particularly in representations of the human body, suggests a strong anatomical awareness from practices such as mummification. Amulets, statues, and symbolic imagery were believed to possess healing powers and were commonly used in medical contexts.[3]

During the Renaissance, artists such as da Vinci and Michelangelo conducted anatomical dissections to enhance the realism of their work, producing drawings that also advanced medical understanding. Medical illustration became a formal discipline, bridging scientific accuracy and artistic skill. Andreas Vesalius published *De Humani Corporis Fabrica* (1543), a highly detailed human body compendium, often in allegorical poses.[2] The dissections performed by da Vinci allowed him to represent the body with a rigor and precision unprecedented for his time, anticipating knowledge that would only be formally established centuries later. He represented individual parts, bones, muscles and internal organs, as well as the mechanics behind them. His drawings contributed greatly to the advances of science and medicine and in medical education.[4,5]

Countless artists have represented the human body and disease, a paradigm of this being *The Anatomy Lesson of Dr. Nicolaes Tulp* (1632) by Rembrandt. In this work, the scientific gaze replaces that of artistic representation, but Rembrandt, by giving the corpse an almost spiritual glow, leads us to reflect on the extent to which the clinical gaze, by objectifying the body, erases the person who once inhabited it. Medicine teaches us to see the body, but it is art that teaches us to see it with a soul.

1. Associated Editor of Nascer e Crescer – Birth and Growth Medical Journal, Unidade Local de Saúde de Santo António. 4099-001 Porto, Portugal. teresa.v.c.tavares@gmail.com
2. Pediatric Nephrology Department, Centro Materno-Infantil do Norte, Unidade Local de Saúde de Santo António. 4050-651 Porto Portugal.

In human history, artists have played a crucial role in documenting, and interpreting, medical experiences related to women's and children's health. In *The fetus in the womb* (1511), da Vinci establishes a delicate analogy between human biology and botany, exploring similarities between the development of seeds and human embryos. *The Sick Child* (1885–1886) a work by Edvard Munch portrays a terminally ill child attended by a caregiver, inspired by Munch's memories of his sister's death from tuberculosis. The painting captures the emotional reality of childhood illness, yet it remains deeply connected to medical history. In *Inheritance* (1897-99), Munch depicts a mother holding a child affected by congenital syphilis. This work confronts the biological and emotional consequences of infectious disease transmission from mother to child, while also addressing stigma and suffering. The *Henry Ford Hospital* (1932) it's an autobiographical painting that represents Frida Kahlo's experience of miscarriage and hospitalization. The work explicitly engages with medical imagery, transforming personal reproductive loss into a powerful visual symbol of women's health and emotional trauma. In *The Broken Column* (1944) and *Without Hope* (1945), Kahlo describe her experience of physical and psychological suffering by creating a visual stark and highly personal symbolic language of chronic pain, in a surrealist and deeply emotional representation.

In 2020, the American Association of Medical Colleges (AAMC) asserted that the practice of medicine requires a grounding in humanistic values, principles, and skills. They published *The Fundamental Role of Arts and Humanities in Medical Education*, which resulted from a review of more than 700 works that evaluated the effect of including art in medical education programs. The report found that through active engagement with diverse forms of artistic expression, students can strengthen skills such as observation and visual perception, humility, tolerance, personal reflection, teamwork, empathy, and communication.[6] The humanities and any type of creative work offer students the possibility of cultivating their creative dimension, which may favor the development of critical reflection on ambiguity, uncertainty, and the social aspects of clinical practice and improve abilities related to moral and ethical aspects.[7,8] Additionally, by stimulating visual thinking strategies and encouraging more in-depth visual analysis, art can facilitate the development of clinical skills and improve patient observation.[8,9] In Portugal, medical schools have also begun to integrate art into medical education, notably the Faculty of Medicine and the School of Medicine and Biomedical Sciences of the University of Porto.

According to the 2019 World Health Organization Report, based on more than 3000 studies worldwide, art has a positive impact on treatment outcomes, preventive care, promotion of healthy behaviors, and even the well-being of health care providers. Art therapy is a clinical modality with medically proven benefits, namely in neurological and psychiatric disorders and to support mental health. Art therapy programs may include music, dance, writing, drama, poetry, painting, and other artistic expressions that promote healing. In this sense art can be medicine.[10]

In the era of precision medicine, new technologies, and artificial intelligence, it is easy to forget that the medical act is also an art and that, above all, it continues to be a human encounter. The physician, like the artist, must interpret the invisible, the signs, the silences. For both, the essence is the same: descriptive observation, understanding, empathy, and sensitivity.

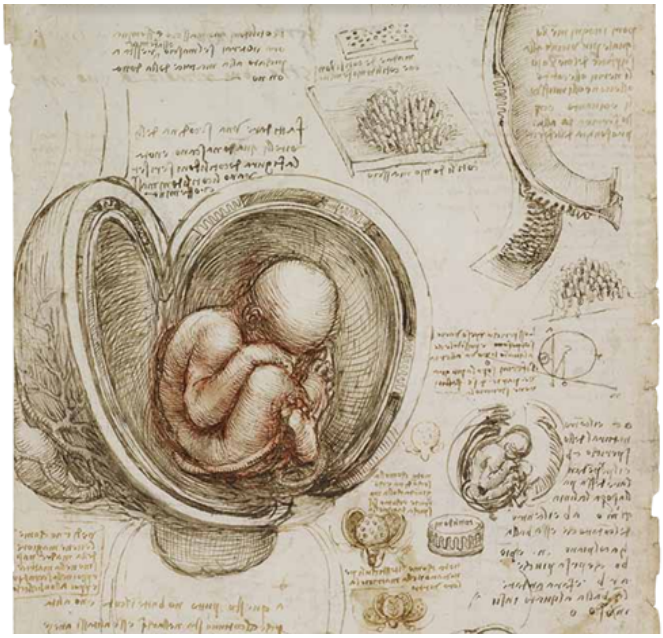


Figure 1 - *The fetus in the womb* (Leonardo da Vinci, c.1511); ROYAL COLLECTION TRUST.

REFERENCES

1. Osler W. The old humanities and the new science: the presidential address delivered before the Classical Association at Oxford, May, 1919. Br Med J 1919; 2(3053):1–7. pmid:20769536
2. Ghosh SK. Human cadaveric dissection: a historical account from ancient Greece to the modern era. Anatomy & Cell Biology. 2015; 48 (3): 153–169.
3. Davies NM. *Health and Medicine in Ancient Egypt*. 2001. London: British Museum Press.
4. Clayton M. Medicine: Leonardo's anatomy years. Nature. 2012; 484: 314–316.
5. Clayton M, Philo R. *Leonardo da Vinci: Anatomist.* 2012. Royal Collection Publications. London.
6. Howley L, Gaufberg E, King B. The Fundamental Role of the Arts and Humanities in Medical Education. Washington, DC: AAMC; 2020.

7. Haven A, Pragt E, van Luijk SJ, Dolmans D, van Mook W. Creativity: a viable and valuable competency in medicine. A qualitative exploratory study. Medical Teacher. 2022; 44 (10): 1158-1164
8. Gilbert M, Leanne Picketts, MEd, Anna MacLeod, PhD, and Wendy A. Stewart, MD, MMEd, PhD. How an Arts-Based Clinical Skills Set Can Be Assessed During OSCEs. AMA Journal of Ethics. July 2022, Volume 24, Number 7: E556-562
9. Cerqueira AR, Ana Sofia Alves, Matilde Monteiro-Soares, Dabney Hailey, Domingos Loureiro, Sofia Baptista. Visual Thinking Strategies in medical education: a systematic review. BMC Medical Education. 2023; 23:536.
10. Fancourt D, Finn S. What is the evidence on the role of the arts in improving health and well-being? A scoping review. Health Evidence Network Synthesis Report. World Health Organization. 2019.

ORIGINAL ARTICLES

Teachers' Knowledge of Attention-Deficit/Hyperactivity Disorder in a Portuguese County

Maria Inês Fernandes[1], Susana Correia de Oliveira[1], Patrícia Sousa[1], Francisca Dias de Freitas[1], Sofia Vasconcelos[1], Maria Isolina Aguiar[1], Bárbara Pereira[1]

ABSTRACT

Introduction and Goals: Attention-Deficit/Hyperactivity Disorder (ADHD) is a common, although often overdiagnosed, disorder among children and adolescents that negatively affects their lives. Teachers play a key role in the academic success of these students, highlighting the importance of dispelling misconceptions in order to improve school performance. The goal of this study is to evaluate teachers' knowledge about this disorder.

Methods: We performed a cross-sectional analytical study using an online, anonymous questionnaire administered to teachers from schools in a Portuguese city. The level of knowledge of each teacher was obtained through the median of the sum of the correct answers.

Results: A total of 131 teachers responded to the survey. Most participants reported having no prior knowledge of ADHD. The median score was 55% (IQR 47-64%). Higher scores were observed among younger teachers and those with less teaching experience (≤45 years old and ≤20 years of teaching; p <0,001 and p = 0,008 respectively), as well as among teachers working in private schools (p <0,001) and those who had received prior training in ADHD (p = 0,002).

Discussion and Conclusion: Although teachers play a vital role in recognition and management of ADHD, our findings indicate that their overall knowledge of the disorder is limited, with a median score of 55%. Several misconceptions were identified throughout the study that should be addressed. Training in this area is crucial to enhance teachers' understanding of ADHD and to improve the educational strategies provided to students with this condition.

Keywords: Attention-Deficit Hyperactivity Disorder; questionnaire; school performance; teachers

1. Pediatrics Department, Hospital Senhora da Oliveira, Unidade Local de Saúde do Alto Ave. 4835-044 Guimarães, Portugal.
maria-ines-coelho@hotmail.com; susanaoliveira@ulsaave.min-saude.pt; patriciasousa@ulsaave.min-saude.pt; mariafranciscafreitas@ulsaave.min-saude.pt; sofiavasconcelos@ulsaave.min-saude.pt; mariaaguiar@ulsaave.min-saude.pt; barbarapereira@ulsaave.min-saude.pt

INTRODUCTION

The American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines Attention-Deficit Hyperactivity Disorder (ADHD) in children as the presence of six or more symptoms in either the inattentive or hyperactive and impulsive domains, or both for more than six months and that occur in two or more settings (for instance, at school and at home).[1]

ADHD is a common (although perhaps over diagnosed) and highly heritable psychiatric disorder, with a prevalence of over 5% within children and adolescents that negatively affects the lives of patients and their parents, being responsible for a significant burden.[2,3] Although knowledge about ADHD over the last few years has improved, assessment and treatment continue to present a challenge, especially when there are wrong beliefs of teachers, who should play a key role in the early detection of signs of behavioral difficulties and in managing them.[3] Some studies have shown a significant correlation between teachers´ knowledge of ADHD and their confidence in effectively teaching children with ADHD, fostering an inclusive classroom, and managing their behavior, ultimately contributing to the academic success of those students.[4-7] Even though psychotropic medication may improve classroom behavior, pharmacologic treatment is rarely enough to overcome the many challenges seen in school setting.[4,8] Teachers' misbeliefs and lack of knowledge about ADHD has been documented in numerous studies both national and international and negatively affects children's school performance.[9,10]

Our main goal is to assess teachers' knowledge of ADHD in our county and identify factors associated with greater knowledge to help promote it.

METHODS

An investigation protocol was elaborated to define the objectives and methodology of the study. The protocol was later approved by the Ethics Committee of the hospital where the study took place.

This was a cross-sectional analytical study conducted in a secondary hospital in the north of Portugal, from the 1st to the 30th of April 2023.

Data collection was carried out using the application of a self-completion questionnaire, disseminated–via email to a convenience sample, answered online and anonymously through Google Forms. The target population of the study consisted of primary and lower secondary school teachers from the county/city of Guimarães.

Guimarães is a medium-sized city located in the northern region of Portugal and combines cultural heritage with a developing socioeconomic profile. The city has a diverse educational landscape, including both public and private schools, and serves urban as well as semi-rural populations. Socioeconomically, Guimarães reflects a mix of middle-income households alongside pockets of social vulnerability, particularly in suburban and rural areas. The local economy is based on traditional industries such as textiles and manufacturing, alongside growing sectors like education and tourism. Educational resources vary across schools, and access to training on neurodevelopmental conditions may differ accordingly. Cultural attitudes toward mental health and special education are gradually evolving but may still be influenced by stigma or lack of information in certain communities. These contextual factors are relevant when interpreting findings related to teachers' knowledge and perceptions of ADHD in this region.

The survey consisted of two parts. The first part aimed to evaluate the socio-professional characteristics of the teachers to characterize participants, namely in terms of gender, age, length of teacher service, teaching cycles, basic training, teaching methods, school where he/she teaches, prior ADHD focused training interventions (including face-to-face workshops and online learning programs) and self-assessment of knowledge on the subject. The second part included a test with 47 items, adapted from the Knowledge of Attention Deficit Disorder (KADDS), constructed by Sciutto and Feldhamer, and of Knowledge Regarding ADHD, constructed by Kos translated and adapted to Portuguese by Alvarez, still pending validation for the Portuguese language.[5,10,11]

This second part of the study addresses three distinct areas of knowledge, divided by Alvarez into "Symptoms/Diagnosis", "Intervention (Treatment/Strategies)" and "Associated Characteristics".[10] The correct answers were scored with one point and incorrect answers were scored zero, with a maximum of 47 points. The level of knowledge of each teacher about ADHD was obtained through the median of the sum of correct answers, which was later transformed in a percentage.

The data obtained was coded and recorded in a computer database (Excel®) and subsequently analyzed using the SPSS v.26.0 program. The Mann-Whitney test was used to compare independent samples and the Chi-Square test was applied when comparing two categorical variables, with p-value <0.05 considered statistically significant.

RESULTS

We received 131 responses to the survey, with a predominance of female teachers (n=104, 79.4%). The median age of teachers was 49 years (IQR 44-56 years) and most have been teaching for 21 years or more (n=95, 72.5%). Of these 131 teachers, only 29.0% (n=38) were 45 years old or younger. Most teachers had a university degree (n=78, 59.5%), while 32 teachers held a master´s degree or a doctorate. Most teachers taught elementary school students (n=65, 49.6%) in public schools (n=98, 74.8%). We found that most teachers reported not having prior training on ADHD (n=98, 74.8%), with this

being more common among those teaching in public schools (22.4 vs. 33.3%, p = 0.155).

In self-assessment of knowledge, the majority of teachers rated their knowledge of ADHD as reasonable (3 out of 5).

Median score on the survey was 55% (IQR 47-64%) and it was slightly higher in females and in teachers with higher academic training (**Table 1**).

We found that teachers with 21 or more years of service had lower ratings than teachers with less experience (median 53%, IQR 45-64% vs. 62%, IQR 55-66%; p-value 0.008). Similarly, younger teachers (≤ 45 years old) had better ratings in the survey compared to teachers aged >45 years (median 62%, IQR 56.5-66% vs. 53%, IQR 45-61%; p-value <0.001).

Teachers who taught in private schools had better ratings than those in public schools (median 62%, IQR 55-66% vs. 53%, IQR 45-62%; p-value <0.001; **Table 2**). The same is true for teachers with prior ADHD training compared to those without training (median 66%, IQR 57-62% vs. 53%, IQR 45-60%; p-value <0.001; **Table 2**).

We verified that teachers with fewer years of service (20 years or less) had more training on ADHD compared to teachers with more teaching experience (44.4% vs. 17.9%; p-value 0.002; **Table 2**).

We found that teachers who rated their knowledge as bad (2), fair (3) or good (4) showed the following median survey scores of 36% (IQR 19-49%), 55% (IQR 46.5- 62%) and 63% (IQR 53-70%), respectively.

We also verified that several questions had frequently incorrect or unknown answers (**Table 3**).

Regarding the three categories of knowledge assessed in the survey (**Table 4**), teachers revealed greater knowledge in the area of "Symptoms/Diagnosis" (median of correct answers of 66.7%), followed by "Intervention (Treatment/Strategies)" (median of correct answers of 53.9%) and, finally, "Associated Characteristics" (median of correct answers of 43.8%), p-value <0.001.

Table 1 - Descriptive analysis of gender, age, length of service, type of teaching, academic qualifications, prior training and self-assessment, as well as the median score and interquartile range (IQR).

		n	%	Score (median, %)	IQR (%)	p-value
Gender	Male	27	20.6	55	40-62	0.372
	Female	104	79.4	57	47.5-64	
Age	≤ 45 y.o.	38	29.0	62	56.5-66	<0.001
	>45 y.o.	93	71.0	53	45-61	
Length of service	≤ 20 y.	36	27.5	62	55-66	0.008
	> 20 y.	95	72.5	53	45-64	
Type of teaching	Public	98	74.8	53	45-62	<0.001
	Private	33	25.2	62	55-66	
Academic training	Bachelor	5	3.8	55	47-64	0.403
	Degree	78	59.6			
	Post-Graduate	3	2.3			
	Post-Graduate with specialization	13	9.9			
	Masters	29	22.1	57	49.5-69	
	Doctorate	3	2.3			
Prior training in ADHD	Yes	33	25.2	66	57-72	<0.001

ADHD: Attention-Deficit Hyperactivity Disorder; IQR: interquartile range; y.o.: years old.

Table 2 - Association between prior training, type of teaching and length of service.

		Prior training in ADHD		No prior training		p-value
		n	%	n	%	
Type of Teaching	Public	22	22.4	76	77.6	0.155
	Private	11	33.3	22	66.7	
Length of service	≤ 20 y.	16	44.4	20	55.6	0.002
	> 20 y.	17	17.9	78	82.1	

ADHD: Attention-Deficit Hyperactivity Disorder; y.: years.

Table 3 - Mostly incorrect or unknown questions

Question	**Original question**	**Number of correct answers (n)**	**Percentage of correct answers (%)**
1.	Most estimates suggest that ADHD occurs in approximately 15% of school age children.	18	13.7
4.	ADHD children are typically more compliant with their fathers than with their mothers.	6	4.6
6.	ADHD is more common in the 1st degree biological relatives (i.e. mother, father) of children with ADHD than in the general population	22	16.8
23.	Reducing dietary intake of sugar or food additives is generally effective in reducing the symptoms of ADHD.	23	17.6
25.	Stimulant drugs are the most common type of drug used to treat children with ADHD.	29	22.1
27.	ADHD children generally experience more problems in novel situations than in familiar situations.	25	19.1
34	Behavioral/Psychological interventions for children with ADHD focus primarily on the child's problems with inattention.	35	26.7
35.	Electroconvulsive Therapy (i.e. shock treatment) has been found to be an effective treatment for severe cases of ADHD	29	22.1
38.	A child who is not overactive, but fails to pay attention, may have ADHD	39	29.8
42.	Children with ADHD always need a quiet environment to concentrate	28	21.4
46.	The cause of ADHD is unknown	39	29.8

ADHD: Attention-Deficit Hyperactivity Disorder.

Table 4 - Questionnaire questions divided by areas of knowledge and their Median score and IQR.

	Number of questions	Questions	Score (median %)	IQR (%)	p-value
Symptoms/ Diagnosis	18	3, 5, 7, 9, 11, 14, 16, 17, 19, 21, 24, 26, 28, 39, 32, 36, 38, 39	66.7	61.1-77.8	<0.001
Intervention (Treatment/ Strategies)	13	2, 8, 10, 12, 15, 18, 20, 23, 25, 34, 35, 44, 45	53.9	38.5-61.5	
Associated Characteristics	16	1, 4, 6, 13, 22, 27, 29, 31, 33, 37, 40, 41, 42, 43, 46, 47	43.8	31.3-56.3	

IQR: interquartile range.

DISCUSSION

The primary goal of this study was to evaluate the teacher's knowledge of ADHD, identify factors associated with greater knowledge and identify misconceptions to develop strategies for improving educational approaches. Despite the crucial role teachers play in early recognition, referral and management of ADHD, the overall median score was only 55%.

One of the limitations of this study lies in the fact that the instruments used as reference — the Knowledge of Attention Deficit Disorders Scale (KADDS) by Sciutto and Feldhammer, and the ADHD Knowledge Questionnaire by Kos, adapted into Portuguese by Álvarez — have not yet been fully validated for the Portuguese population. Although the present questionnaire was developed based on these tools and adapted to the cultural and educational context of the study sample, the absence of formally validated versions in Portuguese may affect the reliability and generalizability of the findings. Future studies should focus on the formal validation and standardization of such instruments for use in Portuguese-speaking contexts, thereby enhancing the methodological robustness of research in this area.

The selection of the KADDS and Kos's questionnaire as references in constructing the present instrument is supported by their widespread use, solid theoretical foundations, and acceptable psychometric properties reported in international studies.[12-14] Both scales have demonstrated content and construct validity in assessing teacher knowledge of ADHD and are specifically designed to address the types of misconceptions commonly observed in educational contexts.[15]

Furthermore, despite the absence of formally validated instruments in Portuguese, the development of the questionnaire for this study ensured the inclusion of key conceptual domains such as etiology, symptoms, diagnosis, treatment, and educational strategies related to ADHD. Moreover, the adaptation of the instrument to the Portuguese educational and cultural context contributed to its ecological validity, making the results more relevant and applicable to the realities experienced by teachers in this setting. The study also offers an original contribution by providing empirical data on teachers' knowledge about ADHD in a Portuguese city, an area with limited research to date. As such, these findings may serve as a valuable baseline for the development of future validation studies, as well as for the design of targeted training programs and awareness campaigns within the educational system.

Through this study, we identified several misconceptions in teachers' knowledge of ADHD (**Table 3**), as we found a high number of questions with a significant proportion of incorrect responses, meaning many teachers actually believe the incorrect information to be valid. While these findings are consistent with other national and international studies, we verified a higher overall score when comparing to these studies - 55% vs. 42,5% in a study in Spain, 42,6% in a study in South Africa, 47,8% in a study in the United States and 46,9% and 46,8% in Portuguese national studies.[5,9,10,14,16] As these studies are over nine years-old, the improvement in our results may reflect the increased awareness of the importance of this issue over the years. Nevertheless, there remains a significant knowledge gap of ADHD, with considerable room for improvement.

We also verified that teachers had a greater knowledge of ADHD symptoms and diagnosis compared to other areas, which aligns with findings from previous studies.[5,9,10,12,17] However, most misconceptions were related to associated characteristics, as seen in other papers.[14,18,19] Despite years of increased study and awareness, the same lack of knowledge in these areas is still observed. It is consensual that school-based interventions are essential to manage this disease, as teachers play a crucial role in managing and minimizing ADHD learning difficulties.[3,4,10,20] Stigma and misconceptions surrounding this illness negatively impact the adequacy of therapeutic interventions.[4] Therefore, efforts must focus on addressing these gaps, with enhanced training needed, particularly in the areas of treatment and associated characteristics.

