NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
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NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL

Year | 2022 **Volume |** 31 **Number |** 01

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Quarterly Publication, indexed and summarized by

Catálogo LATINDEX EMBASE / Excerpta Médica
DOAJ
REDIB
Repositório Científico do CHP
SARC – Serviço de Alojamento de Revistas Científicas
SciELO

Graphic execution and layout

Andrea Buschbeck

Editing

Joana Cavaco Silva

E-ISSN

2183-9417

Legal deposit

4346/91

Publisher

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NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2022, vol 31, n.° 1

NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL PRIZE BEST ORIGINAL PAPER

NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL'S MANAGEMENT ESTABLISHED AN ANUAL PRIZE TO BEST ORIGINAL PAPER PUBLISHED IN JOURNAL. THIS INITIATIVE AIMS TO PROMOTE AND ENCOURAGE THE RESEARCH IN MATERNAL FETAL, NEONATAL AND PEDIATRICS SCIENTIFIC AREAS.

PROCEDURES

1. The prize is aimed at authors of best Original Article published in Nascer e Crescer - Birth and Growth Medical Journal between January and December of which year.

2. The same author can participate with more than one Original Article.

3. In the evaluation of the Original Articles, the Selection Jury will analyze the following items:
   a. Relevance and originality;
   b. Clarity and relevance of goals; Consistency with methodology;
   c. Description of methods/procedures and adequate statistical analysis;
   d. Clear and synthetic presentation of results;
   e. Reasoned discussion;
   f. Importance for the improvement of knowledge. Potential of applicability and impact of results.

4. If there is more than one author, the Prize will be delivered to the first author of the Original Article.

5. You will not need any type of application for the Prize.

6. The process of evaluation/classification of the Prize will be conducted by a selection jury to be chosen opportunely by the journal editors.

7. There will be no appeal against the decisions of the jury.

8. The award of the Prize will be disclosed in issue 4 of Nascer e Crescer - Birth and Growth Medical Journal.

9. It is up to the Board of Nascer e Crescer - Birth and Growth Medical Journal decide on cases not covered by this regulation.

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EDITORIAL

Nascer e Crescer/Birth and Growth Medical Journal - 30 years' publication

Nascer e Crescer/Birth and Growth Medical Journal - 30 anos de publicação

Sílvia Álvares[1,2,3]

"All men by nature desire knowledge"
Aristotle, Introduction to Metaphysics

The first edition of NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL was published in March 1992, by Hospital de Crianças Maria Pia, covering the entire field of pediatrics (**fig 1, 2 and 3**). It had the result of between pediatricians of all the hospitals in the North of Portugal and the Scientific Committee also included international experts from several pediatric specialties. At that time there were few national pediatric publications and the initiative to create this journal responded to the need of the pediatric community to share knowledge and promote post graduate education and scientific research to improve patient care and child health. It was a huge challenge but the editorial team was enthusiastic and committed to the development of the journal. Nascer e Crescer was the initial title, with four issues per year (March, June, September and December) and contents comprised original articles, review articles, case reports and opinion articles. Throughout its history, the journal has employed a rigorous double-blind peer review process to evaluate manuscripts for scientific accuracy, innovation and importance. It rapidly became one of the most widely read national pediatric journal.

Throughout the 30 years of regular publication the front page and layout have changed in order to improve readability, to facilitate key information and increase journal visibility.

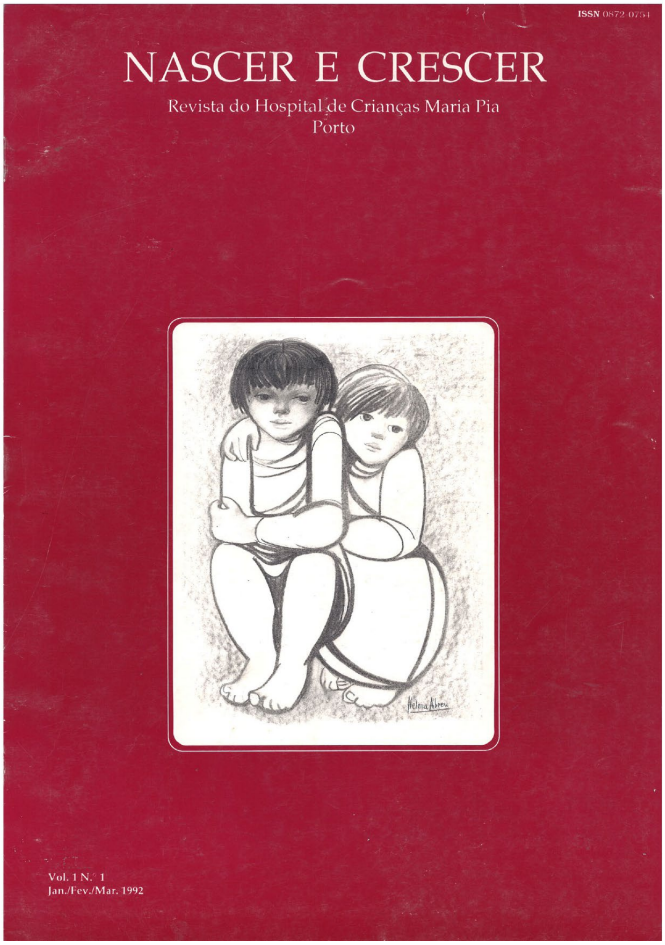

Figure 1 - Nascer e Crescer first cover

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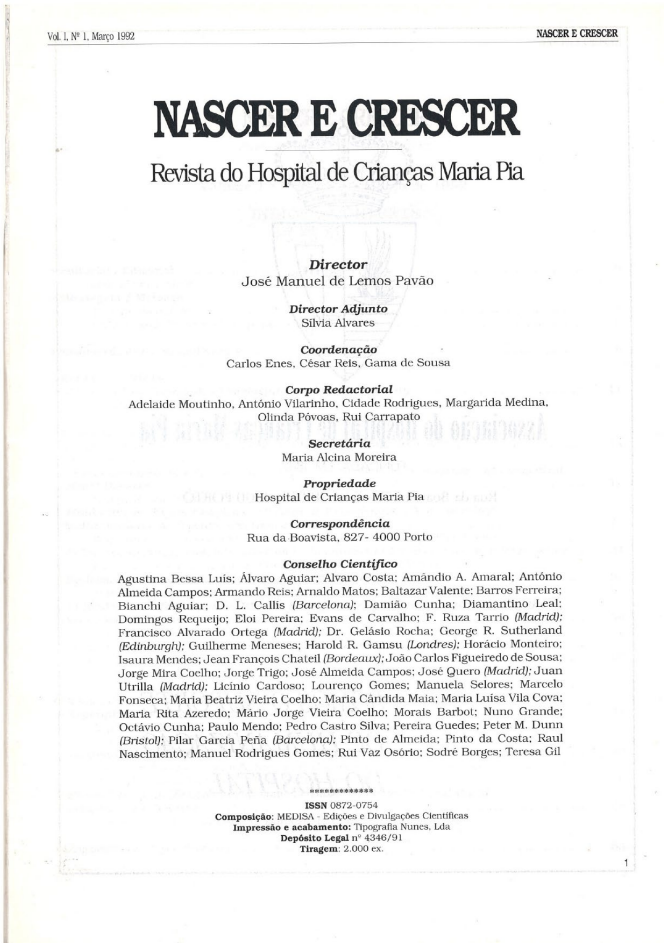