Prior training in ADHD was found to increase knowledge

in several studies which was compatible with our results.[9,10,14,21] However, even though we verified we had a better score than other studies, the percentage of teachers who received prior training was similar.[10,20] The low percentage of teachers with prior training, coupled with a significantly better score than those who didn't have prior training emphasizes the importance of training in order to improve students' outcomes.

On the other hand, similar to some other studies, we verified younger teachers and teachers with less experience scored better in the questionnaire.[9,10,14] These results were not compatible with other studies.[5,21] Although younger teachers theoretically had less teaching experience, they are expected to have more training in ADHD, as it is an increasingly recognized topic.[5,10,21] While older teachers had little contact with the subject during their training process, younger teachers encountered it earlier, helping them overcome the stigma and misbeliefs mostly found in the older age groups. We found that younger teachers had significantly more training than older groups, which can help validate our theory.

We also verified teachers in private schools had more training than those who teach in public schools which may be explained by the greater emphasis private schools place on the quality of education and, consequently, on teacher training. This suggests private schools may better recognize the importance of ADHD related topics. One possible explanation for this finding lies in several structural and contextual advantages typically associated with these institutions. First, private schools often maintain smaller class sizes, allowing teachers to provide more individualized attention to students and to more readily identify behavioral or learning difficulties, including those associated with ADHD.[22-24] In addition, private schools may have more financial resources to invest in ongoing professional development, including specialized training on neurodevelopmental disorders.[25,26] Such paid training opportunities can enhance teachers' understanding of ADHD and equip them with effective classroom strategies. Furthermore, private school environments are frequently shaped by strong parental expectations for high academic achievement.[22] This pressure may motivate schools to adopt early identification and intervention practices, including a greater focus on ADHD, to ensure that all students perform to the best of their potential. Together, these factors may contribute to a more proactive and informed approach to ADHD within private school settings.

However, we did not find a significant relationship between having a higher academic degree and greater knowledge of ADHD, highlighting the need for sustained ADHD teacher training interventions, rather than prioritizing academic qualifications alone.[16]

CONCLUSION

Teacher training in ADHD is insufficient in our study population. As demonstrated by our findings, such training is essential and should be incorporated into teachers' academic curricula. Through our study we identified which areas intervention was warranted, providing guidance for the development of training programs and educational initiatives tailored to this population. Specifically identifying and refuting misconceptions may be a useful strategy, as suggested previously in another study[12]. Although we found better results than some other studies, we still believe improvement is needed.

Teachers play a central role in supporting students with ADHD, and demystifying some wrong beliefs is crucial to strengthening their understanding of the condition. This, in turn, will enable them to create a supportive classroom environment and develop effective strategies for addressing problem behaviors.

AUTHORSHIP

Maria Inês Fernandes – Conceptualization; Data Curation; Formal Analysis; Writing – original draft; Writing – review & editing

Susana Correia de Oliveira - Conceptualization; Data Curation; Formal Analysis; Writing – original draft; Writing – review & editing

Patrícia Sousa - Writing – review & editing

Francisca Dias de Freitas – Writing – review & editing

Sofia Vasconcelos - Writing – review & editing

Maria Isolina Aguiar – Supervision; Writing – review & editing

Bárbara Pereira - Supervision; Project administration; Writing – review & editing

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): American Psychiatric Association; 2013.
2. Posner J, Polanczyk GV, Sonuga-Barke EJS. Attention-deficit hyperactivity disorder. Lancet. 2020;395:450-62. doi: https://doi.org/10.1016/S0140-6736(19)33004-1.
3. Drechsler R, Brem S, Brandeis D, Grünblatt E, Berger G, Walitza S. ADHD: current concepts and treatments in children and adolescents. Neuropediatrics. 2020 Oct;51(5):315-35. doi: https://doi.org/10.1055/s-0040-1701658.
4. Moore D, Richardson M, Gwernan-Jones R, Thompson-Coon J, Ukoumunne O, Rogers M, et al. Non-pharmacological interventions for ADHD in school settings: an overarching synthesis of systematic reviews. J Atten Disord. 2019 Feb;23(3):220-33. doi: https://doi.org/10.1177/1087054715573994.
5. Sciutto MJ, Terjesen MD, Frank B. Teachers' knowledge

and misperceptions of attention-deficit/hyperactivity disorder. Psychol Sch. 2000;37(2):115-22. doi: https://doi.org/10.1002/(SICI)1520-6807(200003)37:2<115::AID-PITS3>3.0.CO;2-5.
6. Bussing R, Gary FA, Leon CE, Garvan CW, Reid R. General classroom teachers' information and perceptions of attention-deficit/hyperactivity disorder. Behav Disord. 2002;27(4):327-39.
7. Ohan JL, Cormier N, Hepp SL, Visser TAW, Strain MC. Does knowledge about attention-deficit/hyperactivity disorder impact teachers' reported behaviours and perceptions? Sch Psychol Q. 2008;23(3):436-49. doi: https://doi.org/10.1037/1045-3830.23.3.436.
8. DuPaul GJ, Gormley MJ, Laracy SD. School-based interventions for elementary school students with ADHD. Child Adolesc Psychiatr Clin N Am. 2014 Oct;23(4):687-97. doi: https://doi.org/10.1016/j.chc.2014.05.003.
9. Valido RT. Perturbação de Hiperatividade com Défice de Atenção: conhecimentos e estratégias pedagógicas dos docentes do 1.º ciclo do ensino básico [thesis]. Lisboa: Instituto Superior de Educação e Ciências; 2016.
10. Alvarez A. Conhecimento, atitudes e crenças dos professores sobre a Perturbação de Hiperatividade com Défice de Atenção (PHDA) [thesis]. Lisboa: Escola Superior de Educação João de Deus; 2014.
11. Kos J. Primary school teachers' knowledge, attitudes and behaviours toward children with attention-deficit/hyperactivity disorder [thesis]. Melbourne: University of Melbourne; 2004.
12. Blotnicky-Gallant P, Martin C, McGonnell M, Corkum P. Nova Scotia teachers' ADHD knowledge, beliefs, and classroom management practices. Can J Sch Psychol. 2015;30(1):3-21. doi: https://doi.org/10.1177/0829573514542225.
13. Lopez-Lopez A, Lopez-Lafuente A, Eiris-Punal J, Mulas F, Cardo E. A study of primary school teachers' knowledge of attention deficit hyperactivity disorder. Rev Neurol. 2018;66(S01):S121-6.
14. Jarque S, Tárraga R, Miranda A. Teachers' knowledge, misconceptions, and lacks concerning attention deficit hyperactivity disorder. Psicothema. 2007;19(4):585-90.
15. Kos JM, Richdale AL, Jackson MS. Knowledge about attention-deficit/hyperactivity disorder: a comparison of in-service and preservice teachers. Psychol Sch. 2004;41(5):517-26. doi: https://doi.org/10.1002/pits.10172.
16. Perold M, Louw C, Kleynhans S. Primary school teachers' knowledge and misperceptions of attention-deficit/hyperactivity disorder (ADHD). S Afr J Educ. 2010;30(3):457-73. doi: https://doi.org/10.15700/saje.v30n3a364.
17. Alkahtani K. Teachers' knowledge and misconceptions of attention-deficit/hyperactivity disorder. Psychology. 2013;4(12):963-69. doi:10.4236/psych.2013.412139.
18. Swanson K, Guerra J, Brown M. Teacher knowledge of attention-deficit/hyperactivity disorder among middle school students in South Texas. Mid-Level Educ Res. 2012;36(3):1-7. doi: https://doi.org/10.1080/19404476.2012.11462096.
19. Dilaimi A. New Zealand primary school teachers' knowledge and perceptions of attention-deficit/hyperactivity disorder (ADHD) [thesis]. Albany (NZ): Massey University; 2013.
20. Oliveira LC. A Perturbação de Hiperatividade/Défice de Atenção (PHDA): do conhecimento dos professores às práticas educativas no 1.º ciclo do ensino básico [thesis]. Braga: Universidade do Minho; 2017.
21. Sciutto MJ, Terjesen M, Michalová Z, Schmiedeler S, Antonopoulou K, Shaker NZ, *et al*. Cross-national comparisons of teachers' knowledge and misconceptions of ADHD. Int Perspect Psychol. 2015;5(1):34-50. doi: https://doi.org/10.1037/ipp0000045.
22. Kern A, Amod Z, Seabi J, Vorster A. South African foundation phase teachers' perceptions of ADHD at private and public schools. Int J Environ Res Public Health. 2015;12(3):3042-59. doi: https://doi.org/10.3390/ijerph120303042.
23. Finn JD, Gerber SB, Boyd-Zaharias J. Small classes in the early grades, academic achievement, and graduating from high school. J Educ Psychol. 2005;97(2):214-23.
24. Dynarski S, Hyman J, Schanzenbach DW. Experimental evidence on the effect of childhood investments on post-secondary attainment and degree completion. J Policy Anal Manage. 2013;32(4):692-717.
25. Aguiar AP, Kieling RR, Costa AC, Chardosim N, Dorneles BV, Almeida MR, *et al*. Increasing teachers' knowledge about ADHD and learning disorders: an investigation on the role of a psychoeducational intervention. J Atten Disord. 2014 Nov;18(8):691-8. doi: https://doi.org/10.1177/1087054712453171.
26. Ward T, Bristow LB, Cooper P, Arnold H, Smith J, Jones L, *et al*. The effects of ADHD teacher training programs on teachers and pupils: a systematic review and meta-analysis. Front Educ. 2022;7:872948. doi: https://doi.org/10.3389/feduc.2022.872948.

CORRESPONDENCE TO

Maria Inês Fernandes
Pediatrics Department
Hospital Senhora da Oliveira
Unidade Local de Saúde do Alto Ave
R. dos Cutileiros 114, Creixomil
4835-044 Guimarães
Email: maria-ines-coelho@hotmail.com

Received for publication: 17.04.2025
Accepted in revised form: 30.12.2025

Birth and Growth Medical Journal
2026;35(1):16-19. doi:10.25753/BirthGrowthMJ.v35.i1.38445

ORIGINAL ARTICLES

Rotavirus vaccination efficacy in a real-world scenario: a 10-year experience from a secondary hospital in Portugal

João Nogueira Oliveira[1], Inês Vivas[2], Inês Pais Cunha[3], Sofia Branco[3], Inês Mazeda[3], Maria José Dinis[3], Gracinda Nogueira Oliveira[3]

ABSTRACT

Introduction: Although recommended, the rotavirus vaccine is not included in Portugal's routine immunization schedule. This provides an opportunity to evaluate its real-world effectiveness. This study aimed to assess the impact of rotavirus vaccination on reducing infection rates and hospitalizations."

Material and Methods: This retrospective study examined all pediatric patients who underwent viral antigen stool testing at our hospital between 2012 and 2022. Patients were classified as either rotavirus-positive or rotavirus-negative. Data on vaccination status and hospitalization were obtained from electronic medical records. A control group, matched in size to the rotavirus-positive group, was randomly selected from the rotavirus-negative patients (N= 126)."

Results: Out of 886 viral antigen stool tests performed, 126 (14.2%) returned positive for rotavirus. The median age in the rotavirus-positive group was 16 months (IQR 6–24), compared to 12 months (IQR 4–29) in the negative group. A total of 81 patients (32%) were vaccinated, with a vaccination rate of 15% (N=19) in the positive group and 49% in the negative group (n=62).

Vaccination was linked to a lower number of infections (OR 0.18–0.34) and a reduced hospitalization rate (OR 0.23–0.43). The vaccine's efficacy beyond the first year of life was also assessed.

Conclusions: This study demonstrates the effectiveness of the rotavirus vaccination in preventing infection and hospitalization at our hospital. These results highlight the importance of considering the inclusion of the rotavirus vaccine in the routine immunization schedule.

Keywords: gastroenteritis; rotavirus; vaccine

1. Department of Pediatrics, Centro Materno-infantil do Norte, Unidade Local de Saúde do Santo António. 4050-651 Porto, Portugal. joaooliveirauni@gmail.com
2. Department of Pediatrics, Unidade Local de Saúde da Póvoa de Varzim / Vila do Conde. 4490-421 Póvoa de Varzim, Portugal. inesvivas26@gmail.com; sofiavarelabranco@gmail.com; ines.mazeda@gmail.com; majodinis@gmail.com; gracenoliveira@gmail.com
3. Department of Pediatrics, Unidade Local de Saúde de São João. 4050-651 Porto, Portugal. 4200-319 Porto, Portugal. inespaiscunha@gmail.com

INTRODUCTION

Before the introduction of vaccines, rotavirus was the leading cause of gastroenteritis, responsible for over two million hospitalizations and 440,000 deaths each year worldwide. The introduction of vaccines transformed this situation, resulting in a significant decrease in hospitalization and death rates with recent studies estimating that global use of rotavirus vaccines could prevent about 37% of rotavirus deaths in children under 5.[1] As a result, the vaccine has been included in the national immunization programs of nearly 90% of the countries participating in the Global Alliance for Vaccines and Immunization.[2]

Despite recommendations from WHO and the vaccination commission of the Portuguese Society of Pediatrics, the rotavirus vaccine has not been incorporated into Portugal's routine immunization schedule for all children.[3] As a result, there is variability in vaccination rates across different regions.

Assessing the real-world vaccine effectiveness (VE) is essential for confirming its benefits and aiding policymakers in developing immunization strategies. While the earliest VE studies were conducted in countries with low child mortality rates, the introduction of the vaccine in high child mortality settings has enabled VE studies in those regions as well.

Although the vaccines demonstrated effectiveness across all settings, recent evidence indicates substantially higher efficacy in countries with lower child mortality. Estimated vaccine efficacy ranged from 69.6% to 94.3% in low-mortality settings and from 18.6% to 85.3% in high-mortality regions.[4] Some studies have also shown a reduction in vaccine effectiveness (VE) during the second year of life, underscoring the importance of expanding vaccine protection beyond the first year. However, further studies have revealed that this decline is primarily limited to children who are HIV-exposed or chronically malnourished.[5]

Considering all the variables that influence vaccine effectiveness (VE), the aim of this study was to assess the vaccination rate in our pediatric population and evaluate its efficacy in reducing infection and hospitalization rates. Additionally, we aimed to determine whether there is a decline in VE beyond the first year of life.

MATERIAL AND METHODS

A retrospective study was conducted, including all pediatric patients who underwent viral antigen stool test performed using enzyme-linked immunosorbent assay (ELISA) at our hospital from 2012 to 2022. These tests were performed either in the emergency department or during a hospital admission. Antigen test results were obtained with the assistance of the pathology and microbiology departments. Patients were then categorized in two groups (either positive or negative for rotavirus). From the pool of patients that had negative stool test (n= 760) a stratified random sampling with the same number of patients as the positive group was performed, ensuring proportional representation by age and gender. Electronic medical records were used to access information on vaccination status, hospitalizations and length of stay. Exclusion criteria were inability to access the vaccination record and/or medical records.

Statistical analyses were conducted using IBM® SPSS® Statistics, version 29.0 (IBM Corp., Armonk, NY, USA). Chi-square tests were performed to assess the presence of statistically significant differences between groups. To assess vaccine effectiveness (VE) in children after their first year of life, we analyzed those older than 12 months in both groups (n= 136)

RESULTS

A total of 886 viral antigen stool tests were conducted, of which 126 (14.2%) tested positive for rotavirus. The percentage of male patients was the same in both groups, at 55% (n=69). The median age was 16 months (IQR 6–24) for the positive group and 12 months (IQR 4–29) for the negative group.

The vaccination rate in the analyzed population (n=252) was 32% (n=81), with the rate in the positive group decreasing to 15% (n=19) and increasing to 49% (n=62) in the negative group (**Figure 1**).

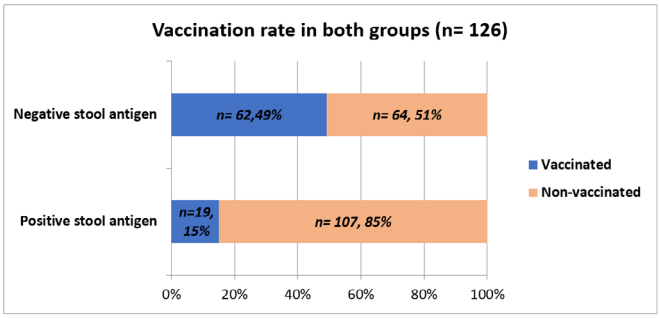


Figure 1 - Vaccination rate in both groups

When comparing vaccinated and unvaccinated individuals, vaccination was associated with a reduced risk of testing positive for the antigen (OR 0.183; 95% CI 0.101 – 0.334; p<0.0001). Among the unvaccinated patients, 63% (n=79) tested positive, compared to only 23% (n=29) of those who were vaccinated.

Hospitalization was required for 100 patients, of whom 85% (n=85) were unvaccinated (**Figure 2**). The hospitalization rate was 50% (n=85) among the unvaccinated, compared to only 19% (n=15) in the vaccinated group (**Figure 3**). Thus, vaccination was associated with a significantly lower risk of hospitalization (OR 0.230; 95% CI 0.122–0.434; p<0.0001).

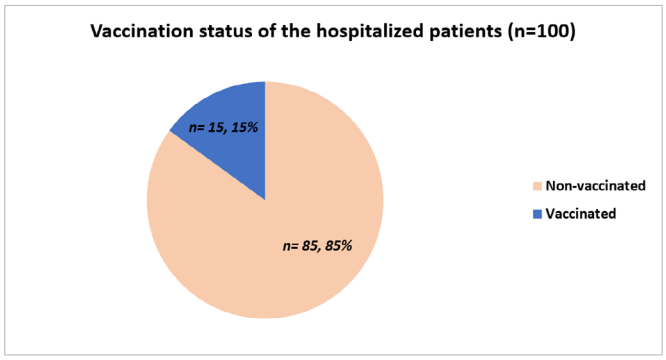


Figure 2 - Vaccination status of the hospitalized patients (n=100)

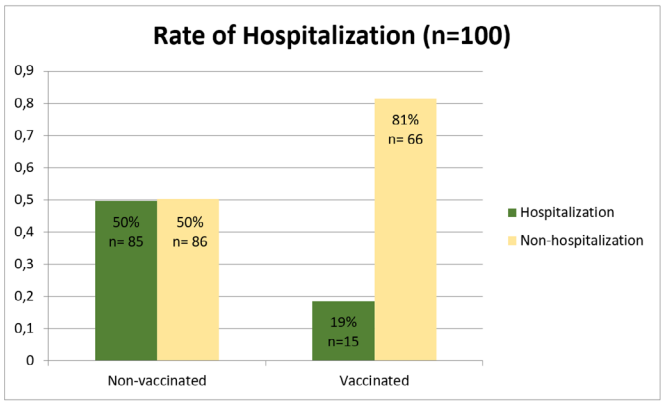


Figure 3 - Comparison of the rate of hospitalization between the non-vaccinated group (n= 171) versus the vaccinated group (n=81)

When evaluating the sub-group of patients older than 12 months (N= 136), we found a vaccination rate of 32% (n=43). From the group that was vaccinated only 20% were hospitalized versus 47% in those non-vaccinated translating a reduced likelihood of hospital admission (OR 0.182; 95% CI 0.074–0.451; p<0.0001). Vaccination was also associated with a lower risk of infection (OR 0.130; 95% CI 0.057–0.301; p<0.0001) with only 20% of those vaccinated presenting a positive stool antigen versus 53% of those non-vaccinated.

DISCUSSION

The findings of this study provide evidence for the efficacy of the rotavirus vaccine in reducing both the incidence of infection and hospitalization due to rotavirus-related illnesses.

This study has several limitations that should be acknowledged. Its retrospective and single-center design limits the generalizability of the findings and introduces potential information bias due to reliance on existing medical records, which may be incomplete or inconsistent. The sample size, although spanning a ten-year period, was relatively small, which may reduce statistical power, particularly for subgroup analyses. Furthermore the high hospitalization rate observed in our sample may, in part, be explained by a selection bias inherent to clinical testing practices. In many settings, stool antigen testing for rotavirus is more likely to be performed in cases presenting with more severe symptoms, particularly those warranting hospital admission. Milder cases of acute gastroenteritis are frequently managed in outpatient settings without laboratory confirmation, leading to underrepresentation of less severe cases in our dataset. Consequently, the sample may overestimate the proportion of hospitalizations relative to the broader population of rotavirus infections.[6]

By substantially decreasing the incidence of rotavirus infection, the vaccine not only alleviates the disease burden on affected individuals but also reduces the strain on healthcare systems by lowering hospitalization rates.

In light of the findings presented in this study, it is important to highlight the relevance of extending the vaccination to the entire population. In Portugal this vaccine is currently only indicated for high-risk groups despite the recommendations of the portuguese pediatric infectious society of extending it.[7] Our results support the potential benefits of extending universal rotavirus vaccination, as they underscore the burden of disease and the likely public health impact of broader vaccine coverage.

Importantly, vaccine effectiveness (VE) was maintained even in children older than 12 months, consistent with studies indicating that a decline in effectiveness is primarily seen in malnourished or immunocompromised children.[8]

The low vaccination rate verified in our population indicates a poor adherence to non-routine immunization practices, underscoring the need to enhance vaccine access and awareness, along with incorporating the vaccine into the national immunization program.[9]

CONCLUSIONS

These results highlight the considerable public health implications of rotavirus vaccination efforts and the need for extensive vaccination initiatives. The significant decline in rotavirus infections observed in this study aligns with numerous other research findings and real-world vaccination campaigns, reinforcing the vaccine's effectiveness.

Its effectiveness combined with the low vaccination rate reinforces the importance of increasing awareness among both caregivers and healthcare practitioners and reiterates the importance of discussing its inclusion in the national immunization program.

AUTHORSHIP

João Nogueira Oliveira - Data curation; Formal analysis; Writing – original draft; Writing – review & editing
Inês Vivas – Writing – review & editing
Inês Pais Cunha – Writing – review & editing
Sofia Branco – Writing – review & editing
Inês Mazeda – Writing – review & editing
Maria José Dinis – Writing – review & editing
Gracinda Nogueira Oliveira - Conceptualization

REFERENCES

1. Clark A, Mahmud S, Debellut F, Pecenka C, Jit M, Perin J, *et al*. Estimating the global impact of rotavirus vaccines on child mortality. Int J Infect Dis. 2023;137:90–97. doi: https://doi.org/10.1016/j.ijid.2023.10.005.
2. World Health Organization. Rotavirus vaccines: WHO position paper – July 2021. Wkly Epidemiol Rec. 2021;96(28):301–320.
3. Directorate-General of Health (DGS). National vaccination program 2020: rotavirus vaccination for children belonging to risk groups. Norm No. 007/2021. Lisbon: DGS; 2021.
4. Prunas O, Asare EO, Sajewski E, Li Y, Pithawala Z, Weinberger DM, *et al*. Global estimates of rotavirus vaccine efficacy and effectiveness: a rapid review and meta-regression analysis. EClinicalMedicine. 2025;81:103122. doi: https://doi.org/10.1016/j.eclinm.2025.103122.
5. Burnett E, Parashar UD, Tate JE. Real-world effectiveness of rotavirus vaccines, 2006–19: a literature review and meta-analysis. Lancet Glob Health. 2020;8(9):e1195–e1202. doi: https://doi.org/10.1016/S2214-109X(20)30262-X.
6. Chua H, Feng S, Lewnard JA, Sullivan SG, Blyth CC, Lipsitch M, *et al*. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. Epidemiology. 2020;31(1):43–64. doi:1 https://doi.org/0.1097/EDE.0000000000001116.
7. Sociedade Portuguesa de Pediatria, Secção de Infecciologia Pediátrica. Rotavirus vaccination: recommendations. Lisbon: Sociedade Portuguesa de Pediatria; 2021. Disponível em: https://www.spp.pt/downloads/VacinacaoRotavirus_2021.pdf.
8. Clark A, van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J, *et al*. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomized controlled trials. Lancet Infect Dis. 2019;19(7):717–727. doi: https://doi.org/10.1016/S1473-3099(19)30126-4.
9. Cohen R, Martinón-Torres F, Posiuniene I, Benninghoff B, Oh KB, Poelaert D. The value of rotavirus vaccination in Europe: a call for action. Infect Dis Ther. 2023;12(1):9–29. doi: https://doi.org/10.1007/s40121-022-00697-7.

CORRESPONDENCE TO

João Nogueira Oliveira
Department of Pediatrics
Centro Materno-infantil do Norte
Unidade Local de Saúde do Santo António
Largo da Maternidade de Júlio Dinis 17
4050-651 Porto
Email: joaooliveirauni@gmail.com

Received for publication: 23.10.2024
Accepted in revised form: 02.01.2026

Birth and Growth Medical Journal
2026;35(1):20-25. doi:10.25753/BirthGrowthMJ.v35.i1.40044

REVIEW ARTICLES

Indirect Consequences of Armed Conflicts in Children

Ana Carolina Alves[1], Elsa Guimarães[1], Mariana Sousa Santos[1], Maria Manuel Zarcos[1]

ABSTRACT

Introduction: The world has witnessed an increase in armed conflicts, with more than 100 active conflicts currently spread across all continents. The conflict between Russia and Ukraine represents the largest armed conflict in Europe since World War II, while the recent escalation between Israel and Gaza has triggered an unprecedented humanitarian crisis. Children living in conflict-affected areas constitute one of the most vulnerable populations.

Objectives: The purpose of this review is to understand the indirect consequences of armed conflicts on the pediatric population and to compile the most up-to-date and relevant evidence on this subject. It aims to make health care professionals aware of the subject.

Development: A narrative review of the literature was conducted including articles published between 2017 and 2024 addressing the indirect effects of armed conflicts on children and adolescents. The reviewed literature highlights significant social consequences, including displacement, family separation, sexual violence, child abuse, and disruption of education. Public health impacts include reduced access to healthcare, increased infectious diseases, vaccination gaps, malnutrition, and environmental contamination. Additionally, neonatal, neuroendocrine, and psychological consequences with long-term implications for development and mental health are consistently reported.

Conclusions: Armed conflicts have profound and lasting indirect effects on children's health, development and well-being. Increasing awareness and preparedness among healthcare professionals is essential to ensure early identification of risk, adequate care, and appropriate long-term follow-up of war-affected and refugee children.

Keywords: armed conflict; child; children; indirect consequences; pediatric; war

1. Pediatrics Department, Unidade Local de Saúde da Região de Leiria. 2410-197 Leiria, Portugal.
anacarolinafigueiralalves@gmail.com; elsamg.04@gmail.com; marianamss.94@gmail.com; maria.zarcos@chleiria.min-saude.pt

INTRODUCTION

Armed conflicts are defined as any form of armed violence that resorts to armed forces and opposes governments, organized armed groups and/or civilians within the same or different state, regardless of intensity or cause.[1–3]

Over time, there has been a shift in the nature and scale of armed conflicts, with progressively larger affected areas and the use of more destructive weapons, leading to increasingly severe consequences, particularly for civilian populations.[3,4]

The current conflict between Russia and Ukraine, which began in February 2022, is the largest armed conflict in Europe since World War II. [5] The attack by Hamas on October 7, 2023, and Israel's response also marked a critical turning point in the ongoing conflict.[6] However, the attention and coverage provided by the media and the international community to these conflicts do not reflect the true extent of this global issue. Currently, there are over 110 active armed conflicts worldwide, spanning across all continents.[7]

Consequently, it is estimated that 246 million children (1 in 10) live in areas affected by armed conflicts, making them one of the most vulnerable groups living in war scenarios. The proportion of child deaths among civilians has increased from 9% to 23% between 2011 and 2016.[8,9] Emerging data suggests that the child mortality rate in the recent escalation of the Gaza conflict, compared to other conflicts, may be disproportionately high, with approximately 14,000 children reported dead so far.[6] Additionally, it is estimated that 20 million children worldwide are currently displaced or refugees due to armed conflicts.[10]

The consequences of these conflicts are not limited to **direct consequences** - any physical injury that may affect any organ or system, caused by any penetrating or blunt trauma, crush injuries, burns, injuries from bombings, explosions, building collapses, shootings and motor vehicle accidents in the context of armed conflict. Any consequence not previously described is considered as an **"indirect consequence"**.[1,2]

OBJECTIVES

The purpose of this research is to understand the impact of armed conflicts on children and adolescents' everyday life and their subsequent implications for their health and development. This review aims to adopt a needs-centered approach by synthesizing current evidence and providing a structured overview for physicians and healthcare professionals with little to non-existing experience in the treatment, management and follow-up care of war-affected and refugee pediatric populations.

METHODS

This study consists of a narrative review of the literature addressing the indirect consequences of armed conflicts on children and adolescents.

A literature search was conducted covering publications from 2017 to 2024. The search was performed using the PubMed/MEDLINE database. In addition, relevant reports and documents from international health and humanitarian organizations were consulted to contextualize the global burden and humanitarian impact of armed conflicts.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including *Child*, *Adolescent*, *Pediatric*, *Armed Conflict*, *War* and *Indirect Consequences*.

Eligible sources included original observational studies, narrative and systematic reviews, as well as reports and policy documents from international organizations addressing the social, public health, neonatal, neuroendocrine and psychological consequences of armed conflicts in pediatric populations. Studies focusing exclusively on adult populations, direct physical injuries only, or published outside the predefined time frame were excluded.

Following abstract screening, 88 articles were initially identified, of which 38 were selected for inclusion in the final review based on relevance to the scope of the study and contribution to understanding the indirect effects of armed conflicts on child and adolescent health and development.

SOCIAL CONSEQUENCES

Sexual Violence

Armed conflicts are intimately related to sexual violence crimes. These crimes are mostly committed against females, not only by the military forces but also by other refugees during migration or within refugee camps.[11] In contrast, in some cases, the primary abuser is part of the nuclear family.[12] A significant contributing factor is the lack of adequate parental care, often leaving children alone and unsupported.[13]

In addition to the psychological trauma, girls who are victims of sexual violence are at greater risk of sexually transmitted infections, unwanted pregnancies, gynecological or obstetric complications and infertility.[9] However, sexual violence also affects males. Adolescent boys often constitute the majority of unaccompanied minors, whether as refugees or part of military forces, making them particularly vulnerable.[9]

A 2017 study revealed that older men in Greek shelters exploit adolescent boys from Afghanistan, Syria, Iraq, Iran, and Bangladesh in exchange for money, food, clean clothes, or other basic needs.[14] In males, the consequences of sexual violence include sexually transmitted infections, incontinence, genital and rectal injuries, infertility, sexual dysfunction and partial or complete castration, along with mental health issues. These boys rarely seek help, because of the shame, fear of social stigma and criminalization in countries where same-sex relationships are illegal.[9,14]

DISPLACEMENT/MIGRATION AND FAMILY SEPARATION

Populations in conflict-affected regions are often forced to migrate internally or to another country, exposing them to risks before, during and after their journeys. Children are often forced to move without being ensured health care and basic needs.[9] Furthermore, refugees often face linguistic barriers, carry little to no medical information, lack identification documents and they are not registered in local health systems, which makes access to health care even more difficult.[15]

Many of these children are forced to travel alone, being separated from their parents or legal guardians, which increases their vulnerability to human trafficking. Among the nearly 90,000 unaccompanied minors who sought asylum in Europe in 2015, the whereabouts of 10,000 remain unknown.[9]

Child Abuse

War disrupts the social environments usually expected to protect children. The prevalence of abuse can reach up to 90% during and after the conflict, including physical abuse, child labour, child marriage and neglect.[16]

The involvement of children in armed conflicts represents one of the most severe violations of international humanitarian law, with children being recruited as soldiers or even coerced into carrying out bomb attacks and suicide missions.[3,32] Reports from humanitarian and legal frameworks highlight that the use of children in hostilities constitutes a war crime.[3] Economic hardship and social fragmentation are two factors that frequently contribute to a higher prevalence of child maltreatment in these contexts. This abuse is often perpetrated by primary caregivers and close relatives, complicating efforts to seek appropriate help.[16]

Inversion of Social Roles and Limited Access to Education

Economic challenges during armed conflicts force children, particularly girls, to leave school and work as a source of family income.[11] Moreover, schools are easy and common targets of military attacks, exacerbating the insecurity and destruction that reinforces school dropout.[17,18] Many of these children find themselves taking the role of their parents' caretakers after the latter either became sick or disabled during war or marry and have children earlier in search of stability.[2,11] In some contexts, children are forcibly recruited as soldiers or used in violent attacks, representing an extreme inversion of their childhood roles.[3,4,9,32]

PUBLIC HEALTH CONSEQUENCES

Decreased Access to Health Care

Conflicts disrupt access to healthcare by destroying health infrastructures and facilities, with consequent deaths of healthcare workers, obstruction of humanitarian corridors and compromised delivery of medication and vaccines.[1] Key functions of the public health departments, such as disease surveillance and screening, are compromised.[9] This affects the administration of routine vaccinations and treatment for conditions like HIV and tuberculosis.[19] Children with chronic illnesses are often unable to receive appropriate care, leading to a deterioration of their conditions. At the same time, the management of acute, severe, and urgent cases is equally challenging, further compromising the overall healthcare response.[2,20]

Increase in Infectious Diseases

Mass displacement, inadequate living conditions in overcrowded refugee shelters, with poor hygiene, sanitation, potable water and food are the enumerated causes to explain the increasing number of infectious diseases.[11] Children under five years are particularly vulnerable.[1,9]

Reduced infection prevention and control measures lead to outbreaks of diseases like gastroenteritis, respiratory tract infections, measles, malaria, and tuberculosis, which are leading causes of child mortality in conflict zones.[9,11,20] Poor water quality and sanitation in refugee camps further exacerbate outbreaks such as cholera, hepatitis B and E.[20]

Vaccination Gaps

Immunization coverage is highly affected by the higher number of armed conflicts all over the world, with devastating effects on the children vaccination coverage.[20] According to a World Health Organization report, Ukraine's immunization coverage against diphtheria, tetanus and pertussis dropped from 76% in 2012 to 23% in 2014 after the annexation of Crimea by Russia. In Syria, childhood vaccination rates fell from 80% to 41%, over 5 years of conflict.[21]

As a result of the decreasing immunization coverage, herd immunity dropped and previously eradicated or vaccine-preventable diseases have been re-emerging, leading to outbreaks, with a high chance of spreading to other countries and causing devastating effects. As an example, poliomyelitis cases in Syria were imported from Pakistan and a measles outbreak in Syria spread to the surrounding countries like Turkey, Jordan and Lebanon. In Somalia, the low immunization coverage, caused by the 2010 and 2011 conflict, led to a measles epidemic that also affected refugee camps in Kenya and Ethiopia.[1,21]

Decreased immunization among children in areas of conflict represent a risk for themselves and surrounding people, undermining the global efforts towards a higher vaccination coverage all over the world.[1]

Malnutrition

Children exposed to conflict are highly vulnerable to malnutrition.[6] Since 1990, 8 major famines have resulted in over 50,000 deaths, with 7 linked to armed conflicts.[20]

During a conflict, attacks frequently target agricultural fields, livestock, grocery stores and food transportation, which compromises the population food supplies chains.[9] Refugee camp conditions increase the risk of enteric pathogens, exacerbating children malnutrition through diarrheal and vomiting episodes.[22]

Severe malnutrition levels in children are associated with anemia and other nutritional deficits, which may lead to a poor psychological development, low intellectual performance, short stature and increased vulnerability to diseases in adulthood.[9,22]

Environmental contamination

The use of weapons, bombings, missiles and the intense use of vehicles contribute to the air and soil pollution, resulting in water contamination as well. Armed conflicts often result in acute pollution events involving carcinogenic and teratogenic substances, particularly heavy metals, which remain stable over time and persist in the environment.[23]

Additionally, partially destroyed buildings at high risk of collapse, landmines and unexploded ordnance represent a significant risk to the children, not only during the conflict, but also long after combat has ended.(2)

Neonatal Consequences

Stress, malnutrition (with a more pronounced impact during the third trimester) and limited access to healthcare, consequently compromising prenatal surveillance, are commonly identified as factors causing perinatal complications.[24]

A study conducted in Israel, between 2003 and 2008, describes a significant association between stress and gestational complications, with an increased incidence of premature membrane rupture.[25]

Moreover, literature describes a higher neonatal morbimortality, with an increased prevalence of low birth weight neonates, APGAR scores below 7 at 5 minutes and fetal and perinatal death.[24,26,27]

Breastfeeding is commonly neglected and seen as a minor concern during the conflict. As a consequence, children are mostly fed with formula milk, which deprives them of breastfeeding benefits and exposes them to unsafe water used in formula preparation.[28]

Neuroendocrine Consequences

Exposure to adverse events, trauma and stress is related to physical and psychological changes regulated by the hypothalamic–pituitary–adrenal axis. Cortisol, a key marker of this axis, is frequently used in studies to assess the effects of armed conflicts and stress exposure.[2,29,30] The literature reports inconsistent findings regarding cortisol levels in children exposed to armed conflicts.[29,30] Studies show that children exposed to acute stress and in a first phase after the traumatic event exhibit cortisol hypersecretion. However, long-term stress exposure seems to be related to a hyposecretion due to negative feedback mechanisms.[29,30] Regardless of cortisol secretion levels, hypothalamic–pituitary–adrenal axis disruption can compromise child development and its physiopathologic responses.[29]

Age at menarche is influenced by many personal, family and environmental factors, namely the genotype, nutritional status, stress and economic conditions. Considering its sensitivity, it is easily and strongly affected by the existence of an armed conflict.[31]

PSYCHOLOGICAL CONSEQUENCES

Neurodevelopmental changes

Violence against children has consequences that may take years to manifest, with adolescents being particularly vulnerable to neurocognitive insults.[17,32]

Brain development may be impaired, associated with architectural and neuroendocrine dysfunction, leading to visible repercussions and maladaptive behaviours persisting into adulthood. Cognitive developmental delays, compromising basic (memory, attention, concentration, sensation and perception) and superior functions (thinking, consciousness and reasoning) are common and are related to decreased academic performance and learning difficulties.[17,32]

Mental health problems

Exposure to traumatic events during the first year of life has a detrimental effect on the development of the child and can shape the individuals' lives for decades.[33]

Mental health problems can be considered direct consequences of war when they result from direct exposure to traumatic events, such as military attacks, the forced recruitment of children as soldiers, or, for those who survive, their involvement in violent acts such as bomb attacks.[9,32] However, mental health issues caused by displacement, migration, social disintegration and loss of loved ones are considered indirect consequences of armed conflicts.[11]

Exposure to armed conflicts is associated with higher prevalence of anxiety, post-traumatic stress disorder (PTSD) and depression among children and adolescents. The estimated prevalence of anxiety and depression in populations affected by these conflicts is two to four times higher than the global prevalence.[9,20] Furthermore, exposure to armed conflicts during childhood increases susceptibility to psychiatric disorders in adulthood.[34]

One study revealed that almost one-third of individuals displaced by the conflict between 1958 and 2002 in Latin America had two or more mental health problems.[35]

Headaches are the most common somatic symptom in the pre-conflict stage. During the conflict, other symptoms emerge as a consequence of disruption of the parent-child relationships and social activities such as feelings of terror, nervousness, sadness and shame. Posteriorly, violent behaviours might also prevail years after the conflict and depressive symptoms, anxiety disorders, sleep disturbances, somatic complaints and hypersensitivity may emerge.[32]

It is also important to mention that the psychological damages in children can result from parental exposure to armed conflicts, even when the children themselves are not directly exposed. Parental trauma can be transmitted to subsequent generations through epigenetic and narrative mechanisms, increasing their children's susceptibility to psychological problems.[34] Parental emotional stress levels strongly influence post-traumatic symptoms in young children. A 2012 study conducted in refugee camps found a correlation between maternal post-traumatic symptoms and psychological problems in their children.[25] Furthermore, all these problems affect not only children who live in areas of conflict and their surrounding regions, but also those all over the world due to media coverage of war events, often featuring extremely violent images, which reinforces the need to supervise access and adapt the information given about war.[9,36]

Sleep disorders

Traumatic events are often accompanied by sleep disorders. A literature review on sleep disorders in children with PTSD found a high rate of nightmares and other sleeping problems. Generally, nightmares are more common in younger children (vs. adolescents) and their presence is a strong predictor for development of PTSD.[37] Enuresis is also a problem that frequently arises during a conflict.[32]

Drug abuse and Violent behaviours

Exposure to armed conflict and its associated trauma can have profound effects on children and adolescents, often leading to the adoption of risk behaviours and the perpetuation of cycles of violence. In 2013, a study conducted

in adolescents of Indonesia in a post-conflict area found that 94.1% of boys and 89.1% of girls were involved in at least one bullying behaviour. There was also a higher prevalence of group fights and external aggression (with or without weapons) in a context where violence was used as a symbol of power and a way to overcome personal conflicts.[38] Moreover, violence was often associated with other risk behaviours such as substance abuse and school absenteeism.[32,38]

LIMITATIONS

This review has some limitations, namely the use of articles published in the last seven years, the predominance of cross-sectional and retrospective studies, with limited long-term/longitudinal follow-up and the difficulty in establishing a direct causal relationship between the different findings due to the presence of multiple confounding factors.

CONCLUSION

The world has witnessed a rise in armed conflicts, with approximately 90% of the victims being civilians, most of them women and children.[24] Conflicts have a harmful and deep negative impact on children, with long-term consequences for their growth, development, education and health.[9]

Reducing the frequency and intensity of armed conflicts is an explicit goal of the 2030 Sustainable Development Goals.[20] However, achieving this goal requires global and multidimensional efforts focused primarily on conflict prevention. On the other hand, mitigation of the consequences of conflicts mostly relies on humanitarian aid and human resources such as technicians, psychologists and healthcare professionals.[24]

Healthcare professionals play a crucial role in minimizing the impact of conflicts on health, focusing on preventive interventions, reduction of risk and implementation of protective mechanisms to avoid or reduce undesirable short- and long-term consequences.[11]

Post-conflict reconstruction plans are also important to re-establish essential infrastructures, improve access to essential needs and prevent overcrowding in shelters.[24]

In this review, we aim to provide the most up-to-date and relevant information about this subject, with the goal of enhancing knowledge and understanding of this complex issue and equipping the medical community to manage and support refugee patients.

AUTHORSHIP

Ana Carolina Alves - Conceptualization of the study; Literature review; Writing – original draft; Writing – review & editing

Elsa Guimarães - Literature review; Writing – original draft; Writing – review & editing

Mariana Sousa Santos - Literature search; Writing – original draft; Writing – review & editing

Maria Manuel Zarcos – Supervision; Writing – original draft; Writing – review & editing

REFERENCES

1. Ngo NV, Pemunta NV, Muluh NE, Adedze M, Basil N, Agwale S. Armed conflict, a neglected determinant of childhood vaccination: some children are left behind. Hum Vaccines Immunother [Internet]. 2020;16(6):1454–63. Available from: https://doi.org/10.1080/21645515.2019.1688043
2. Kadir A, Shenoda S, Goldhagen J. Effects of armed conflict on child health and development: A systematic review. PLoS One. 2019 Jan 16;14(1):e0210071. doi: 10.1371/journal.pone.0210071. Erratum in: PLoS One. 2019 Feb 11;14(2):e0212393. doi: 10.1371/journal.pone.0212393.
3. How does law protect in war? - Online casebook [Internet]. [cited 2022 May 29]. Available from: https://casebook.icrc.org/
4. General Secretariat Council of the European Union. WORKING PARTY ON PUBLIC INTERNATIONAL LAW (COJUR) Report on the EU guidelines on promoting compliance with international humanitarian law. 2020;
5. List of ongoing armed conflicts [Internet]. Available from: https://en.wikipedia.org/wiki/List_of_ongoing_armed_conflicts
6. Boukari Y, Kadir A, Waterston T, Jarrett P, Harkensee C, Dexter E, et al. Gaza, armed conflict and child health. BMJ Paediatr Open. 2024;8(1):1–5.
7. Geneva Academy of International Humanitarian Law and Human Rights. Today's Armed Conflicts [Internet]. 2024 [cited 2024 Dec 30]. Available from: https://geneva-academy.ch/galleries/today-s-armed-conflicts
8. Guha-Sapir D, Schlüter B, Rodriguez-Llanes JM, Lillywhite L, Hicks MH. Patterns of civilian and child deaths due to war-related violence in Syria: a comparative analysis from the Violation Documentation Center dataset, 2011-16. Lancet Glob Health. 2018 Jan;6(1):e103-e110. doi: 10.1016/S2214-109X(17)30469-2.
9. Hageman JR, Alkureishi LA. The effects of armed conflict on children. Pediatr Ann. 2021;50(10):e396–7.
10. Pettoello-Mantovani M, Namazova-Baranova L, Carrasco-Sanz A, Lucian Pop T, Vural M, Hoey H, et al. Advocating for Children Trapped in the Midst of Armed Conflicts. J Pediatr [Internet]. 2022;246:290-291.e2. Available from: https://doi.org/10.1016/j.jpeds.2022.04.002
11. Garry S, Checchi F. Armed conflict and public health: Into the 21st century. J Public Heal (United Kingdom). 2020;42(3):E287–98.
12. Stark L, Asghar K, Yu G, Bora C, Baysa AA, Falb KL. Prevalence and associated risk factors of violence against conflict-affected female adolescents: A multi-country, cross-sectional study. J Glob Health. 2017;7(1).
13. Nyangoma A, Ebila F, Omona J. Child Sexual Abuse and Situational Context: Children's Experiences in Post-Conflict Northern Uganda. J Child Sex Abus. 2019;28(8):907–26.
14. Chynoweth SK, Freccero J, Touquet H. Sexual violence against men and boys in conflict and forced displacement: implications for the health sector. Reprod Health Matters.