Vol. I, Nº 1, Março 1992 NASCER E CRESCER

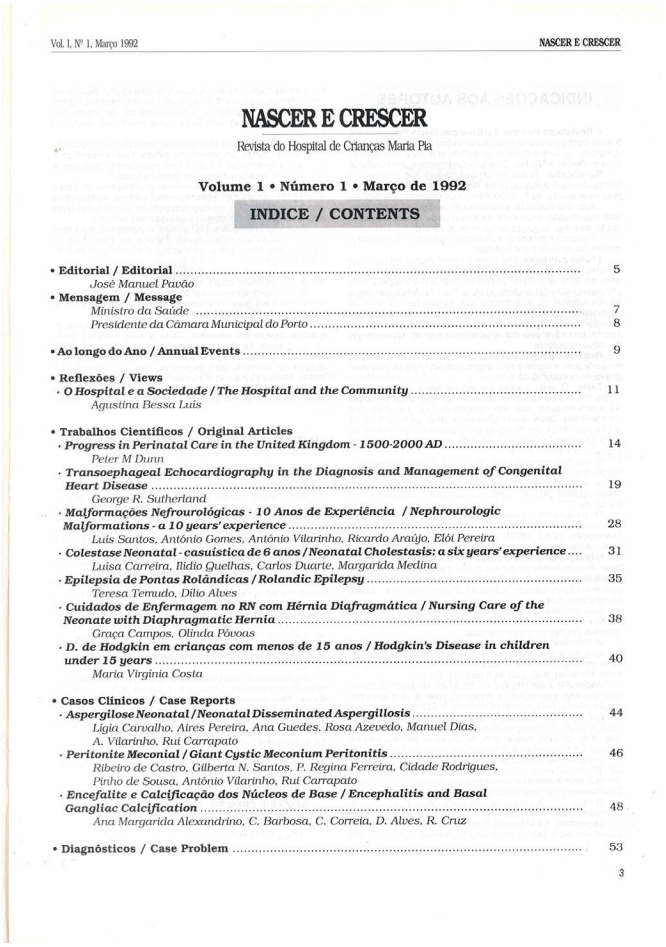
NASCER E CRESCER

Revista do Hospital de Crianças Maria Pia

ISSN 0872-0754
Composição: MEDISA - Edições e Divulgações Científicas
Impressão e acabamento: Tipografia Nunes, Lda
Depósito Legal nº 4346/91
Tiragem: 2.000 ex.

1

Figure 2 - Nascer e Crescer first masthead



Vol. I, Nº 1, Março 1992 NASCER E CRESCER

NASCER E CRESCER

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Figure 3 - Nascer e Crescer first Journal Summary

We wish to emphasize some major historic milestones in its history:

The merging of Hospital de Crianças Maria Pia in the Centro Hospitalar Universitário do Porto in 2010 and the integration of Nascer e Crescer in the Department of Ensino, Formação e Investigação (DEFI) represented an opportunity for change and development with innovative solutions to improve the publication.

The aim and scope was enlarged to include maternal-fetal, neonatal and pediatric health, fostering collaboration between the various disciplines related to maternal and child care.

In 2011, the journal was indexed in the Scielo platform (Scientific Electronic Library Online)

This indexing gave access to all articles, increasing the journal visibility, impact and credibility.

The widespread of the internet and the evolution of digital technology transformed dramatically scientific publication: the pressure to move to on-line printing and the shift from subscription to open access (OA) models. The new technologies enable the communication of research more quickly, broadly and openly and provide resources (enhanced media, data, linked resources, etc) only possible in a digital form. Most of Medical Journals gradually moved from a printed format to a hybrid process (electronic and printed) or exclusively to online printing.

Concomitantly, the movement of OA based on the concept that medical and scientific knowledge should be widely shared to allow further and faster advances was embraced enthusiastically by academic institutions, medical researchers, libraries, the public and governments. The Budapest Open Access Initiative (February 2002), the Bethesda Statement on Open Access Publishing (June 2003), and the Berlin Declaration on Open Access to Knowledge in the Science and Humanities (October 2003), also mentioned as the BBB (3Bs), state essentially "that OA allows its users to read, download, copy, print, search, distribute, or link to the full text of works, permitting the use for any legitimate purpose, as long as access to the material is possible through the internet".