2017;25(51):90–4.
15. Malik MA, Akhtar SN, Albsoul RA, Alshyyab MA. Conflict driven displacement and child health: Evidence based on mother's nationality from Jordan Population and Family Health Survey. PLoS One. 2021;16(9 September):1–17.
16. Saupe LB, Gößmann K, Catani C, Neuner F. Understanding the link between child maltreatment and adolescent future expectations in Northern Uganda: A serial mediation analysis. Child Abuse Negl. 2020 Aug;106:104511. doi: 10.1016/j.chiabu.2020.104511..
17. Stanton B, Davis B, Laraque-Arena D. Global Burden of Violence. Pediatr Clin North Am. 2021;68(2):339–49.
18. Raqib S. Far-reaching consequences of wartime attacks on education. Nat Hum Behav. 2017;1(11):768.
19. Meteke S, Stefopulos M, Als D, Gaffey MF, Kamali M, Siddiqui FJ, et al. Delivering infectious disease interventions to women and children in conflict settings: A systematic review. BMJ Glob Heal. 2020;5:1–17.
20. Bendavid E. Europe PMC Funders Group The effects of armed conflict on the health of women and children. 2022;397(10273):522–32.
21. Fozouni L, Weber C, Lindner AK, Rutherford GW. Immunization coverage among refugee children in Berlin. J Glob Health. 2019;9(1):1–7.
22. Dahab R, Bécares L, Brown M. Armed conflict as a determinant of children malnourishment: A cross-sectional study in the Sudan. BMC Public Health. 2020;20(1):1–10.
23. Baraquoni N Al, Qouta SR, Vänskä M, Diab SY, Punamäki RL, Manduca P. It takes time to unravel the ecology of war in gaza, palestine: Long-term changes in maternal, newborn and toddlers' heavy metal loads, and infant and toddler developmental milestones in the aftermath of the 2014 military attacks. Int J Environ Res Public Health. 2020;17(18):1–22.
24. Le K, Nguyen M. Armed conflict and birth weight. Econ Hum Biol [Internet]. 2020;39:100921. Available from: https://doi.org/10.1016/j.ehb.2020.100921
25. Keren M, Abdallah G, Tyano S. WAIMH position paper: Infants' rights in wartime. Infant Ment Health J. 2019;40(6):763–7.
26. Behboudi-Gandevani S, Bidhendi-Yarandi R, Panahi MH, Mardani A, Prinds C, Vaismoradi M. Perinatal and Neonatal Outcomes in Immigrants From Conflict-Zone Countries: A Systematic Review and Meta-Analysis of Observational Studies. Front Public Heal. 2022;10(March).
27. Butie C, Matthes KL, Hösli I, Floris J, Staub K. Impact of World War 1 on placenta weight, birth weight and other anthropometric parameters of neonatal health. Placenta. 2020;100(February):150–8.
28. Carroll GJ, Lama SD, Martinez-Brockman JL, Pérez-Escamilla R. Evaluation of nutrition interventions in children in conflict zones: A narrative review. Adv Nutr. 2017;8(5):770–9.
29. Dajani R, Hadfield K, van Uum S, Greff M, Panter-Brick C. Hair cortisol concentrations in war-affected adolescents: A prospective intervention trial. Psychoneuroendocrinology. 2018;89(December 2017):138–46.
30. Shaheen M, Schindler L, Saar-Ashkenazy R, Bani Odeh K, Soreq H, Friedman A, et al. Victims of war—Psychoendocrine evidence for the impact of traumatic stress on psychological well-being of adolescents growing up during the Israeli–Palestinian conflict. Psychophysiology. 2020;57(1):1–11.
31. Liczbińska G, Czapla Z, Piontek J, Malina RM. Age at menarche in Polish University students born before, during and after World War II: Economic effects. Econ Hum Biol. 2018;28:23–8.
32. Piñeros-Ortiz S, Moreno-Chaparro J, Garzón-Orjuela N, Urrego-Mendoza Z, Samacá-Samacá D, Eslava-Schmalbach J. Consecuencias de los conflictos armados en la salud mental de niños y adolescentes: revisión de revisiones de la literatura. Biomédica. 2021;41(3):424–48.
33. Benjet C, Axinn WG, Hermosilla S, Schulz P, Cole F, Sampson L, et al. Exposure to Armed Conflict in Childhood vs Older Ages and Subsequent Onset of Major Depressive Disorder. JAMA Netw Open. 2020;3(11):1–12.
34. Kara B, Selçuk B. Under Poverty and Conflict: Well-Being of Children Living in the East of Turkey. Am J Orthopsychiatry. 2019;90(2):246–58.
35. Gómez-Restrepo C, Cruz-Ramírez V, Medina-Rico M, Rincón CJ. Mental health in displaced children by armed conflict - National Mental Health Survey Colombia 2015. Actas Esp Psiquiatr [Internet]. 2018;46(2):51–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29616713
36. Jayuphan J, Sangthong R, Hayeevani N, Assanangkornchai S, McNeil E. Mental health problems from direct vs indirect exposure to violent events among children born and growing up in a conflict zone of southern Thailand. Soc Psychiatry Psychiatr Epidemiol. 2020;55(1):57–62.
37. Harb GC, Schultz JH. The nature of posttraumatic nightmares and school functioning in war-affected youth. PLoS One. 2020;15(11 November):1–12.
38. Fausiah F, Turnip SS, Hauff E. Gender differences and the correlates of violent behaviors among high school students in a post-conflict area in Indonesia. Asia-Pacific Psychiatry. 2020;12(3).

CORRESPONDENCE TO

Ana Carolina Alves
Pediatrics Department
Unidade Local de Saúde da Região de Leiria
Rua das Olhalvas,
2410-197 Leiria
Email: anacarolinafigueiralalves@gmail.com

Received for publication: 27.01.2025
Accepted in revised form: 18.02.2026

Birth and Growth Medical Journal
2026;35(1):26-29. doi:10.25753/BirthGrowthMJ.v35.i1.36883

CLINICAL CASE REPORTS

Stigma and denial of illness in a male adolescent with Anorexia Nervosa – A case report

Rui Sampaio[1], Rita Rodrigues[2], Mafalda Marques[1], Maria do Céu Ribeiro[3], Filipa Martins Silva[2]

ABSTRACT

Denial of illness is common in adolescents suffering from Anorexia Nervosa (AN) and represents a major barrier to early diagnosis and treatment. Males with AN may experience a "double stigma" as they face not only the burden of a mental disorder, but also one traditionally perceived as predominantly affecting females. We report the case of a 13-year-old male with restrictive-type AN, who exhibited marked illness denial, experiential avoidance, and stigma regarding his psychiatric condition, and discuss how these factors contributed to a delay in the recognition of the disorder and initiation of its treatment. Organic and psychiatric differential diagnoses are discussed. Particular attention is given to the patient's late childhood, characterized by obesity and low self-efficacy, which may have acted as predisposing factors for the development of the disorder. Treatment focused primarily on promoting illness acceptance, resulting in progressive clinical improvement. This case highlights the need to raise awareness of AN in males to ensure timely intervention.

Keywords: anorexia nervosa; psychological denial; social stigma

1. Child and Adolescent Psychiatry Service, Department of Psychiatry and Mental Health, Unidade Local de Saúde do Tâmega e Sousa. 4560-136 Penafiel, Portugal. rui.pires95@gmail.com; 74706@chts.min-saude.pt
2. Child and Adolescent Psychiatry Service, Department of Child and Adolescent Psychiatry and Mental Health, Unidade Local de Saúde de Santo António. 4050-651 Porto, Portugal. u11349@chporto.min-saude.pt; filipamartinssilva.pedopsiquiatria@chporto.min-saude.pt
3. Pediatrics and Neonatology Service, Department of Women's and Children's Health, Unidade Local de Saúde do Tâmega e Sousa. 4564-007 Penafiel, Portugal. 72361@chts.min-saude.pt

INTRODUCTION

Anorexia nervosa (AN) is a severe psychiatric disorder characterized by an intense fear of weight gain, distorted body image, and persistent behaviors aimed at restricting food intake, leading to significant weight loss and malnutrition.[1]

AN primarily affects adolescents and young adults, and it is approximately ten times more prevalent in females, contributing to the "double stigma" experienced by males with AN (a term referring to the stigma associated with having a mental disorder combined with the stigma of suffering from a disorder perceived to be specific of the female gender).[2] This stigma contributes to the delay in both the recognition of the illness and the initiation of treatment observed in males with AN.[3]

There are notable differences in the presentation of AN between female and male patients, particularly regarding weight-control behaviors and body image concerns. Girls often exhibit a desire for thinness whereas male adolescents may focus more on achieving a lean, muscular physique, frequently adopting a pattern of "bulking and cutting"—alternating between episodes of high-protein or caloric intake (bulking) aimed at building muscle and periods of extreme caloric restriction (cutting) to reduce body fat. Males are also more likely to engage in excessive exercise as a means of controlling weight and achieving their idealized body image.[4]

Denial of illness is common in AN, particularly among adolescents, and represents a significant barrier to early recognition and treatment of the disorder.[5] It is a complex concept with multiple causes and can be broadly divided into non-deliberate and deliberate denial.[6] Non-deliberate denial is attributable to a form of anosognosia (referring to the lack of awareness or concern regarding emaciation), limited insight (characteristic of the overvalued ideas regarding body image) and narrowed consciousness (namely indifference to hunger signals). In contrast, deliberate denial is used by patients to avoid the consequences of acknowledging the disease (namely to avoid treatment) and as to preserve a sense of self-determination.

The authors report a case in which denial of illness and the "double stigma" associated with AN in males is evident and discuss their relevance to the diagnosis and management of the disorder.

CASE REPORT

A 13-year-old male adolescent presented to the pediatric emergency room accompanied by his mother, with complaints of lightheadedness, fatigue and cold intolerance. His mother reported that over the previous three months the patient had been restricting his food intake and engaging in excessive exercise, resulting in a rapid weight loss of approximately 17 kg. She also stated that he had expressed fear of gaining weight. However, the patient lacked recognition of the seriousness of the current low body weight, minimizing the severity of his dietary restriction and excessive physical activity, while admitting that he felt better about his body image after his recent weight loss. He denied purgative behaviors. On examination, his body-mass index (BMI) was 13.7 kg/m^2 (weight 35.0 kg, height 161 cm, BMI-for-age percentile: 0.1). He presented with hypotension (blood pressure 88/48mmHg) and bradycardia (heart rate 46 beats per minute). Physical examination revealed muscular atrophy, dry skin and cold extremities. Laboratory tests showed hypoglycemia (45 mg/dL), hypophosphatemia (3.1 mg/dL), and hypercholesterolemia (236 mg/dL), while the complete blood count, renal function, electrolyte panel and liver enzyme were within normal range. Urinalysis was normal. Electrocardiogram and echocardiogram revealed bradycardia but no other abnormalities.

The patient was admitted to a Pediatric Inpatient Unit for clinical stabilization and refeeding. Additional investigations were conducted to exclude medical conditions that may cause weight loss, including celiac disease, Crohn's disease and hyperthyroidism. Tissue transglutaminase antibodies and total IgA levels were within normal limits, ruling out celiac disease, and a stool calprotectin test was normal, excluding Crohn's disease. Thyroid function tests were also normal. Tuberculosis was considered unlikely, as the patient had no history of cough, fever or night sweats, and pulmonary auscultation was clear. Type 1 diabetes was ruled out due to the presence of fasting hypoglycemia. Fatigue, loss of appetite, and weight loss may indicate malignancy; however, the absence of focal findings on physical examination or laboratory abnormalities made this possibility unlikely.

During hospitalizations, the patient was evaluated by a Child and Adolescent Psychiatrist. Potential psychiatric differential diagnoses of AN were considered, namely avoidant/restrictive food intake disorder (ARFID), body dysmorphic disorder (BDD) and major depressive disorder (MDD). ARFID is an eating disorder characterized by restricted eating that can lead to significant weight loss or nutritional deficiencies, often due to sensory sensitivities, lack of interest in food, or fear of adverse consequences such as choking.[7] However, none of these features were present, while excessive exercise and body image concerns are unusual in ARFID, ruling out this diagnosis. Body dysmorphic disorder involves a preoccupation with perceived physical flaws in specific body parts rather than concerns about overall weight.[7] Although the patient demonstrated a distorted perception of his body, his focus on dietary restriction and excessive exercise to achieve weight loss were more consistent with AN than with BDD. Major depressive disorder often presents with reduced appetite, weight loss and fatigue,[7] which may overlap with the patient's symptoms. However, weight loss associated with MDD occurs due to anhedonia or loss of appetite rather than fear of gaining weight or body image concerns. This patient did not report pervasive low mood, hopelessness, or other core depressive symptoms, making MDD less likely. The patient denied engaging in purgative behaviors (self-induced vomiting or the use of laxatives and diuretics), and his mother reported not observing such behaviors. However, patients with AN may conceal these behaviors. For this reason, indirect signs and findings commonly associated with purging behaviors were investigated. These include Russell's sign (calluses or lesions on the knuckles resulting from self-induced vomiting), which was not observed, as well as laboratory findings such as metabolic alkalosis with hypochloremia and hypokalemia, which were also absent.[8] A diagnosis of AN, restrictive

subtype was established, and after discharge the patient started outpatient treatment.

The patient had a history of obesity (at age 12 he weighed 60 kg; BMI 23.4 kg/m^2; BMI-for-age percentile: 97) and had been bullied by his peers for this reason. Prior to the clear onset of AN he had decided to reduce his intake of highly caloric foods without displaying others symptoms of an eating disorder. This resulted in a slow and steady weight loss of 8 kg over approximately ten months. During this period, his peers complimented him on his appearance and his ability to lose weight. Subsequently, the patient intensified his food restriction, started exercising daily, developed a fear of gaining weight, and failed to acknowledge the rapid weight loss that led to his low bodyweight. This period was marked by high expressed emotion in the family, with the patient's father reacting with anger to the patient's restrictive eating behavior, while his mother attempted to pacify the father and simultaneously accommodated the restrictive eating and excessive exercise. The family later reported that they had been unaware of the possibility of a diagnosis of AN, which contributed to the delay in treatment initiation. Following psychoeducation regarding their son's mental illness, both parents came to understand and accepted the diagnosis.

Prior to the onset of the illness, the patient had been involved in minor acts of misconduct with his school peers, and his academic performance had been declining. The patient had demonstrated minor learning difficulties since his early school years, which had been partially mitigated through private tutoring and educational adaptations. However, in the months preceding the onset of AN, he had been dedicating less time to his studies, resulting in a marked deterioration in his academic performance. This led to frequent arguments with his parents, who eventually threatened to enroll him in a boarding school if his behavior and grades did not improve. The patient reported feeling frightened by this possibility, therefore deciding to improve his behavior, apply himself to his studies, and distance himself from his peers, which coincided with the intensification of the eating disorder symptoms.

After three months of non-responsive outpatient treatment, the patient was admitted to a Child and Adolescent Psychiatry Inpatient Unit. During hospitalization, he did not exhibit restrictive or purgative behaviors or excessive exercise but continued to deny his illness and symptoms. He adopted a passive stance during all psychotherapeutic activities and appeared to focus primarily on gaining weight in order to be discharged from the Unit. He later revealed that he had felt ashamed of his fear of gaining weight and of suffering from AN. He was discharged after 58 days with a weight of 44,6 kg (BMI 17,2 kg/m^2; BMI-for-age percentile: 24.4) and maintained a healthy weight and remission of restrictive eating and excessive exercise in the following months. Psychoeducation regarding AN, along with the promotion of illness acceptance and healthier patterns of family communication, played a major role in the treatment plan.

DISCUSSION

We report the case of a young male adolescent suffering from AN who exhibited marked denial of illness, which appeared to be partly motivated by stigma and shame related to his diagnosis. The delay in recognition of the disorder by those around the patient may reflect a broader societal lack of awareness of AN in males.

AN is associated with several medical complications due to severe malnutrition and its effects on multiple organ systems.[9] This patient exhibited signs and symptoms commonly observed in this context, including lightheadedness, fatigue, cold intolerance, cold extremities, dry skin, hypotension, and bradycardia, and well as laboratory abnormalities such as hypoglycemia, hypophosphatemia and hypercholesterolemia.

When symptoms such as food restriction, excessive exercise, or purgative behaviors are concealed or denied by the patient, or go unnoticed by the family, it is particularly important to consider medical conditions that may cause weight loss int the differential diagnosis of AN.[10] These include celiac disease, Crohn's disease, hyperthyroidism, type 1 diabetes, tuberculosis and malignancy.[11]

Alternative psychiatric diagnoses that involve food avoidance or loss of appetite with subsequent weight loss should also be considered, namely ARFID and major depressive disorder, while the prominent preoccupation with body image also makes body dysmorphic disorder a relevant differential diagnosis of AN.[12]

Although this patient engaged in excessive exercise, his behavior appeared to be motivated by a desire to lose weight rather than to achieve an ideal of muscularity. He also did not engage in "bulking and cutting" as a strategy to achieve this goal, unlike other male adolescents as reported in the literature.[4]

The patient, who had previously been obese, experienced a period of healthy weight loss prior to the onset of illness, which was reinforced by positive comments from friends and family, who not only complimented the patient on his body image but also praised his efforts to lose weight. This may have reinforced the patient's low self-efficacy and contributed to the onset of his illness. According to Erik Eriksson's theory of psycho-social developmental, late childhood, roughly corresponding to ages 6-12, is characterized by the psychosocial crisis of "Industry versus Inferiority", and the patient, aged 13 at the onset of illness, had a history of academic difficulties that may have contributed to a sense of inferiority relative to his peers, consistent with low self-efficacy.[13]

Additionally, in attempting to distance himself from peers to avoid further misconduct, his peers started bullying him once more regarding his weight, which intensified his restrictive eating and exercise behaviors, precipitating the onset of AN at a time when he became socially isolated and therefore more psychologically vulnerable.

The patient's passivity during treatment may be understood in terms of experiential avoidance, which refers to an unwillingness to remain in contact with aversive experiences, such as painful feelings, thoughts, and emotions, and is believed to contribute to the maintenance of almost all emotional disorder).[14] Shame and self-stigma related to mental illness, which the patient acknowledged at a later stage of treatment, likely contributed to this unwillingness to confront and admit to having thoughts and behaviors characteristic of AN. Additionally, high parental expressed emotion known to be associated with poor treatment

outcomes in AN, may have acted as a maintenance factor of the illness.[15]

Treatment focused particularly on promoting illness acceptance in both the patient and his family, and on reducing the stigma associated with AN. Over time, the patient progressively demonstrated acceptance of his condition and became more capable of confronting his overvalued ideas regarding weight and eating behaviors, which he admitted to having caused intense shame.

In conclusion, we present a case of a male adolescent with AN in which both denial of illness and the "double stigma" of suffering from a mental disorder that is more prevalent in females may have delayed early recognition and treatment and acted as maintenance factors of the illness. Clinicians, and school communities in particular, should be aware of the possibility of AN affecting male adolescents, in order to avoid delays in illness recognition and initiation of treatment.

AUTHORSHIP

Rui Sampaio – Conceptualization; Investigation; Writing – original draft

Rita Rodrigues – Conceptualization; Investigation; Writing – review & editing

Mafalda Marques – Investigation; Writing – review & editing

Maria do Céu Ribeiro – Investigation; Writing – review & editing

Filipa Martins Silva – Conceptualization; Supervision; Writing – review & editing

REFERENCES

1. Treasure J, Duarte TA, Schmidt U. Eating disorders. Lancet. 2020 Mar 14;395(10227):899-911. doi: https://doi.org/10.1016/S0140-6736(20)30059-3.
2. Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Current Opinion in Psychiatry. 2006;19(4):389-394. doi: https://doi.org/10.1097/01.yco.0000228759.95237.78.
3. Räisänen U, Hunt K. The role of gendered constructions of eating disorders in delayed help-seeking in men: a qualitative interview study: Table 1. BMJ Open. 2014;4(4):e004342. doi: https://doi.org/10.1136/bmjopen-2013-004342.
4. Gorrell S, Murray SB. Eating Disorders in Males. Child and Adolescent Psychiatric Clinics of North America. 2019;28(4):641-651. doi: https://doi.org/10.1016/j.chc.2019.05.012.
5. Couturier JL, Lock J. Denial and minimization in adolescents with anorexia nervosa. Intl J Eating Disorders. 2006;39(3):212-216. doi: https://doi.org/10.1002/eat.20241.
6. Maágorzata Starzomska, Ryszard Tadeusiewicz. Pitfalls in anorexia nervosa research: The risk of artifacts linked to denial of illness and methods of preventing them. Psychiatria Danubina. 2016;28(3):202-210.
7. American Psychiatric Association. DSM-5-TR. Diagnostic and Statistics Manual 5th Ed. Text Revision. 5th Edition.
8. Strumia R. Dermatologic Signs in Patients with Eating Disorders: American Journal of Clinical Dermatology. 2005;6(3):165-173. doi: https://doi.org/10.2165/00128071-200506030-00003.
9. Gibson D, Workman C, Mehler PS. Medical Complications of Anorexia Nervosa and Bulimia Nervosa. Psychiatric Clinics of North America. 2019;42(2):263-274. doi: https://doi.org/10.1016/j.psc.2019.01.009.
10. Mitchell JE, Peterson CB. Anorexia Nervosa. Solomon CG, ed. N Engl J Med. 2020;382(14):1343-1351. doi: https://doi.org/10.1056/NEJMcp1803175.
11. Mairs R, Nicholls D. Assessment and treatment of eating disorders in children and adolescents. Arch Dis Child. 2016;101(12):1168-1175. doi: https://doi.org/10.1136/archdischild-2015-309481.
12. Martin A, Bloch MH, Volkmar FR. Lewis's Child and Adolescent Psychiatry A Comprehensive Textbook. 5th Edition. Wolters Kluwer; 2017.
13. Erikson E. Identity and the Life Cycle. WW Norton; 1994.
14. Hayes AM, Feldman G. Clarifying the Construct of Mindfulness in the Context of Emotion Regulation and the Process of Change in Therapy. Clinical Psychology: Science and Practice. 2004;11(3):255-262.
15. Rienecke RD, Lebow J, Lock J, Le Grange D. Family Profiles of Expressed Emotion in Adolescent Patients With Anorexia Nervosa and Their Parents. Journal of Clinical Child & Adolescent Psychology. 2017;46(3):428-436. doi: https://doi.org/10.1080/15374416.2015.1030755.