OA was initially classified into two main categories: green and gold OA. Green OA allows free access to articles through institutional or central repositories, and in gold OA the articles are available on the

publisher's Web sites. However the author may be charged by the publisher and fees may be as high as € 9500 (journal Nature[1]), or the journal may establish an embargo of a 6 -12 months' period to OA.

Currently, in spite of the strong benefits of OA towards science democratization, it also brings a new paradigm to the publishing practice: a shift of the financing path from the readers to the authors or their funders. The term "platinium" or "diamond" OA has emerged to indicate that there are no fees involved for the authors in order to make a clear distinction between these situations. There are now 17.550 journals registered in the Directory of Open Access Journals and 12.279 (70%) do not charge processing fees (*www.doaj.org*).

Nascer e Crescer also adhered to the movement of OA and electronic printing. In 2012 the publication was made openly available upon deposit in the Repository of Centro Hospitalar Universitário do Porto. The Journal was published in paper and hybrid mode until 2016 when it moved to online publication and embraced free OA policy without charging the processing fees to the authors in order to promote the sharing of knowledge and proximity to the scientific community. The expenses with editorial staff, typesetting and copyediting are still significant and the sustainability of Nascer e Crescer depends on institutional funding but also this guaranties that this scientific journal is independently generated and maintained.

Nascer e Crescer integrated the Scientific Open Access Repository of Portugal (RCAAP) particularly the Scientific Journal Hosting Service (SARC). The service provides a publication and management platform, including on line submission and manuscript tracking, through the website http://revistas.rcaap.pt/nascercrescer. Electronic submission substantially reduces editorial processing and shortens reviewing and overall publication times and allows monitoring by authors of the peer review process.

In 2017 we faced a new challenge: the publication in English language in order to increase the visibility of the publication and thereby enhance global communication and collaboration in the scientific community worldwide. The title of the Journal also reflected this evolution and was changed to Nascer e Crescer-Birth and Growth Medical Journal.

At present Nascer e Crescer- Birth and Growth Medical Journal is an electronic, open access peer-reviewed journal that publishes research articles, original articles, review articles, case reports and opinion articles on a broad range of topics related to maternal and child health.

1 See "Nature-Branded Journals Announce First Open-Access Deal"

The Editorial Board includes highly qualified professionals from across all the country committed to innovation and improvement of the scientific quality of the Journal. The specialized Section Editors have three main roles: journal development, peer review and journal advocacy. The Scientific Committee *encompasses* national and international experts in maternal and child health. The Journal is indexed and summarized in some of the most important international databases of scientific papers: SciELO, DOAJ, REDIB, Embase/Excerpta Medica, Catálogo Latindex and Index das Revistas Médicas Portuguesas.

The future of medical publication will certainly continue to change, and present new challenges. As for Nascer e Crescer- Birth and Growth Medical Journal, with a distinguished 30-year history, we will pursue to maintain a high standard of content to address the scientific needs of our target audience and promote collaboration between the various disciplines interested in maternal and child health as well as cooperation with international researchers. We will strive to be included in Medline PubMed, PubMed Central, Scopus to increase visibility and readership and consequently attract more high quality submissions.

On behalf of our Editorial Board, Editors and Editorial Office we thank our Publisher for support, our reviewers whose guidance and advice represent a fundamental pillar in the quality of the Journal, our authors for the submission of their work and, last but not the least, our loyal and engaged readers.