CORRESPONDENCE TO

Rui Sampaio
Child and Adolescent Psychiatry Service
Department of Psychiatry and Mental Health
Unidade Local de Saúde do Tâmega e Sousa
Avenida do Hospital Padre Américo, nº 210
4560-136 Penafiel
Email: 74360@ulsts.min-saude.pt

Received for publication: 31.07.2024
Accepted in revised form: 17.07.2025

Birth and Growth Medical Journal
2026;35(1):30-33. doi:10.25753/BirthGrowthMJ.v35.i1.37269

CLINICAL CASE REPORTS

New-onset iatrogenic diabetes in a teenager with ulcerative colitis – an additional challenge

Cristiana Costa[1], Ana Laura Fitas[1], Sofia Bota[2], Isabel Afonso[2], Catarina Diamantino[1], Lurdes Lopes[1]

ABSTRACT

Introduction: Glucocorticoids (GC) are long-established agents for the induction of remission in inflammatory bowel disease (IBD). Hyperglycemia is a known complication of GC, and this risk increases when combined with immunosuppressive treatments, particularly with mycophenolate mofetil (MMF). In patients with IBD, there is insufficient information regarding the adverse outcomes of using both therapies concerning hyperglycemia and new-onset diabetes.

Case Report: A 13-year-old girl with ulcerative colitis (UC), two years after diagnosis, started MMF along with GC. She developed polydipsia and polyuria one week earlier. Follow-up laboratory workup revealed hyperglycemia (696 mg/dL), without ketosis or acidosis, a baseline HbA1c of 7.4%. Insulin treatment was initiated, MMF was suspended, and GC weaning was attempted again. New-onset diabetes complicated the management of a previously diagnosed depressive and anxiety disorder. On follow-up, insulin needs progressively decreased, and insulin was discontinued after five months.

Conclusion: The concomitant use of GC and MMF might have posed a cumulative risk. This case highlights the importance of a multidisciplinary team when establishing a healthcare plan for an adolescent with multifactorial chronic disease burden.

Keywords: diabetes; glucocorticoids; immunosuppression; inflammatory bowel disease; mycophenolate mofetil

1. Pediatric Endocrinology Unit, Hospital Dona Estefânia, Unidade Local de Saúde de São José. 1169-045 Lisboa, Portugal. cristiana.costa@ulssjose.min-saude.pt; ana.fitas@ulssjose.min-saude.pt; catarina.diamantino@ulssjose.min-saude.pt; mlurdes.lopes@ulssjose.min-saude.pt
2. Pediatric Gastroenterology Unit, Hospital Dona Estefânia, Unidade Local de Saúde de São José. 1169-045 Lisboa, Portugal. sofia.bota@ulssjose.min-saude.pt; isabel.afonso@ulssjose.min-saude.pt

INTRODUCTION

Comorbid diseases in ulcerative colitis (UC) include several immune-mediated conditions, among which type 1 diabetes mellitus (T1DM) is one of the most frequently associated. [1] A large case-control study involving 488 children with UC showed that it is associated with a higher prevalence of T1DM compared to controls (OR = 2.7, 95% CI: 1.1-6.6), with an overall prevalence of 2049 cases per 100,000 children.[2] To confirm the association between diabetes and steroid therapy, it is necessary to rule out an autoimmune background. The presence of autoantibodies to GAD and anti-α tyrosine phosphatase (IA-2) confirms the diagnosis of T1DM.[10]

Glucocorticoids (GC) are long-established and widely used agents for the induction of remission in inflammatory bowel disease (IBD). They are the first-line agents for induction in moderate to severe UC and are also used in IBD patients admitted to the hospital with severe disease relapses.[3,4] Steroids are well known for causing drug-induced diabetes. While the effect of steroids on blood sugar regulation is well-documented, it is essential to consider other medications in these cases as well.

In organ transplant recipients, immunosuppressive therapies have been associated with a markedly increased risk of hyperglycemia and new-onset diabetes. [6] This risk is heightened when GC are combined with other immunosuppressants, particularly mycophenolate mofetil (MMF).[7] This combination has the highest hyperglycemia rate (81.3%) with a significant reporting odds ratio value of 8.38 (95% CI 2.33-30.16).[8] The combined use of GC and other immunosuppressive therapies may contribute to the high metabolic and hyperglycemic adverse effects observed in these patients.[7,8] In patients with IBD, there is insufficient information regarding the adverse outcomes of using GC and MMF in relation to hyperglycemia and new-onset diabetes.

CASE REPORT

A 13-year-old girl was evaluated at the Pediatric Gastroenterology outpatient clinic with UC and sclerosing cholangitis for two years (diagnosed at the age of 11), both evolving with a pattern of severe and relapsing disease. Disease control had been particularly challenging, with little improvement achieved using prednisolone (PDN), infliximab, or azathioprine. At diagnosis, an autoimmunity workup was performed, including tests for anti-pancreatic antibodies and C-peptide levels. Attempts to taper corticosteroids led to multiple relapses, and the introduction of corticosteroid-sparing drugs (namely infliximab and azathioprine) was unsuccessful, as the patient continued to require high doses of PDN. Hyperglycemia screening was conducted approximately every 3 months, since diagnosis.

Two years after diagnosis, MMF (500 mg twice daily) was initiated in combination with PDN (0.5 mg/kg/day). One month after starting MMF, follow-up laboratory workup revealed hyponatremia (126 mmol/L), marked hyperglycemia (696 mg/dL), with corrected sodium level for hyperglycemia within normal range (137.9 mmol/L). Capillary ketonemia was negative (0.1 mmol/L) and there was no metabolic acidosis (pH 7.39, HCO3 24.3 mEq/L). Glucosuria was high, above 1000 mg/dL. When questioned, the patient reported mild symptoms of polyuria and polydipsia, which had previously gone unnoticed.

She was hemodynamically stable, without clinically evident dehydration. She had lost 2 kg in one month (6% of her body weight). Anthropometric data were: height 134.5 cm (z-score -2.6), weight 32 kg (z-score -1.7), body mass index (BMI) 17.7 kg/m2 (z-score -0.4). Her Tanner stage was II.

Initial HbA1c was 7.4 %, and both C-peptide (2.0 ng/mL, normal range: 0.9-7.1) and insulin levels (4.2 mUI/L, normal range: 1.9-23) were normal. Anti-protein tyrosine phosphatase islet antigen-2, anti-insulin and anti-GAD autoantibodies were negative. Antibodies to Langerhans cells and zinc transporter were not tested.

She was admitted to the ward to achieve glycemic control and intensive diabetes education. Intravenous fluid therapy was started with isotonic saline solution 10 mL/ kg over one hour, followed by subcutaneous insulin in a basal-bolus regimen. The total daily dose was titrated to 0.9 units/Kg/day (40% glargine, with insulin aspart according to glycemia and carbohydrate counting), with adequate glycemic profile. On the second day of admission, MMF was suspended and PDN weaning was initiated to the lowest dose of 2.5 mg daily (0.1 mg/Kg/day). She was discharged after five days. Three weeks later, she was started on oral vancomycin 500 mg three times a day, with progressively significant improvement in gastrointestinal symptoms. The stool culture, Yersinia test, Clostridium difficile, stool virus test (astrovirus, adenovirus, norovirus, rotavirus and enterovirus), stool parasitology test and Giardia test were all negative.

Soon after the diabetes diagnosis, the teenager developed a reactive depressive and anxiety disorder, and she was followed in Pediatric Psychiatry consultations and undergoing psychotherapy. In this setting, the diabetes education process, guidance, and lifestyle counseling were very challenging, and she had difficulty in coping with the disease, especially with insulin administration. Anxiety symptoms, including trichotillomania with severe eyebrow picking, had a significant impact on her daily life. The pharmacological approach began with a benzodiazepine (lorazepam 1 mg/day) and four months after diagnosis, a mood stabilizer (oxcarbazepine 300 mg/day) was added. The patient always complied with the treatment for UC, but her adherence to psychiatric medication was poor, and she only took the medication for a few months. The entire process involved a multidisciplinary team approach, with a pediatric psychiatrist, gastroenterologist, and endocrinologist, as well as specialized nursing educators and a nutritionist.

On follow-up, insulin needs progressively decreased, and basal insulin was stopped after two months. Five months after

diabetes onset, continuous glucose monitoring (CGM) showed 90-100% time in range (70-180 mg/dL), without hypoglycemia or other acute complications, with a total daily insulin dose of 0.2 units/Kg/day. Bolus insulin was then also suspended, and after two months without insulin therapy, HbA1c was 5.3%. Lowering the burden of capillary blood tests, CGM use, and insulin shots was helpful in improving depressive and anxiety symptoms, allowing for progressive weaning of oxcarbazepine.

DISCUSSION

The differential diagnosis of new-onset diabetes in an adolescent with UC is challenging. Indeed, there were overlapping risk factors related to the underlying condition and potential iatrogenic effects.

The hypothesis of T1DM associated with UC as a coexisting autoimmune disease became less likely because pancreatic autoimmunity was negative and baseline insulin and C-peptide levels were normal. The fact that insulin requirements decreased after MMF withdrawal, simultaneously with the weaning of the GC strongly suggests that this was a case of iatrogenic diabetes. In this case, the prognosis is good, although the likelihood of developing T1DM is higher when compared to the general population.

CONCLUSIONS

The concomitant use of corticosteroid therapy (PDN) along with an immunosuppressive agent (MMF) may have had a additive risk effect. Priority should be given, when feasible, to corticosteroid-sparing therapies. In the setting of combined immunosuppressive therapeutics, it is essential to accurately monitor blood glucose levels and investigate signs and symptoms of hyperglycemia as part of routine medical practice.[5]

This case highlights the importance of a multidisciplinary team approach when establishing a healthcare plan for adolescents with a complex, multifactorial chronic disease burden.

AUTHORSHIP

Cristiana Costa - Writing original draft; conceptualization
Ana Laura Fitas - Writing - review and editing, supervision, validation
Sofia Bota - Writing - review and editing , supervision
Isabel Afonso - Supervision
Catarina Diamantino - Supervision
Lurdes Lopes - Writing - review and editing, validation

REFERENCES

1. Maconi G, Furfaro F, Sciurti R, Bezzio C, Ardizzone S, Franchis R. Glucose intolerance and diabetes mellitus in ulcerative colitis: pathogenetic and therapeutic implications." World J Gastroenterol 2014;20(13):3507-3515.
2. Kappelman M, Galanko J, Porter C, Sandler R. Association of paediatric inflammatory bowel disease with other immune-mediated diseases. Arch Dis Child 2011;96:1042–1046.
3. Gomollón F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay J, *et al*. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management, J Crohns Colitis. 2017;11(1):3-25.
4. Ford A, Bernstein C, Khan K, Abreu M, Marshall J, Talley N, *et al*. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(4):590-600.
5. McDonnell M, Harris_R, Borca_F, Mills T, Downey L, Dharmasiri S, *et al*. High incidence of glucocorticoid-induced hyperglycaemia in inflammatory bowel disease: metabolic and clinical predictors identified by machine learning. BMJ Open Gastro 2020;7:e000532.
6. Tamez-Pérez H, Quintanilla-Flores D, Rodríguez-Gutiérrez R, González-González J, Tamez-Peña A. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. World J Diabetes. 2015;6(8):1073-1081.
7. Hwang JL, Weiss RE. Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev. 2014;30(2):96-102.
8. Galindo R, Wallia A. Hyperglycemia and Diabetes Mellitus Following Organ Transplantation. Curr Diab Rep. 2016;16(2):14.
9. Abdel-Razaq W, Ismail W, Anazi A, Alissa A. The risk of hyperglycemia associated with the use of prescribed medications. Int J Pharm Sci Res. 2017;8(9):3991-3999.
10. Knop-Chodyla K, Piasecka Z, Kochanowska-Mazurek A, Głaz A, Wesołek E, Rudziki G. Steroid therapy in patients with inflammatory bowel disease complicating diabetes diagnosis. Qual Sport. 2024;18:51010.
11. de Wit M, Gajewska KA, Goethals ER, McDarby V, Zhao X, Hapunda G, *et al*. ISPAD Clinical Practice Consensus Guidelines 2022: Psychological care of children, adolescents and young adults with diabetes. Pediatr Diabetes. 2022 Dec;23(8):1373-1389. doi: https://doi.org/10.1111/pedi.13428.
12. Sang MM, Sun ZL, Wu TZ. Inflammatory bowel disease and diabetes: Is there a link between them? World J Diabetes 2022; 13(2): 126-128.
13. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, *et al*. Management of Paediatric Ulcerative Colitis, Part 2: Acute Severe Colitis-An Evidence-

1. based Consensus Guideline From the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Aug;67(2):292-310. doi: https://doi.org/10.1097/MPG.0000000000002036.
2. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, *et al*. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Aug;67(2):257-291. doi: 10.1097/MPG.0000000000002035. Erratum in: J Pediatr Gastroenterol Nutr. 2020 Dec;71(6):794. doi: https://doi.org/10.1097/MPG.0000000000002967.
3. Tosur M, Viau-Colindres J, Astudillo M, Redondo MJ, Lyons SK. Medication-induced hyperglycemia: pediatric perspective. BMJ Open Diabetes Res Care. 2020 Jan;8(1):e000801. doi: https://doi.org/10.1136/bmjdrc-2019-000801.

CORRESPONDENCE TO

Cristiana Costa
Hospital Dona Estefânia
Unidade Local de Saúde de São José
Rua Jacinta Marto
1169-045 Lisboa
Email: cristianaccosta.med@gmail.com

Received for publication: 26.08.2024
Accepted in revised form: 21.08.2025

Birth and Growth Medical Journal
2026;35(1):34-37. doi:10.25753/BirthGrowthMJ.v35.i1.41559

CLINICAL CASE REPORTS

Splenic Infarction in a Child with Sickle Cell Trait

Beatriz Henriques[1], Rita Ribeiro Martins[1], Ana Ventura[1], Teresa Faria[1]

ABSTRACT

Sickle cell trait is a benign condition, though rare complications were reported, often triggered by well-established trigger factors. We report a case of a seven-year-old male child with sickle cell trait, who presented to the Emergency Department with progressively worsening abdominal pain over the previous three days, radiating to the left shoulder, which began during a trip to high altitude mountains. On admission, the child had signs of peritonitis, as diffuse tenderness and general tympany. The ultrasound revealed splenomegaly with a peripheral triangular area, lacking blood flow, suggestive of infarction. He was admitted to the hospital for hydration and pain management, obtaining symptoms control. Further investigation revealed a recent asymptomatic Epstein-Barr virus infection, which may have been an additional precipitating factor alongside the high altitude. This case highlights the relevance of knowing the portability of HbS for achieving a better control of the risk factors that may cause complications in the long run.

Keywords: pediatrics; sickle cell trait; splenic infarction

1. Pediatrics Department, Hospital Professor Doutor Fernando Fonseca, Unidade Local de Saúde Amadora Sintra. 2720-276 Amadora, Portugal. beatrizfer.henriques@gmail.com; anaritamartins96@gmail.com; ana.ventura@ulsasi.min-saude.pt; ana.ventura@ulsasi.min-saude.pt

INTRODUTION

Sickle cell syndromes encompass a group of qualitative hemoglobinopathies characterized by the presence of a haemoglobin variant, HbS, which results from a mutation in the gene responsible for encoding the β-globin chains.[1-3] The disease manifests only when two mutated genes are present, either in homozygosity or in combination with other hemoglobinopathies.[1,3]

Sickle cell trait is defined by the presence of only one abnormal β-globin allele.[2] It is more prevalent in regions where malaria is endemic, as it provides protection against severe forms of the infectious disease.[1-4] Due to migratory phenomena, its current distribution is all over the world.[2,3] It is considered a benign condition that typically does not require specific medical care or regular follow-up, except in the context of family planning, where partner screening is essential to prevent more severe forms of haemoglobinopathy.[2,3] In most cases, carriers are asymptomatic, with a life expectancy and quality of life comparable to individuals without the mutation.[2,3,5]

However, certain metabolic and environmental conditions can promote HbS polymerization, potentially leading to complications.[2,3,5] Hypoxia, often associated with high altitudes (typically above 1,100 meters) or intense physical exertion, alters the solubility of HbS, leading to polymerization and subsequent sickling of red blood cells.[2,6] These sickled erythrocytes exhibit reduced deformability, promoting thrombosis and resulting in tissue infarction, commonly in the spleen.[2,5] It is known that the percentage of HbS can influence the prevalence of complications, with increased risk observed when levels exceed 35%.[6]

Urogenital complications, such as haematuria, progression to chronic kidney disease, and renal medullary carcinoma, are well known in this population.[2] Another well-documented complication is the risk of vision loss following traumatic hyphaemia.[2] There is also a slightly increased risk of sudden death and rhabdomyolysis associated with extreme physical exertion in individuals with sickle cell trait.[2,4,7] In addition to splenic infarction, it has been suggested that sickle cell trait may be connected with other complications.[2,4]

CASE PRESENTATION

This case is about a seven year old Portuguese male, previously healthy, known to be HbS carrier (40.7% in the last test). There was no relevant family history.

He presented to the Pediatric Emergency Department with progressively worsening abdominal pain in the previous three days, radiating to the left shoulder. He also reported anorexia and a single episode of vomiting. The symptoms began suddenly during a car trip to a high mountain in the country side, while ascending in altitude, without associated physical exertion. He denied trauma, fever, bowel habit changes, or recent infections.

Upon admission, he was in discomfort, afebrile, with age-appropriate vital signs. In the physical examination it was noticed pale skin, tympany in the abdomen with diffuse tenderness on palpation, signs of peritonitis, and a palpable spleen 1 cm below the left costal margin.

The laboratory tests (**Table 1**) revealed haemoglobin 11.2 g/dL, reticulocyte count 90,000/µL, platelet count 314,000/µL, and high LDH (601 U/L).

Table 1 - Laboratory evaluation (on the admission date)

Reference value (RV); Mean Corpuscular Volume (MCV); Mean Corpuscular Haemoglobin (MCH); White Blood Cells (WBC); Erythrocyte Sedimentation Rate (ESR); Aspartate Aminotransferase (AST); Alanine Aminotransferase (ALT); Lactate Dehydrogenase (LDH); C-reactive Protein (CRP); Thyroid Stimulating Hormone (TSH); Free Thyroxine (FT4)

Haemoglobin	11.2g/dL (RV: 11.0 – 14.0)	**ESR**	9mm (RV: < 13)
MCV	76.7fL (RV: 72.0 – 86.6)	**AST**	49U/L (RV: < 44)
HGM	26.7pg (RV: 26.0 – 34.0)	**ALT**	75U/L (RV: < 37)
WBC	11,8x10^9/L (RV: 4.5 – 13.0)	**Total Bilirubin**	0.62mg/dL (RV: ≤ 1.20)
Lymphocytes	3,9 x10^9/L (RV: 1.0 – 7.8)	**Direct Bilirubin**	0.16mg/dL (RV: ≤ 0.20)
Platelets	314 x10^9/L (RV: 140 – 440)	**LDH**	601U/L (RV: 120 - 300)
Reticulocytes	90 x10^9/L (RV: 50-100)	**Creatinine**	0.47mg/dL (RV: 0.40 - 0.60)
INR	1.0 (RV: < 1.2)	**Urea**	23.7mg/dL (RV: 15.0 - 36.0)
APTT	23.8s (RV: 23.0 - 31.9)	**CRP**	1.52mg/dL (RV: < 0.50)
Fibrinogen	3.2g/L (RV: 1.8 - 3.5)	**TSH**	3.25mUI/L (RV: 0.60 - 4.84)
D-dimers	2261mcg/L (RV: < 500)	**FT4**	1.37ng/dL (RV: 0.97 - 1.67)

The abdominal ultrasound (**Figure 1**) showed a slightly enlarged spleen (11.5 cm bipolar diameter) with heterogeneous echotexture in the upper third, where a well-defined, hypoechoic, triangular peripheral area measuring approximately 28 mm in its greatest dimension was observed. There was no vascular flow within this area, suggesting splenic infarction.

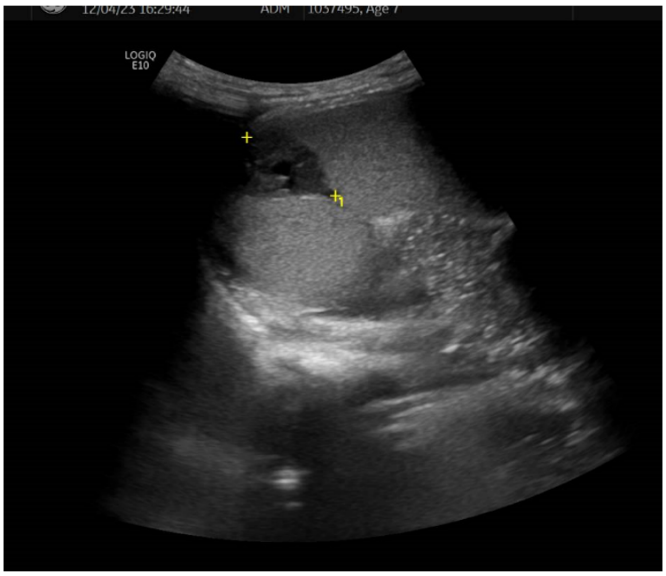


Figure 1 - Abdominal ultrasound showing findings consistent with splenic infarction

The patient was admitted for supportive therapy (intravenous fluids, rest, and pain management) and further studies. A rapid symptomatic improvement was observed.

Further investigation identified an asymptomatic acute/recent Epstein-Barr virus (EBV) infection (negative EBV nuclear antigen [EBNA] IgG, positive viral capsid antigen [VCA] IgG and IgM). The patient was not immune to CMV. The peripheral blood smear showed activated lymphocytes and a pleomorphic lymphocyte population.

The diagnosis of splenic infarction was established in a patient with sickle cell trait, probably triggered by altitude exposure and recent mononucleosis. He was discharged two days later, fully asymptomatic with unchanged spleen palpation findings. Preventive guidance was provided regarding avoidance of trigger risk factors, and he was referred to pediatric haematology follow-up.

About one month after the episode, a repeated abdominal ultrasound confirmed a significant reduction in the infarcted area and resolution of the splenomegaly. Clinically, he remained asymptomatic. Repeated EBV serology supported the hypothesis of recent infection (EBNA IgG positive).

DISCUSSION AND CONCLUSIONS

This child is a carrier of sickle cell trait with an Hb S level >35%, which increases the risk of complications related to blood circulation and tissue oxygenation.

He was brought to an area with an altitude significantly higher than the place he was used to live (1,990 meters above sea level), exposing him to hypoxic conditions. Additionally, the patient had a recent asymptomatic EBV infection. The literature describes several cases of splenic infarction associated with EBV infection.[8,9] Although the exact mechanism is not yet well understood, proposed explanations include splenic hypercellularity and a transient hypercoagulable state.[8,9]

Splenic infarction is typically self-limited, with complete resolution in most cases following supportive therapy.[2,9]

Although sickle cell trait is considered a benign condition, carriers may develop complications, particularly when exposed to certain precipitating factors.[1,3] Identifying these factors and providing appropriate counselling is therefore of critical relevance, both to help avoiding risk exposures and to educate patients and caregivers about symptoms that warrant timely medical evaluation. Such guidance can significantly reduce the morbidity and mortality associated with this condition.[2]

Preventive measures should include maintaining adequate hydration, engaging in moderate and progressive physical activity tailored to individual fitness levels combined with rest periods.[2,5] Patients should also be instructed to recognize early signs and symptoms of complications and to stop activity immediately if they occur.[2,5] In high-altitude settings, a gradual acclimatisation should be encouraged to reduce complications.[2]

It is important to highlight that preconception genetic counselling in essential in these individuals once they plan family life. Their partner should be studied and a medical review should happen before the pregnancy. Fertility techniques may be needed to prevent more severe forms of haemoglobinopathy if the parents have relevant abnormalities.[2]

This case highlights the importance of recognizing and understanding the interaction between genetic, infectious, and environmental factors in managing patients with sickle cell trait.

ETHICAL CONSIDERATIONS

The authors declare no conflicts of interest. Informed consent was obtained from the child's legal guardian, and confidentiality of the patient's data was ensured.

AUTHORSHIP

Beatriz Henriques - Investigation; Data curation, Writing –

original draft
Rita Martins - Writing – original draft
Ana Ventura - Conceptualization; Writing – review & editing; supervision
Teresa Ferreira - Writing – review & editing; supervision

REFERENCES

1. Kotila TR. Sickle Cell Trait: A Benign State? Acta Haematol. 2016;136(3):147-51. doi: https://doi.org/10.1159/000446526. Epub 2016 Jul 16.
2. Pinto VM, De Franceschi L, Gianesin B, Gigante A, Graziadei G, Lombardini L, *et al*. Management of the Sickle Cell Trait: An Opinion by Expert Panel Members. J Clin Med. 2023 May 12;12(10):3441. doi: https://doi.org/10.3390/jcm12103441.
3. Ashorobi D, Ramsey A, Killeen RB, Bhatt R. Sickle Cell Trait. 2024 Feb 25. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 30725815.
4. Naik RP, Haywood C Jr. Sickle cell trait diagnosis: clinical and social implications. Hematology Am Soc Hematol Educ Program. 2015;2015(1):160-7. doi: https://doi.org/10.1182/asheducation-2015.1.160.
5. Shephard RJ. Sickle cell trait: what are the costs and benefits of screening? J Sports Med Phys Fitness. 2016 Dec;56(12):1562-1573. Epub 2016 Feb 3. PMID: 26842866.
6. Jefferson JM, Sims WM, Umeh N, Byeon YJJ, Abdallah KE, Bonham VL, *et al*. Splenic infarction in sickle cell trait: A comprehensive systematic review of case studies. EJHaem. 2021 Aug;2(3):585-600. doi: https://doi.org/10.1002/jha2.248. Epub 2021 Jul 11.
7. Thompson AA. Sickle cell trait testing and athletic participation: a solution in search of a problem? Hematology Am Soc Hematol Educ Program. 2013;2013:632-7. doi: https://doi.org/10.1182/asheducation-2013.1.632.
8. Batista M, Silva C, Gonçalves FMF, Machado M, Freitas S, Silva J, *et al*. Splenic Infarction: A Rare Complication of Infectious Mononucleosis. Cureus. 2023 Apr 11;15(4):e37414. doi: https://doi.org/10.7759/cureus.37414.
9. Heo DH, Baek DY, Oh SM, Hwang JH, Lee CS, Hwang JH. Splenic infarction associated with acute infectious mononucleosis due to Epstein-Barr virus infection. J Med Virol. 2017 Feb;89(2):332-336. doi: https://doi.org/10.1002/jmv.24618. Epub 2016 Jul 6.
10. Nofal R, Zeinali L, Sawaf H. Splenic infarction induced by epstein-barr virus infection in a patient with sickle cell trait. J Paediatr Child Health. 2019 Feb;55(2):249-251. doi: https://doi.org/10.1111/jpc.14376.
11. Ma Z, Wang Z, Zhang X, Yu H. Splenic infarction after Epstein-Barr virus infection in a patient with hereditary spherocytosis: a case report and literature review. BMC Surg. 2022 Apr 9;22(1):136. doi: https://doi.org/10.1186/s12893-022-01580-5.

CORRESPONDENCE TO

Beatriz Henriques
Pediatrics Department
Hospital Professor Doutor Fernando Fonseca
Unidade Local de Saúde Amadora Sintra
IC 19 - Venteira
2720-276 Amadora
Email: beatrizfer.henriques@gmail.com

Received for publication: 06.05.2025
Accepted in revised form: 15.09.2025

Birth and Growth Medical Journal
2026;35(1):38-40. doi:10.25753/BirthGrowthMJ.v35.i1.36907

CLINICAL CASE REPORTS

Surgical approach to rare and atypical odontomas in pediatric age

Jéssica Lourenço[1], Rita Maria Cabral[1], Daniela Alves Pereira[1], Cristina João Cipriano[1], José Amorim[1]

ABSTRACT

Odontomas are classified as benign tumors of the jaws.

In pediatric patients, they typically present as solitary intraosseous lesions. These anomalies may be triggered by traumatic, infectious, or genetic factors, and are often associated with the retention of deciduous teeth, delayed eruption of permanent teeth, agenesis, tooth displacement, occlusal changes, and cortical bone expansion.

Radiographically, they appear as radiopaque lesions with well-defined external margins, sometimes surrounded by a radiolucent halo, reflecting their slow growth and non-aggressive behavior.

Surgical planning should be performed with the aid of intraoral and panoramic radiographs, complemented when necessary by computed tomography. Due to the possibility of interfering with normal tooth eruption and the (reduced) risk of associated cystic lesions or secondary tumors, such as ameloblastomas, enucleation with bone curettage is recommended.

The present study aims to describe two cases of atypical presentations of odontomas, along with their surgical approach and follow-up.

Keywords: agenesis; benign tumors; odontoma; radiograph

1. Stomatology and Maxillofacial Surgery Department, Unidade Local de Saúde de Santo António. 4099-001 Porto, Portugal.
jessica_lorr@hotmail.com; ritacabral19@hotmail.com; danielaalvespereira@hotmail.com; cristinajoao3@gmail.com; resingao@gmail.com

INTRODUCTION

Odontomas are benign tumors of the jaws, also referred to as hamartomas. Hamartomas are malformations that will rarely have the potential to become malign. It can grow in any part of the body, in the same proportion as neighboring cells, but it develops disorganized.[1]

Odontomas originate from the odontogenic epithelium and ectomesenchyma, with reports describing abnormally excessive growth of organic enamel cells with a characteristic structural derangement. The most frequent types are compound odontoma, formed by material identical to small teeth, and complex odontoma, composed of disorganized dental tissue.[2,3]

The compound odontoma typically presents radiographically as a jaw lesion containing small tooth-like structures (denticles), with a predilection for the anterior maxilla (second sextant). Complex odontoma, characterized by an amorphous radiopaque mass of disorganized dental tissue, is usually found in the posterior sextants (fourth and sixth), often requiring differential diagnosis from other benign tumors or bone lesions.[3,4]

CLINICAL CASES

We present two clinical cases of odontomas, with special interest due to their atypical location, number and presentation.

Case 1: A healthy ten-year-old female presented with slight bulging of the jugal mucosa in the canine region (third quadrant). A panoramic radiograph was taken (**Figure 1**). On clinical examination, no additional alterations were observed.

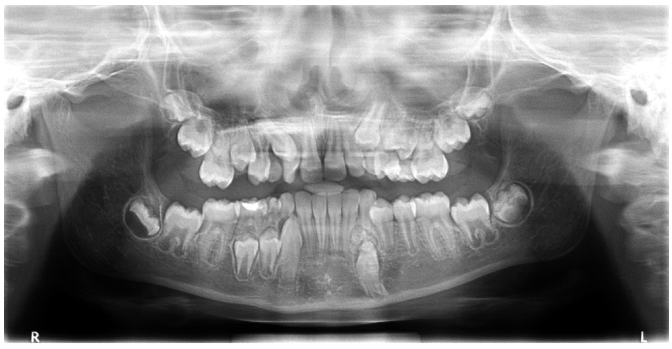


Figure 1 - Lesion in the 3rd quadrant that conditions delay in the progression of the definitive canine eruption, compared to the contralateral canine.

Case 2: A twelve-year-old male with a history of multi-relapsing nephrotic syndrome seeking care for abnormal dental positioning. Clinical examination revealed mixed dentition with the persistence of teeth 75 and 85 in the lower arch. Panoramic radiography and computed tomography were performed (**Figures 2 and 3**).

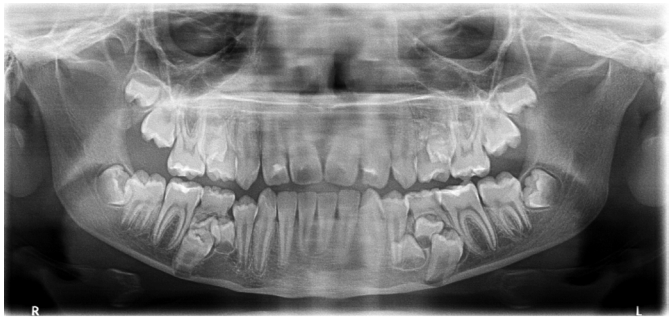


Figure 2 - Bilateral lesions in the lower arch conditioning the eruption of teeth 35 and 45, suggestive of supernumerary teeth or odontomas.

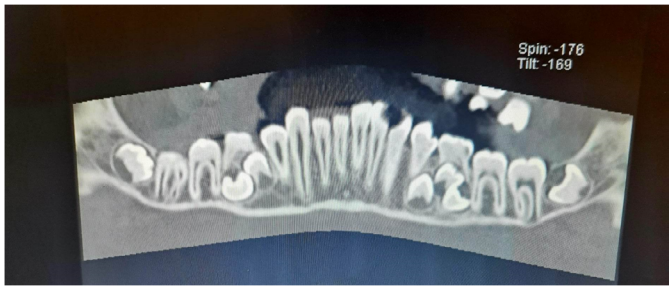


Figure 3 - Computed tomography that corroborates the diagnostic hypothesis.

In both cases, surgical enucleation of the lesion was planned under general anesthesia. The procedure included raising a mucoperiosteal flap, exposure of the vestibular cortical region with visualization of the mental nerve, followed by osteotomy to access the lesion. The tooth-like structures were removed, and alveoloplasty was carried out to regularize the alveolar bone ridges. Gingivoplasty was then performed for flap closure (**Figures 4 and 5**).

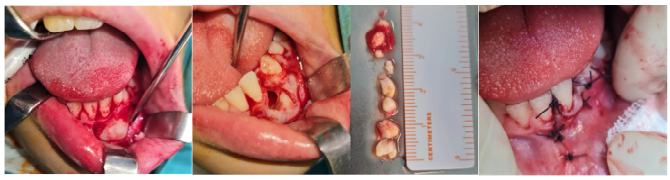


Figure 4 - Image sequence of the operative moment of clinical case 1

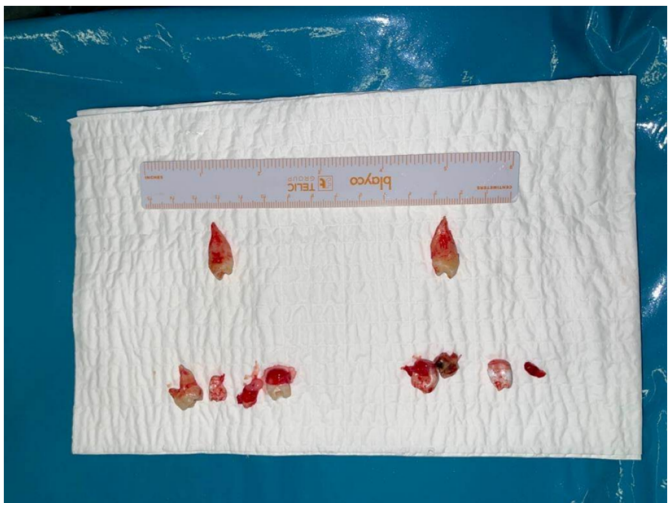


Figure 5 - Photographic record of the lesions removed from the lower arch in clinical case 2

DISCUSSION AND CONCLUSION

In most cases, odontomas are suspected based on imaging findings, however, definitive diagnosis requires intraoperative examination and histopathological confirmation. Histology allows for identification of the dental tissue components present and the degree of structural disorganization.[4,5]

In Case 1, the lesion was located in the fifth sextant, an atypical site. Histological examination identified fragments of fibrous connective tissue consistent with dental pulp, along with cementum-like material. These findings supported the diagnosis of compound odontoma.

In Case 2, lesions were observed bilaterally, also in an atypical presentation. Computed tomography suggested the presence of supernumerary or rudimentary teeth. Histopathological examination confirmed organized dental structures resembling small teeth, but with no eruptive potential. These findings supported the diagnosis of compound odontoma. Postsurgical imaging revealed successful removal of the odontomas and proper eruption of the second premolars.

Odontomas can lead to several complications, including mucosal bulging resembling ectopic eruption, retention of deciduous teeth, delayed eruption of permanent teeth, agenesis, dental displacement, malocclusion, cortical bone expansion, pain, sensory disturbances, and a (reduced) risk of cystic or tumoral transformation. For these reasons, enucleation combined with bone curettage is recommended.[5]

This procedure remains the standard treatment for odontomas; however, careful preoperative imaging and surgical planning are essential to preserve adjacent permanent teeth.

The two cases reported highlight the clinical significance of recognizing atypical presentations and the value of imaging and histopathological examination to confirm the diagnosis and guide appropriate treatment.

AUTHORSHIP

Jéssica Lourenço – Conceptualization; Data curation; Formal Analysis; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing

José Amorim - Conceptualization; Data curation; Formal Analysis; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing

Rita Maria Cabral – Data curation; Validation; Visualization; Writing – review & editing

Daniela Alves Pereira – Data curation; Validation; Visualization; Writing – review & editing

Cristina João Cipriano - Data curation; Validation; Visualization; Writing – review & editing

REFERENCES

1. Olivares DAD, Simonato LE, Tomo S. Compound odontoma: a literature review. Rev Ibero-Am Humanid Cienc Educ. 2022;8(5):1179–1199. doi: https://doi.org/10.51891/rease.v8i5.5523.
2. Jaeger F, López Alvarenga R, Lage FO, Reis IA, Leal RM. Odontoma composto: relato de caso clínico. Rev Port Estomatol Med Dent Cir Maxilofac. 2012;53(4):252–257.
3. Fernandez MS, Santos LA, Barreto RGS, Oliveira CCC, Viana VS. Impactação de dentes permanentes associado a odontoma composto em paciente infantil: relato de caso. Arch Health Investig. 2021;10(3):396–401. doi: https://doi.org/10.21270/archi.v10i3.4921.
4. Neville DD, Allen CM, Chi AC. Oral and maxillofacial pathology. 4th ed. St. Louis: Elsevier; 2016.
5. Longo BC, Kuhn L, Tomasin MFM, Tomasin Neto A, Grizza G, Souza MDB. Tratamento cirúrgico e ortodôntico de odontoma complexo em região anterior de maxila. J Bras Patol Med Lab. 2020;56:1–6. doi: https://doi.org/10.5935/1676-2444.20200050.

CORRESPONDENCE TO

Jéssica Lourenço
Stomatology and Maxillofacial Surgery Department
Unidade Local de Saúde de Santo António
Largo Prof. Abel Salazar
4099-001 Porto
Email: jessica_lorr@hotmail.com

Received for publication: 01.08.2024
Accepted in revised form: 06.10.2025

CLINICAL CASE REPORTS

The Role Of Fungi In Cystic Fibrosis: Actors Or Bystanders? - Two Cases Report

Isabel Morais Ribeiro[1], Dora Fonseca Sousa[1], Ana Ascensão Matias[1], Ana Lúcia Cardoso[2], Telma Barbosa[3]

ABSTRACT

Introduction: Fungal infections increasingly contribute to morbidity in patients with cystic fibrosis (CF). Despite their rising incidence, there is considerable controversy surrounding the treatment and eradication of these infections in CF.

Case presentation: We present two CF patients: the first patient was largely asymptomatic despite intermittent detection of *Scedosporium spp*, while the second case experienced frequent pulmonary exacerbations (PEx) with persistent detection of both *Aspergillus fumigatus* (*A. fumigatus)* and *Scedosporium spp*. Both patients showed improvement after initiating the modulator therapy. Case 1 achieved complete eradication of fungal colonization, while case 2 remained sensitized to *A. fumigatus* but experienced fewer fungal exacerbations.

Discussion: These case reports underscore the variable clinical significance of fungal infections in CF and highlight the ongoing uncertainty regarding their role in disease progression. Further research is essential to elucidate their impact on CF and develop more tailored treatment strategies.

Keywords: antifungal agents; cystic fibrosis; fungi; hypersensitivity; pulmonary aspergillosis

1. Department of Pediatrics, Centro Materno-Infantil do Norte, Unidade Local de Saúde de Santo António. 4050-651 Porto, Portugal. u14510@chporto.min-saude.pt; u13467@chporto.min-saude.pt; u15017@chporto.min-saude.pt
2. Cystic Fibrosis Reference Center, Centro Materno-Infantil do Norte, Unidade Local de Saúde de Santo António. 4050-651 Porto, Portugal. u11135@chporto.min-saude.pt
3. Pediatric Pulmonology Unit, Department of Pediatrics, Centro Materno-Infantil do Norte, Unidade Local de Saúde de Santo António. 4050-651 Porto, Portugal. telmab@gmail.com

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder that affects multiple organ systems, particularly the respiratory and digestive systems. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which lead to the production of abnormally thick and sticky mucus in the airways, pancreas, and other organs.[1] This mucus obstructs the airways and impairs the clearance of bacteria and other microorganisms, leading to recurrent infections and chronic inflammation in the lungs.

CF is the most common genetic disorder among Caucasians and its prevalence varies significantly according to the geographic location. The highest incidence was observed in individuals of Northern European descent. Globally, it is estimated that approximately 162,428 individuals [range: 144,606–186,620] are living with CF across 94 countries, of whom around 105,352 (65%) have been formally diagnosed.[2]

Despite significant advances in treatment and management, CF remains a life-limiting disease, with a median predicted survival age of approximately 40 years. The clinical course of CF can vary widely, and patients may experience a range of symptoms and complications including respiratory distress, malnutrition, pancreatic insufficiency, and diabetes.

The respiratory system is one of the most frequently implicated in CF, and chronic infections are major contributors to morbidity and mortality. The thick and sticky mucus that characterizes CF provides an ideal environment for bacteria and other microorganisms to grow and thrive, leading to recurrent respiratory infections. These infections trigger an exaggerated and prolonged inflammatory response in the airway, leading to tissue damage and scarring. Chronic inflammation and lung damage can lead to respiratory failure and other complications. The management of respiratory infections in CF is a key component of patient care and involves aggressive and targeted use of antibiotics, airway clearance techniques, and other therapies aimed at preventing or minimizing lung damage.

In recent years, fungal respiratory infections have emerged as significant contributors to the morbidity and disease progression in patients with CF. However, the extent of fungal infection in the airways remains unclear, and the prevalence and clinical significance of fungal communities in sputum are not well understood.[3,4] The complex pathogenesis involves a combination of genetic, environmental and microbiological factors, with thick CF mucus that promotes fungal colonization.[2] Additionally, the use of antibiotics and other CF therapies can disrupt the respiratory microbiome, further promoting fungal growth and exacerbating the underlying lung disease.

Despite the increasing incidence of fungal infections in CF, there is considerable controversy surrounding their treatment and eradication.[3] This is partly due to the lack of guidelines for managing fungal infections in this disease. Given the potential of these infections to exacerbate lung disease and worsen clinical outcomes, further research is needed to guide clinical practice and improve patient care. In this report, we present two pediatric CF cases of fungal infections and discuss their clinical implications and management strategies.

Case 1

Presentation: A six-year-old girl presented to the pediatric pulmonology consultation with four episodes of pneumonia over four years, each requiring antibiotic treatment and poor weight gain since twelve months of age. Despite treatment with inhaled corticosteroids and antihistamines, the patient continued to suffer from a persistent, productive cough that was non-seasonal. Additionally, she reported frequent mucus passage in her stools, although steatorrhea was not observed. Family history was unremarkable.

Upon physical examination, the patient presented with a thoracic deformity, digital clubbing, nasal turbinate hypertrophy, and occasional crackles in the lungs during auscultation.

Diagnosis: A sweat test was positive, with chloride levels of 110 mmol/L and 130 mmol/L. Genetic testing confirmed the diagnosis of cystic fibrosis (CF) at six years of age, revealing the presence of the F508del mutation in both CFTR alleles. Comprehensive evaluations indicated additional CF-related complications, including hepatic steatosis on abdominal ultrasound and low levels of vitamins A and D, suggestive of malabsorption and nutritional deficiencies. Pancreatic insufficiency was also detected, with fecal elastase levels < 15 µg/g. Initial thoracic CT revealed bronchial wall thickening, tubular bronchiectasis, and laminar and subsegmental atelectasis (**Figure 1**).

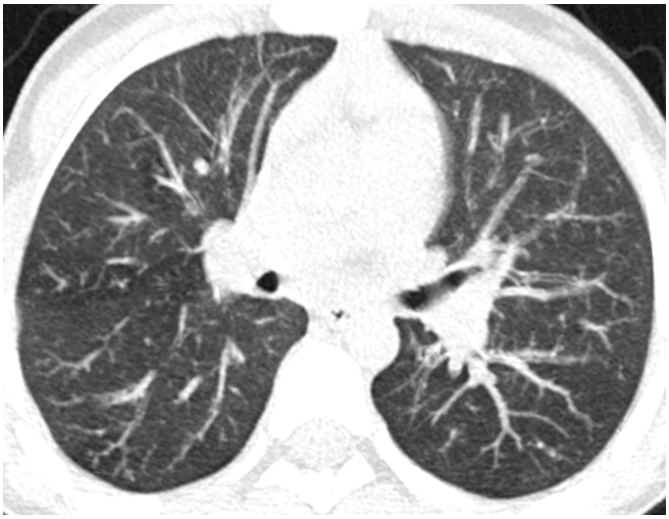


Figure 1 - Thoracic CT revealing thickening of the bronchial walls, tubular bronchiectasis, and laminar and subsegmental atelectasis

Initial Treatment: The patient began treatment with pancreatic enzyme replacement therapy (pancreatin), inhaled dornase alfa, and salbutamol, accompanied by respiratory physiotherapy and swimming exercises.

Progression and Complications: She experienced mild and sporadic pulmonary exacerbations (PEx), during which *Serratia marcescens* and *Achromobacter species* were intermittently identified. These exacerbations responded well to the oral outpatient antibiotic treatment. At age seven, *Aspergillus fumigatus (A. fumigatus)* was first detected in her sputum, and from age eight onwards, *Scedosporium spp.* were intermittently identified. Despite these fungal detections, the patient did not exhibit any clinical signs of fungal infections such as persistent or worsening cough or brown/black plugs in sputum. There was no eosinophilia, and both the total and specific IgE levels for *A. fumigatus* were consistently negative. Despite the occasional identification of *Scedosporium spp*, there was no increase in the frequency of pulmonary exacerbations, and her lung function remained stable, with a recent FEV1 (Forced Expiratory Volume in one second) of 85%. Accordingly, the patient did not require antifungal therapy or corticosteroids.

Advanced Treatment: At the age of nine years, the patient started combination therapy with lumacaftor/ivacaftor, resulting in a significant improvement in overall health, control of cough and gastrointestinal symptoms, reduced frequency of exacerbations and antibiotic courses. Prior to lumacaftor/ivacaftor initiation, the patient's FEV1 was 83% predicted. After one year of lumacaftor/ivacaftor therapy, FEV1 increased to 103% predicted.

At age 11, she transitioned to elexacaftor/tezacaftor/ivacaftor (ETI) therapy, which further stabilized her condition with FEV1 further improving to 126% predicted. Her chloride level was last measured at 37 mmol/L, and since starting this regimen, there has been no further detection of fungal species in her sputum. No adverse effects were observed.

Case 2

Presentation and Diagnosis: A newborn girl was diagnosed with cystic fibrosis through the neonatal screening program. Genetic testing revealed a heterozygous F508del mutation, characterized by a deletion in exon 16 and a duplication in exon 19, with no additional mutations identified after whole CFTR gene sequenced.

Since birth, elevated sweat chloride levels (Cl^- 113 mmol/L) have consistently been observed. The patient also presented with severe pancreatic insufficiency (fecal elastase <15 µg/g) in the first few months of life, as well as progressive respiratory insufficiency, requiring noninvasive ventilation during sleep and oxygen therapy.

Progression and Complications: The patient developed chronic bacterial colonization of the respiratory tract during the first year of life (*Table 1 – Bacterial colonization*), associated with frequent pulmonary exacerbations (PEx). The first eradication of *Pseudomonas aeruginosa* was achieved at six months of age.

She was started on continuous inhaled antibiotic therapy with tobramycin before the age of 2, in addition to standard baseline treatment with pancreatin, inhaled dornase alfa, and daily respiratory physiotherapy. At 4 years of age, the inhaled antibiotic was switched to colistimethate sodium, and by age 5, she transitioned to alternating cycles of aztreonam and colistin.

Pulmonary exacerbations were intermittently caused by *Stenotrophomonas maltophilia, Serratia marcescens,* and *Pseudomonas aeruginosa*. In the first six years of life, she required an average of 2.5 intravenous antibiotic courses per year, in addition to multiple oral antibiotic treatments. Due to the COVID-19 pandemic, spirometry to assess lung function was not yet feasible during this period.

Table 1 - Chronic bacterial colonization during the first 6 years of life and after ETI initiation.

Age of life	***Chronic bacterial colonization***
<12 months	***Pseudomonas aeruginosa, Stenotrophomona maltophilia,*** *Meticillin-Sensitive Staphylococcus aureus (MSSA),* ***Haemophilus*** *influenzae, Moraxella*
2 years	***Pseudomonas aeruginosa,*** *MSSA*
3 years	*MSSA****, Pseudomonas aeruginosa, Haemophilus*** *influenzae*
4 years	*MSSA,* ***Stenotrophomona maltophilia****, Enterobacter Cloacae,* ***Haemophilus*** *influenzae, Achromobacter xylosoxidans, Moraxella catarrhalis*
5 years	*MSSA,* ***Stenotrophomonas maltophilia,*** *S. aureus*
6 years	*MSSA, Pseudomonas putida, S.aureus, Haemophilus parainfluenzae,* ***Stenotrophomonas maltophilia****, Enterobacter cloacae*
9 – 10 years	***Haemophilus*** *influenzae*

Fungal infection with *Aspergillus fumigatus* was first detected at 5 years of age. One year later, the patient experienced a clinical exacerbation characterized by anorexia and cough with brownish sputum plugs, fulfilling diagnostic criteria for Allergic Bronchopulmonary Aspergillosis (ABPA). The diagnosis was supported by the following findings: specific IgE to *A. fumigatus* of 49.78 kUA/L, anti-*Aspergillus* IgG of 67 mg/L, a peak total IgE of 2404 kU/L, and an eosinophil count of 690/µL. Thoracic computed tomography (CT) revealed pulmonary infiltrates and segmental collapse (**Figure 2**). Over the course of corticosteroid and itraconazole treatment (two and four months respectively), a favorable clinical response was observed with reduction in exacerbations and a progressive decline in total IgE levels to 656 kU/L.

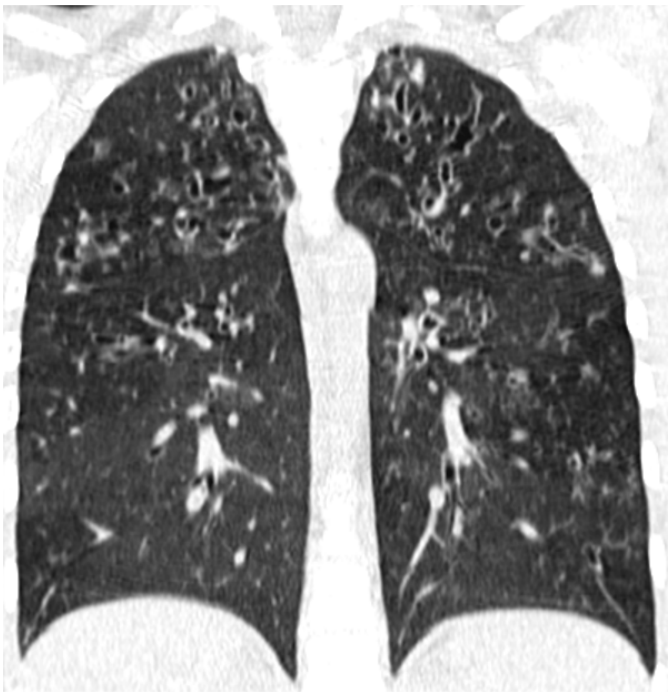


Figure 2 - CT thoracic - Multiple varicose and cystic type bronchiectasis, scattered bilaterally with a central predominance. Presence of endoluminal content at the level of the bronchial structures in the left upper lobe and both lower lobes.

The patient's first lung function assessment with spirometry was performed six months after the ABPA episode, revealing an FEV_1 of 0.93 L (77% predicted) and an FVC of 1.08 L (80% predicted).

Subsequent respiratory cultures showed persistent colonization with *Scedosporium* spp., accompanied by continued elevation of total IgE levels. These findings prompted multiple courses of antifungal therapy (voriconazole and terbinafine) as well as repeated corticosteroid treatment. Although a modest improvement in lung function was observed [FEV_1 1.09 L (82%), FVC 1.30 L (88.4%)], clinical exacerbations recurred upon discontinuation of corticosteroids.

Chronic bacterial colonization of the respiratory tract also persisted during this period, with an increase in pulmonary exacerbations to approximately four/five episodes per year.

Advanced Treatment: At 8.5 years of age, the patient experienced a marked clinical improvement following the initiation of CFTR modulator therapy with elexacaftor/tezacaftor/ivacaftor (ETI). Her lung function improved significantly, with FEV_1 rising to 1.68 L (105.9% predicted), and pulmonary exacerbations became well controlled. This clinical stability allowed for the discontinuation of both corticosteroid therapy and continuous inhaled antibiotic treatment. Over the subsequent three years, she remained free from any antibiotic courses.

Despite the clinical improvement, the patient continued to show markers of sensitization to *A. fumigatus*, with a total IgE of 1809 kU/L, IgG anti-*Aspergillus* of 89.4 mg/L, and specific IgE to *Aspergillus fumigatus* at 22.6 kUA/L. ImmunoCAP® ISAC testing further identified specific IgE sensitization to Asp f 1 (6.2 ISU-E) and Asp f 6 (4.5 ISU-E).

DISCUSSION

The prevalence of fungal identification in respiratory samples from patients with cystic fibrosis (CF) has increased significantly over recent decades. This rise has been attributed to several factors, including prolonged use of inhaled antibiotics and corticosteroids, an aging CF population, and improvements in sample processing and microbiological detection methods.[4,5]

Therefore, fungal diseases are now common in CF, with a wide variety of fungal species identified in the respiratory secretions of CF patients.[6] Multiple factors contribute to the increased susceptibility of CF airways to fungal infections, including the CFTR defect, which leads to impaired mucociliary clearance, thickened mucus, immune dysfunction, and structural lung changes such as bronchiectasis. These alterations predispose patients to colonization, particularly by *Aspergillus fumigatus*.[7]

Aspergillus species, especially *A. fumigatus*, are the most frequently isolated fungi in the respiratory tracts of CF patients. These ubiquitous, spore-forming saprophytes can exacerbate lung disease and accelerate structural damage, especially in children.[7,8] In some cases, *A. fumigatus* causes allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity-mediated lower airway disorder. However, other fungi, such as *Candida albicans* and *Scedosporium* species, have also been implicated. The broader term "allergic bronchopulmonary mycosis" (ABPM) has been proposed to encompass these reactions, including those driven by *Scedosporium*, which may contribute to disease progression.

Diagnosing ABPA in patients with CF is challenging, as many

of its diagnostic criteria overlap with common manifestations of CF-related lung disease, making accurate diagnosis difficult.[9,10] Despite the high prevalence of fungal infections in CF, there is no clear consensus on the clinical significance of *Aspergillus* colonization or the need for routine screening and treatment in the absence of ABPA.[8]

Scedosporium species are the second most common filamentous fungi found in CF airways. While generally well tolerated, they can cause bronchitis and allergic manifestations such as ABPM.[7]

While the presence of fungal species in the respiratory secretions of CF patients has been associated with worse clinical outcomes, including lung function decline and increased exacerbations, the role of fungi in CF disease progression remains unclear. Whether fungi serve as markers of disease progression or act as independent contributors to accelerated lung damage is still debated.[5]

A significant subset of CF patients exhibit evidence of type 2 (T2) inflammation, demonstrated by blood and airway eosinophilia, elevated total IgE, and allergen sensitization. This T2 inflammatory state contributes to disease severity and exacerbation frequency.[13] The advent of CFTR modulator therapy has revolutionized CF management, but its impact on pre-existing T2 inflammation remains unclear.[13]

The two cases presented in this study illustrate the variability in the impact of fungal infections on CF progression, highlighting the challenges in their management.

In **Case 1**, the patient exhibited relatively well-controlled disease, with only mild, sporadic pulmonary exacerbations and occasional identification of *Serratia marcescens* and *Achromobacter* species. However, the persistent presence of *Scedosporium* species from age 8 onwards did not correlate with the clinical symptoms of fungal infection. There was no increase in the frequency of pulmonary exacerbations or a decline in lung function, suggesting that *Scedosporium* colonization in this case may not have been clinically significant. The cessation of fungal sputum identification following the initiation of Elexacaftor/Tezacaftor/Ivacaftor therapy further supports the notion that better-controlled disease may reduce fungal colonization.

In contrast, **Case 2** involved a patient with a more severe clinical course, characterized by frequent exacerbations and persistent lung function impairment despite intensive and targeted therapies, including systemic and inhaled corticosteroids, antifungals and antibiotics. The patient met diagnostic criteria for ABPA and responded well to systemic corticosteroids and itraconazole. While corticosteroids remain the mainstay of ABPA treatment, their long-term efficacy is uncertain, and side effects are considerable. Azole antifungals like itraconazole are recommended for targeting *A. fumigatus*.[10]

Despite antifungal and corticosteroid therapy, this patient showed continued *Scedosporium* colonization and elevated total IgE levels, with recurrent exacerbations, suggesting that hypersensitivity to *Scedosporium* may have contributed to disease progression. Omalizumab was considered but deferred due to the opportunity to initiate modulator therapy. Following CFTR modulator initiation, the patient experienced a marked clinical improvement, with no further hospitalizations and significantly fewer pulmonary exacerbations.

While CFTR modulators do not directly address T2 inflammation, they improve mucociliary clearance and reduce mucus production, thereby decreasing fungal colonization. Indirectly, this may help reduce IgE levels.[13] One study demonstrated that CFTR modulators reduce exaggerated reactive oxygen species (ROS) production in CF immune cells infected with *Aspergillus*, suggesting a potential immunomodulatory effect.[11] Other studies have reported decreased *Aspergillus* colonization following initiation of ivacaftor.[12]

In our cases, a temporal relationship was observed between CFTR modulator therapy and reduced fungal colonization, though with variable clinical outcomes. **Case 1** showed complete eradication of fungal colonization, while **Case 2** maintained sensitization to *A. fumigatus* but experienced fewer exacerbations. These findings highlight ongoing uncertainties regarding the role of fungal infections in CF and the potential immunomodulatory and antimicrobial effects of modulator therapy.

Further research is needed to clarify the clinical impact of fungal colonization on CF progression and to inform more tailored management strategies.

CONCLUSION

These cases underscore the need for greater awareness and understanding of fungal infections in CF patients, emphasizing the importance of a personalized approach to patient care. The concept of ABPM provides a useful framework for managing CF patients with fungal diseases, although further research is needed to determine whether early fungal infections independently contribute to accelerated lung disease progression.

The successful use of modulator therapy in both cases demonstrates the potential benefits of this new class of drugs in managing CF patients with fungal infections, and warrants further investigation in larger studies.

CONSENT

Written informed consent was obtained from the patients for the publication of this report in accordance with the journal's patient consent policy.

AUTHORSHIP

Isabel Morais Ribeiro - Conceptualization; Data curation; Writing – original draft; Writing – review & editing

Dora Fonseca Sousa – Data curation; Writing – review & editing

Ana Ascensão Matias - Data curation; Writing – review & editing

Ana Lúcia Cardoso – Conceptualization; Supervision; Critical review; Writing – original draft; Writing – review & editing

Telma Barbosa – Conceptualization; Supervision; Critical review; Writing – review & editing

REFERENCES

1. King PT. The pathophysiology of bronchiectasis. Int J Chron Obstruct Pulmon Dis. 2009;4:411–419. doi: https://doi.org/10.2147/COPD.S6133.
2. Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros. 2022;21(3):456–462. doi: https://doi.org/10.1016/j.jcf.2022.01.009.
3. Liu JC, Modha DE, Gaillard EA. What is the clinical significance of filamentous fungi positive sputum cultures in patients with cystic fibrosis? J Cyst Fibros. 2013;12(3):187–193. doi: https://doi.org/10.1016/j.jcf.2013.02.003.
4. Nguyen LD, Viscogliosi E, Delhaes L. The lung mycobiome: an emerging field of the human respiratory microbiome. Front Microbiol. 2015;6:89. doi: https://doi.org/10.3389/fmicb.2015.00089.
5. Singh A, Ralhan A, Schwarz C, *et al*. Fungal pathogens in CF airways: leave or treat? Mycopathologia. 2017;183(1):119–137. doi: https://doi.org/10.1007/s11046-017-0184-y.
6. Engel TG, Slabbers L, de Jong C, *et al*. Prevalence and diversity of filamentous fungi in the airways of cystic fibrosis patients: a Dutch multicentre study. J Cyst Fibros. 2019;18(2):221–226. doi: https://doi.org/10.1016/j.jcf.2018.11.012.
7. Bouchara JP, Le Govic Y, Kabbara S, *et al*. Advances in understanding and managing Scedosporium respiratory infections in patients with cystic fibrosis. Expert Rev Respir Med. 2020;14(3):259–273. doi: https://doi.org/10.1080/17476348.2020.1705787.
8. Breuer O, Schultz A, Garratt LW, *et al*. Aspergillus infections and progression of structural lung disease in children with cystic fibrosis. Am J Respir Crit Care Med. 2020;201(6):688–696. doi: https://doi.org/10.1164/rccm.201908-1585OC.
9. Balfour-Lynn IM, editor. Clinical guidelines: care of children with cystic fibrosis. 9th ed. London: Royal Brompton Hospital; 2023. Available from: https://www.rbht.nhs.uk/childrencf
10. Francis NZ, Southern KW. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis. Cochrane Database Syst Rev. 2022;9:CD002204. doi: https://doi.org/10.1002/14651858.CD002204.pub5.
11. Currie AJ, Main ET, Wilson HM, *et al.* CFTR modulators dampen Aspergillus-induced reactive oxygen species production by cystic fibrosis phagocytes. Front Cell Infect Microbiol. 2020;10:372. doi: https://doi.org/10.3389/fcimb.2020.00372.
12. Bessonova L, *et al*. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. Thorax. 2018;73(8):731–740. doi: https://doi.org/10.1136/thoraxjnl-2017-210394.
13. Mehta AM, Lee I, Li G, *et al*. The impact of CFTR modulator triple therapy on type 2 inflammatory response in patients with cystic fibrosis. Allergy Asthma Clin Immunol. 2023;19:66. doi: https://doi.org/10.1186/s13223-023-00822-2.

CORRESPONDENCE TO

Isabel Morais Ribeiro
Department of Pediatrics
Centro Materno-Infantil do Norte
Unidade Local de Saúde de Santo António
Largo da Maternidade de Júlio Dinis 17
4050-651 Porto
Email: u14510@chporto.min-saude.pt

Received for publication: 05.01.2025
Accepted in revised form: 17.10.2025

CLINICAL CASE REPORTS

Prenatal Diagnosis of Townes-Brocks Syndrome with Multicystic Renal Dysplasia: A Multisystem Genomic Perspective

Miguel Martins[1], Beatriz Sousa Ferreira[1], Rosário Almeida Lopes[1], Ana Isabel Correia[1], Rosário Pinto Leite[2], Márcia Martins[2], Rosete Nogueira[3,4,5], Osvaldo Moutinho[1]

ABSTRACT

Background: Townes-Brocks syndrome (TBS) is a rare autosomal-dominant disorder characterized by the anal-auricular-digital triad and frequent renal anomalies.

Case Presentation: A male fetus was first examined at 18w3d, showing unilateral multicystic renal dysplasia and preaxial polydactyly. Standard karyotype (46,XY) and chromosomal

microarray (Agilent 4 × 180 K) were normal. Rapid trio-exome sequencing detected a *de novo* truncating *SALL1* variant (c.1147_1151del), confirming the diagnosis of TBS. After multidisciplinary counselling, medical termination of pregnancy was performed at 23w6d.

Fetal autopsy confirmed sonographic findings and additionally disclosed intestinal malrotation.

Discussion: This case illustrates the diagnostic value of prenatal exome analysis in fetuses with atypical renal and limb anomalies and underscores that recognizing the classic anal-auricular-digital pattern remains pivotal.

Conclusion: When multicystic renal dysplasia coexists with imperforate anus and preaxial limb defects, targeted *SALL1* gene analysis should be prioritized. Integrating imaging, genomics and autopsy enables precise phenotyping and informed recurrence-risk assessment.

Keywords: case report; fetal anomalies; genomics; multicystic renal dysplasia; prenatal diagnosis and autopsy correlation; sall1; townes-brocks syndrome

1. Gynecology and Obstetrics Department, Unidade Local de Saúde de Trás-os-Montes e Alto Douro. 5000-508 Vila Real, Portugal. intgomiguel.martins@gmail.com; bia.sousaferreira@gmail.com; rosarioalmeidalopes@gmail.com; anacorreia87@gmail.com; osvaldomoutinho@gmail.com
2. Genetics Department, Unidade Local de Saúde de Trás-os-Montes e Alto Douro. 5000-508 Vila Real, Portugal. mlleite@chtmad.min-saude.pt; marciam@chtmad.min-saude.pt
3. Escola de Medicina da Universidade do Minho. 4710-057 Braga, Portugal. rosetenogueira@gmail.com
4. Instituto de investigação de ciências da vida e saúde (ICVS); ICVS/3B´s PT Laboratório Associado, 4710-057 Braga - Guimarães, Portugal. rosetenogueira@gmail.com
5. Placental and Embryo-Fetal Pathology Unit, LAP, Unilabs. 4250-170 Porto, Portugal. rosetenogueira@gmail.com

INTRODUCTION

Townes-Brocks syndrome or anus-hand-ear syndrome (TBS; OMIM#107480) stems from pathogenic variants in the *SALL1* gene and classically presents with imperforate anus, dysplastic ears and preaxial radial ray defects.[1] Although renal involvement occurs in up to 50% of cases, prenatal recognition is challenging, particularly when renal anomalies dominate the phenotype.[2] Advances in rapid trio-based exome sequencing (ES) have markedly improved elucidation of syndromic fetal malformations. Here, we report a fetus with unilateral multicystic renal dysplasia in whom ES yielded a definitive diagnosis of TBS, allowing informed counselling in line with the ethical principles of the Declaration of Helsinki.

CASE DESCRIPTION

A 29-year-old primigravida was referred at 18w3d after routine ultrasonography revealed a markedly enlarged, multicystic left kidney with absent contralateral abnormalities. Amniotic fluid volume was normal and there were no dysmorphic facial features. Detailed fetal ultrasound detected duplication of the left thumb without radial hypoplasia. Unfortunately, ultrasound images from local hospitals were unavailable for review.

Invasive testing via amniocentesis demonstrated a normal male karyotype (46,XY). Chromosomal microarray (Agilent 4 × 180 K) was unremarkable. Given the association of renal dysplasia and preaxial anomalies, rapid trio-ES was undertaken (turnaround ≈ 10 days). Analysis identified a heterozygous frameshift variant in the *SALL1*gene [NM_002968.4:c.1147_1151del p.(Lys383Argfs*62)] absent from gnomAD and predicted to escape nonsense-mediated decay, consistent with dominant-negative pathogenesis.[3,4] Parental ES confirmed the variant was *de novo*. American College of Medical Genetics and Genomics (ACMG) criteria classified it as pathogenic (PVS1, PS2, PM2).[5]

A multidisciplinary meeting involving obstetrics, clinical genetics, neonatology and pediatric nephrology discussed the reserved renal prognosis and variable neurodevelopmental outcomes. Following comprehensive counselling, the parents opted for medical termination of pregnancy at 23w6d.

Autopsy Findings

External examination (**Figures A and B**) revealed a coarse facies, low-set, posteriorly rotated ears with a preauricular pit, and left thumb duplication. No radial hypoplasia was present. The feet showed asymmetric camptodactyly and clinodactyly.

Internal examination (**Figures C, D and E**) revealed complete absence of the anal canal, consistent with a high anorectal malformation. The gastrointestinal tract showed intestinal malrotation, with abnormal positioning of the stomach and ileocecal appendix. The urinary tract demonstrated unilateral multicystic renal dysplasia on the left kidney, with normal bladder, prostate, and urethra.

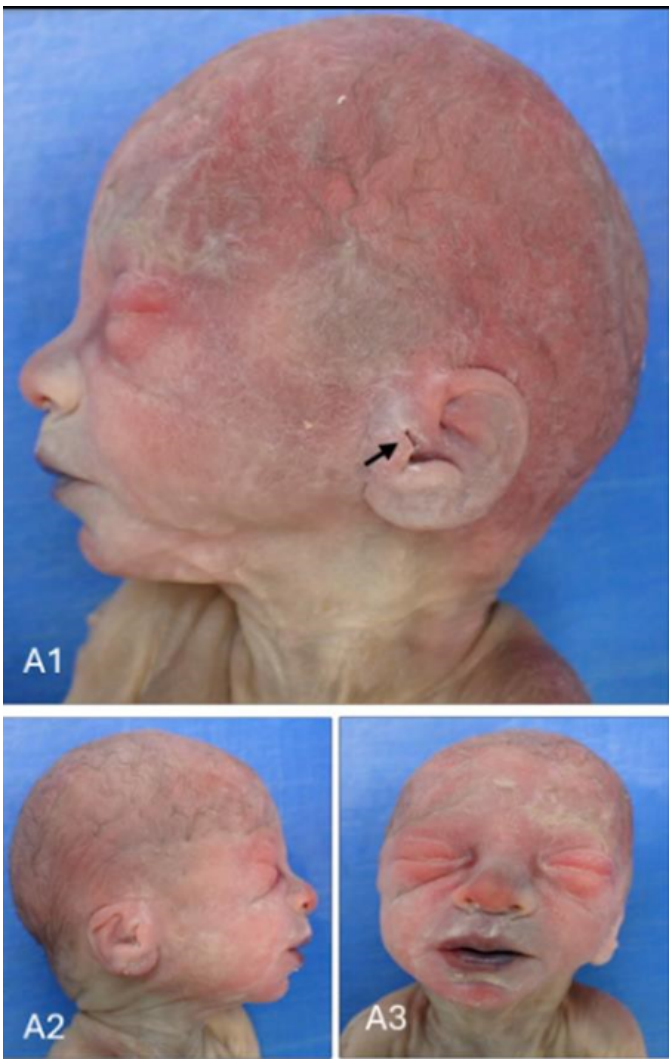


Figure A - External findings – (A1, 2), Dysplastic, low-set ears with a preauricular pit (arrow); (A3), coarse facial features.

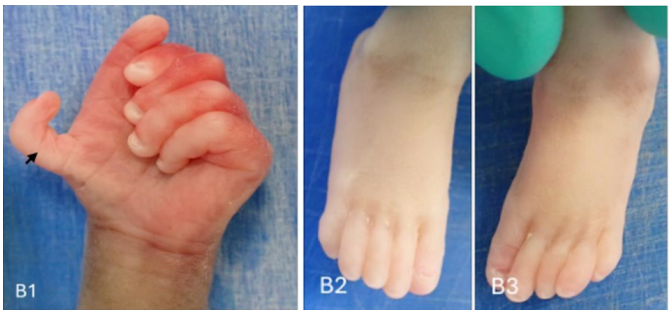


Figure B - External Findings – (B1) Malformation of the left thumb (small arrow) without radial hypoplasia; (B2, B3) Asymmetric camptodactyly and clinodactyly of the feet.

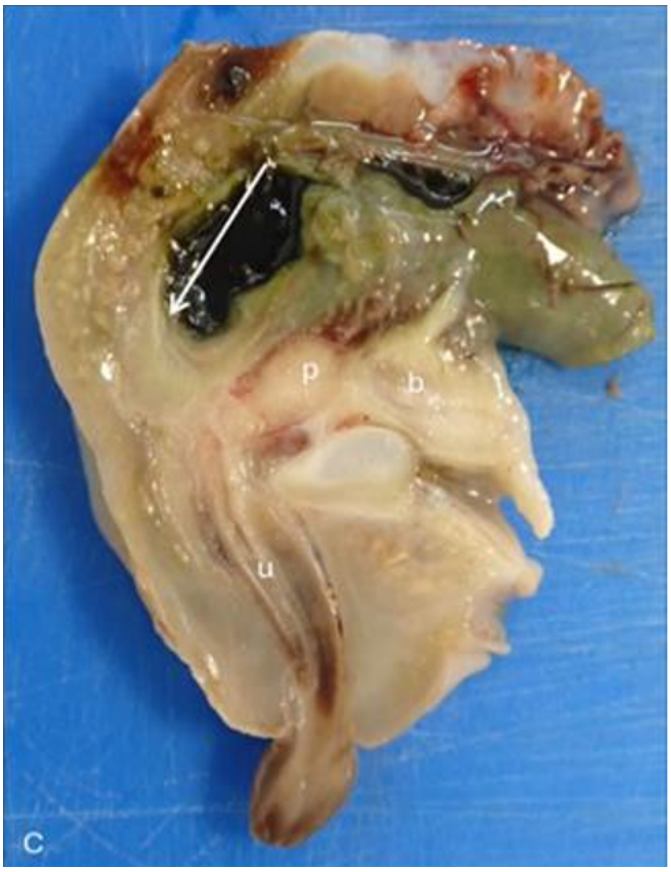


Figure C - Internal findings – anorectal malformation (arrow) with anal atresia; bladder (b), prostate (p), and urethra (u) are identified.

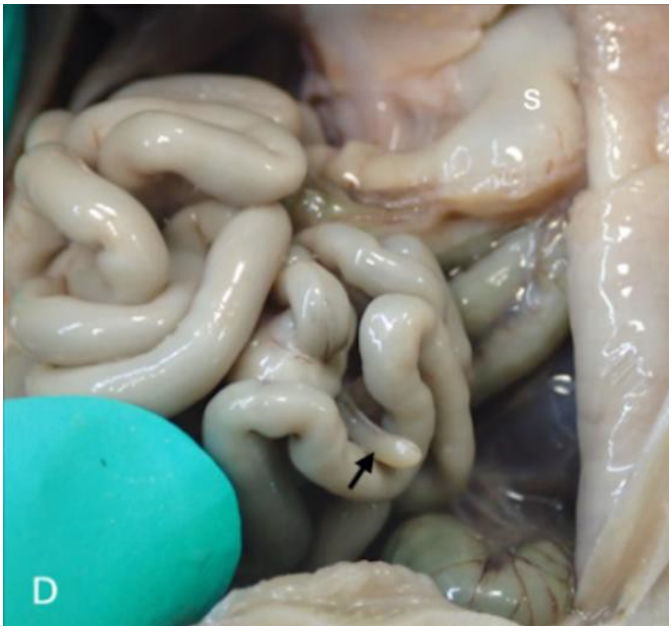


Figure D - Internal findings – Intestinal malrotation; stomach (s) and ileocecal appendix (arrow).

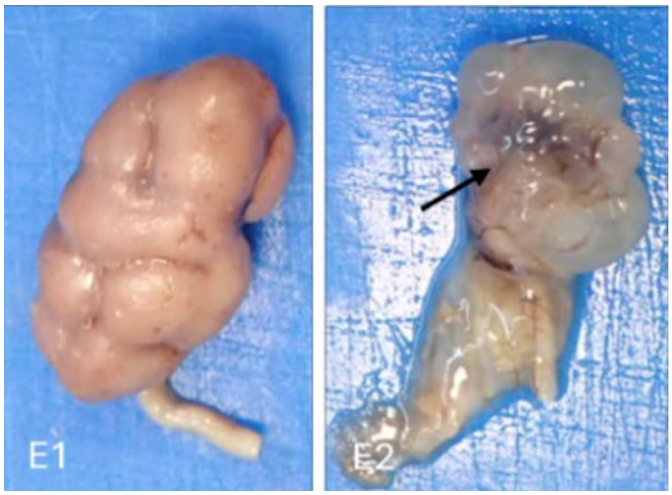


Figure E - Internal findings – (E1,2) Dysplastic kidneys with unilateral multicystic phenotype (arrow).

DISCUSSION

TBS is attributed predominantly to frameshift or nonsense variants clustering within exon 2 of the *SALL1* gene, resulting in truncated proteins that exert a dominant-negative effect during embryogenesis.[1,4] The identified variant expands the mutational spectrum and reaffirms exon 2 as a hotspot. Prenatal differentiation between TBS and VACTERL association or autosomal-recessive polycystic kidney disease (ARPKD) can be elusive when renal or limb anomalies appear isolated. Rapid trio-ES now achieves diagnostic yields of 20–40% in structurally abnormal fetuses, providing actionable information within a clinically relevant timeframe.[3] Our case exemplifies its benefit by clarifying prognosis well before fetal viability and facilitating parental decision-making. Importantly, a negative microarray does not obviate monogenic disorders; hence ES should be considered early when combinations of renal and limb anomalies are detected.

Renal outcomes in TBS vary from asymptomatic mild dysplasia to end-stage kidney disease (ESKD) in childhood. Although unilateral multicystic renal dysplasia may carry a favorable neonatal prognosis, long-term data remain limited, and renal failure has been reported even with apparently unilateral lesions. Imperforate anus and ear anomalies may be subtle prenatally, underscoring the need for meticulous limb and ear assessment whenever renal cystic disease is noted.

The ethical dimension of prenatal genomic testing mandates clear discussion of uncertain prognoses and psychosocial impact. Our counselling adhered to the Declaration of Helsinki, ensuring voluntary parental choice and respect for autonomy.

LIMITATIONS

Absence of longitudinal postnatal data precludes assessment of the full phenotypic spectrum. Functional validation of the novel *SALL1* variant was not feasible within the clinical timeline.

CONCLUSION

Multicystic renal dysplasia accompanied by preaxial thumb duplications should prompt targeted *SALL1* gene analysis. Rapid trio-exome sequencing offers a timely, cost-effective route to definitive diagnosis, enabling personalized counselling and accurate recurrence-risk estimation. Integration of imaging, genomics and autopsy remains the cornerstone of diagnosis in contemporary fetal medicine.

ETHICAL COMPLIANCE

This case report was prepared in accordance with the ethical principles of the Declaration of Helsinki. Formal approval from an ethics committee was not required for a single anonymized case report. Written informed consent for genomic analysis and publication was obtained from both parents.

AUTHORSHIP

Miguel Martins – Conceptualization; Data curation; Investigation; Methodology; Project administration; Visualization; Writing – original draft; Writing – review & editing

Beatriz Sousa Ferreira - Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing

Rosário Almeida Lopes - Data curation; Investigation; Project administration; Writing – original draft; Writing – review & editing

Ana Isabel Correia - Investigation; Project administration; Writing – original draft; Writing –
review & editing

Rosário Pinto Leite- Investigation; Resources; Validation; Writing – original draft

Márcia Martins - Investigation; Resources; Validation; Writing – original draft

Rosete Nogueira - Conceptualization; Methodology; Supervision; Validation; Visualization; Writing – original draft

Osvaldo Moutinho – Conceptualization; Supervision; Project administration; Visualization; Writing – original draft

REFERENCES

1. Kohlhase J, Wischermann A, Reichenbach H, Froster U, Engel W. High incidence of the R276X SALL1 mutation in sporadic Townes-Brocks syndrome. Hum Mutat. 2003;22:378-380.
2. Lin FJ, Lu W, Gale D, Yao Y, Zou R, Bian F, *et al*. Delayed diagnosis of Townes-Brocks syndrome with multicystic kidneys and renal failure caused by a novel *SALL1* nonsense mutation: A case report. Exp Ther Med. 2016 Apr;11(4):1249-1252. Doi: https://doi.org/10.3892/etm.2016.3035.
3. Liberalesso PBN, de Campos TE, Medeiros PFV, *et al*. Phenotypic and genotypic aspects of Townes-Brocks syndrome in Brazilian patients. Eur J Med Genet. 2017;60:195-200.
4. Innoceta AM, Romano MT, Sirleto P, *et al*. Chromosomal microarray identifies novel SALL1 deletion in Townes-Brocks syndrome. Clin Dysmorphol. 2023;32:148-151.

CORRESPONDENCE TO

Miguel Martins
Gynecology and Obstetrics Department
Unidade Local de Saúde de Trás-os-Montes e Alto Douro
Av. da Noruega, Lordelo
5000-508 Vila Real
Email: intgomiguel.martins@gmail.com

Received for publication: 20.06.2025
Accepted in revised form: 03.11.2025

INSTRUCTIONS FOR AUTHORS

The *Birth and Growth Medical Journal* is a peer-reviewed scientific publication dedicated to advancing knowledge in Maternal–Fetal, Neonatal, and Pediatric Health and it continues the legacy of *Nascer e Crescer – Birth and Growth Medical Journal*, which was published from 1992 to August of 2025.

Throughout its history, the journal has provided a trusted platform for the dissemination of high-quality research, clinical insights, and educational content. It is published by the Department of Education and Training (DEFI) of the Unidade Local de Saúde de Santo António (ULSSA) and is indexed in international databases including SciELO, DOAJ, EMBASE, and Latindex.

The transition to the *Birth and Growth Medical Journ*al represents a strategic step forward, strengthening the journal's commitment to scientific excellence, international visibility, and open access. The journal maintains a quarterly publication schedule and welcomes submissions of original research articles, reviews, clinical case reports, image cases, letters to the editor, and current perspectives.

All content is freely available under a Creative Commons license (CC BY-NC 4.0), with no article processing or submission fees charged. The editorial process is overseen by a qualified and experienced editorial board, ensuring the integrity, relevance, and scientific rigor of all published material.

AUTHORSHIP CRITERIA AND RESPONSIBILITIES

Birth and Growth Medical Journal adheres to the guidelines for manuscript submission to biomedical journals developed by the *International Committee of Medical Journal Editors* (ICMJE) and the *Committee on Publication Ethics* (COPE).

Authorship in a scientific article must be based on the criteria outlined in the ICMJE's *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*. Authorship or co-authorship requires the following four conditions to be met:

- Substantial contributions to the conception or design of the study; or the acquisition, analysis, or interpretation of data;
- Participation in drafting the manuscript and in critically revising its content;
- Final approval of the version to be published;
- Agreement to be accountable for the accuracy and integrity of the entire work.

The cover letter must specify the individual contribution of each author to the work.

Anyone who contributed to the research but does not meet all four authorship criteria must be acknowledged in the Acknowledgements section.

A Conflict of Interest Statement and Authorship Form must be completed and signed by all authors and submitted along with the other required documents.

ETHICS AND CONSENT

Authors must ensure that the study on which the submitted manuscript is based complied with ethical and professional standards, as well as all applicable legislation and regulations, in accordance with the principles set out in the Declaration of Helsinki.

Where applicable, authors are required to state that informed consent was obtained from participants, and that the study protocol was approved by the Ethics Committee of the institutions involved.

Submission of a Conflict of Interest and/or Funding Declaration is mandatory.

USE OF ARTIFICIAL INTELLIGENCE (AI)

Birth and Growth Medical Journal permits the use of artificial intelligence (AI) tools in the preparation of manuscripts, provided that such use is clearly and appropriately disclosed by the authors.

Authors must specify, either in the Acknowledgements section or in a footnote, the type of tool used (e.g., *ChatGPT, Grammarly*, etc.) and the nature of its contribution (e.g., support in drafting, language editing, image generation, or data analysis).

The responsibility for the accuracy, originality, and scientific integrity of the content remains entirely with the authors. The use of AI does not exempt authors from ethical standards, nor does it replace human authorship.

FUNDING

Sources of funding must be mentioned at the end of the manuscript.

EDITORIAL PROCESS AND PEER REVIEW

Submissions must be made exclusively online through the journal's platform. Upon submission, the corresponding author will receive an automatic confirmation email. All manuscripts are evaluated by the Editorial Board and undergo double-blind peer review. Editorial decisions include acceptance, revision, or rejection.

If revisions are requested, authors must submit the revised manuscript clearly indicating where changes were made. Additionally, a Word document must be provided with a point-by-point response to the reviewers' comments, justifying the changes made or explaining why certain suggestions were not

followed.

OPEN ACCESS AND LICENSING

The journal provides immediate open access to all content under the Creative Commons Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) licence. There are no submission or publication fees. Digital preservation is ensured through systems such as CLOCKSS.

ARTICLE PROCESSING CHARGES

There are no article processing charges (APCs) for publication in BGMJ.

PUBLICATION GUIDELINES

SUBMISSION

Manuscripts must be submitted via the journal's online platform: https://revistas.rcaap.pt/bgmj.

The manuscript should be submitted in a recent version of Microsoft Word, accompanied by a cover letter and the authorship and conflict of interest declaration.

All submissions must be written in English and follow the structure below:

1 – Title;
2 – Authors;
3 – Abstract and Keywords;
4 – Main Body of the Article;
5 – References;
6 – Figures;
7 – Tables;
8 – Figure and Table Legends;
9 – Acknowledgements and Disclosures.

The pages should be numbered according to the sequence mentioned above.

On the first page

A clear and concise title, never identifying the institution where the study was conducted;

The authors' names (first and last, or clinical name), followed by their respective affiliations (Service, Department, Institution), email contacts, ORCID ID, and each author's contribution (see: https://credit.niso.org/);

Identification of the corresponding author for correspondence, including postal address, email, and telephone number.

On the second page

An abstract, avoiding the use of abbreviations;

Abstracts must follow the specific structure according to the article type submitted;

Following the abstract, keywords should be listed in alphabetical order to serve as the basis for article indexing. Terms should be consistent with the *Medical Subject Headings* (MeSH).

TEXT

Editorials

Submitted by invitation from the Editor or Editorial Board, these are commentaries on current topics. They must not exceed 1,200 words, with a maximum of two figures or tables, and 15 bibliographic references. Abstracts are not required.

Original Articles

The manuscript should be structured into Introduction, Materials and Methods, Results, Discussion, and Conclusions. It should not exceed 5,000 words, eight tables or figures, and 40 bibliographic references. The abstract should follow the structure of the text and not exceed 250 words. A maximum of seven keywords should be provided.

Review Articles

Following the structure: Introduction, Objectives, Development, and Conclusions, these should not exceed 7,000 words, five tables or figures, and 80 bibliographic references. The abstract, with a maximum of 250 words, should follow the structure of the text. A maximum of seven keywords should be provided.

Clinical Case Reports

This article type describes one or more clinical cases which, due to their rarity, therapeutic innovation, or other relevant factors, are considered of interest to the scientific community. Cases should be exemplary, thoroughly studied, and discussed, including a brief introduction, case description(s), and a concise discussion with a summary conclusion. The text should not exceed 2,500 words and may include up to 15 bibliographic references. The abstract, with a maximum of 150 words, should follow the structure of the text. A maximum of seven keywords should be provided.

Image Cases

Dedicated to clinical cases in which imaging is fundamental for diagnosis. Images may relate to clinical observation or

complementary diagnostic methods. The text, with a maximum of 2,000 words, should begin with a case description and end with the question: *What is your diagnosis?* This is followed by the diagnosis presentation, patient management, and a brief discussion. Up to 10 bibliographic references may be included. The abstract and keywords (maximum of five) should appear at the end of the article text.

Letters to the Editor

Letters to the editor are comments on an article published in *BGMJ* or notes on a topic or clinical case. They should not exceed 500 words or include more than five bibliographic references and may include one figure or table. Comments on articles published in the journal must refer to articles from the last six months. Authors will be given the opportunity to respond. Both the letter and the authors' response will be published in the same issue of the journal.

Current Perspectives

Comprising invited articles addressed by the Editorial Board, this section may cover current topics related to the journal's scope. Articles should not exceed 1,200 words and may include up to ten bibliographic references, as well as one figure or table. Authors wishing to submit an article to this section must first send an abstract, including authors' names, affiliations, and the article title, to the Editor-in-Chief for assessment of its suitability.

General Guidelines

Abbreviations used must be specified. When necessary, they should be fully spelled out the first time they appear in the text. If more than six abbreviations are used, the inclusion of a table explaining all abbreviations is recommended. Abbreviations are not accepted in article titles.

Measured parameters or values should be expressed in international units (SI units, *The SI for the Health Professions*, WHO, 1977), using the abbreviations adopted in Portugal.

Numbers from one to nine should be written in full, except when used as units of measurement or accompanied by decimals. Numbers greater than nine should be written in Arabic numerals, except when starting a sentence.

Regarding results, information should not be duplicated in both the text and tables; the main results should be highlighted in the text.

BIBLIOGRAPHIC REFERENCES

References should be listed and numbered in the order they appear in the text, using Arabic numerals formatted as superscripts (e.g., [4]).

Sequential references should be indicated by listing only the first and last numbers, separated by a hyphen (e.g., [4-7]). Non-sequential references should be separated by commas (e.g., [4,7,9]). References must always be placed at the end of each sentence, after the full stop.

Authors must ensure that all references comply with the *Uniform Requirements for Manuscript submitted to biomedical journals* (www.nlm.nih.gov/bsd/uniform_requirements.html) and use the abbreviated journal titles adopted by the *Index Medicus*. Authors can consult the *NLM's Citing Medicine* page for formatting recommendations for various reference types.

Some examples follow:

Medical journal article: List the first six authors followed by *et al.* (in italics) if there are more than six authors; article title; journal name; year; volume; issue; and page numbers. Example: Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, *et al*. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-5. https://doi: 10.1097/00006454-198611000-00004.

Book chapter: Author(s), chapter title, editor(s), book title, edition number, city, publisher, year of publication, first and last pages of the chapter. Ex.: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Book: Author(s), book title, edition number, city, publisher, year of publication, and total number of pages. Example: Jenkins PF. Making sense of the chest x-ray: a hands-on guide. 2nd edition. London: Taylor & Francis; 2013. p. 120.

Electronic reference: Electronic journal article. Example: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. January 2010. (Accessed May 8, 2013). Available from: http://www.uptodate.com.

FIGURES AND TABLES

Figures and tables should be submitted on separate pages, in high-quality digital format, accompanied by a title and an explanatory legend when necessary.

Each table and figure must be numbered sequentially using Arabic numerals, in the order they are cited in the text.

All abbreviations or symbols used must be explained in the legend.

If a figure or table is a direct copy or modified version from a published source, its origin must be acknowledged, and permission for use should be obtained when appropriate.

Photographs or diagnostic images of patients must ensure anonymity, and must be accompanied by written consent for publication from the patient or their legal guardian.

The total number of figures and tables should not exceed the limits specified for each article type.

ACKNOWLEDGEMENTS AND DISCLOSURES

Acknowledgements, statements regarding the presence or absence of any conflicts of interest for any of the authors, as well as information on the sources of funding for the study, should appear on the last page.