REFERENCES

1. Álvares S. The importance of peer review. Nascer e Crescer - Birth and Growth Medical Journal. 2019;28(1): 7-8. doi:10.25753/BirthGrowthMJ.v28.i1.17614.
2. Kharasch ED, Avram MJ, Clark JD, Davidson AJ, Houle TT, Levy JH, *et al*. Peer Review Matters: Research Quality and the Public Trust Anesthesiology 2021, 134: 1–6. https://doi.org/10.1097/ALN.0000000000003608.
3. Ibáñeza B, Rodés-Cabaud J. Present and future of medical journals. REC Interv Cardiol. 2019;1:11-12 DOI: https://doi.org/10.24875/RECICE.M19000005.
4. Galli C, Colangelo MT, Guizzardi S. Striving for Modernity: Layout and Abstracts in the Biomedical Literature. Publications. 2020; 8(3):38. https://doi.org/10.3390/publications8030038.
5. Loscalzo J. The Future of Medical Journal Publishing: The Journal Editor's Perspective: Looking Back, Looking Forward. Circulation 2016 Apr 19;133(16):1621-4. https://doi.org/10.1161/CIRCULATIONAHA.116.022519.
6. Groom RC. The Journey to Open Access. J Extra Corpor Technol. 2015;47(3):143.
7. Faxon DP. Changes in Medical Publishing. The Challenges for an Interventional Journal. Circ Cardiovasc Interv 2013;6:2-4.
8. Hellems MA, Gurka KK, Hayden GF A review of the Journal of

Pediatrics: the first 75 years J Pediatr . 2009;155(1):16-20, 20.e1. https://doi.org/10.1016/j.jpeds.2008.08.049. Epub 2008 Oct 16.

9. Balistreri WF, Helton ML . Reflections on the Past, Present, and Future of the Journal of Pediatrics J Pediatr . 2009;155(1):3-5. https://doi.org/10.1016/j.jpeds.2009.04.041.
10. Campbell G, Poppalardo P. Looking Ahead to the Next 75 Years for The Journal of Pediatrics and Medical Publishing J Pediatr 2009;155(1):6-7.
11. Suzuki K, Edelson A, Iversen LL, Hausmann L, Schulz JB, Turner AJ. A Learned Society's Perspective on Publishing. J Neurochem 2016 139: 17-23. https://doi.org/10.1111/jnc.13674.
12. Schulz JB, Hausmann L. 60 Years of the Journal of Neurochemistry. J Neurochem 2006; 139: 5-6. https://doi.org/10.1111/jnc.13853.
13. Álvares S, Pereira JM. From the Post-Gutenberg Galaxy to the era of Skywriting Nascer e Crescer 2016; 25(2):63.
14. Barić H, Polšek D, Andrijašević L, Gajović S. Open access - is this the future of medical publishing?. Croat Med J. 2013;54(4):315-8. https://doi.org/10.3325/cmj.2013.54.315.
15. Grossmann A, Brembs B. Current market rates for scholarly publishing services Research 2021; 10:20. https://doi.org/10.12688/f1000research.27468.2.
16. Ellingson MK, Shi X, Skydel JJ, Nyhan K, Lehman R, Ross JS, Wallach JD. Publishing at any cost: a cross-sectional study of the amount that medical researchers spend on open access publishing each year. BMJ 2021;11(2):e047107. https://doi.org/10.1136/bmjopen-2020-047107. PMID: 33526505; PMCID: PMC7852964.
17. Smith E, Haustein S, Mongeon P, Shu F, Ridde V, Larivière V. Knowledge sharing in global health research - the impact, uptake and cost of open access to scholarly literature. Health Res Policy Syst. 2017 Aug 29;15(1):73. https://doi.org/10.1186/s12961-017-0235-3. PMID: 28851401; PMCID: PMC5576373.
18. Álvares S. A ciência fala inglês? em tempos de mudança...Nascer e Crescer 2016; 25 (3):133-5.
19. Di Bitetti MS, Ferreras JA. Publish (in English) or perish: The effect on citation rate of using languages other than English in scientific publications. Ambio. 2017;46(1):121-127. https://doi.org/10.1007/s13280-016-0820-7.

ORIGINAL ARTICLE

Acute Campylobacter spp. gastroenteritis in the Pediatric Emergency Department of a level II hospital

Gastroenterite aguda por Campylobacter spp. no Serviço de Urgência Pediátrica de um hospital de nível II

Liliana Sá[1], Teresa Pinheiro[1], Joana Silva[1], Adriana Pedrosa[2], Laura Soares[1], Miguel Costa[1], Cristina Rocha[1]

ABSTRACT

Introduction: *Campylobacter* spp. is the main cause of pediatric acute bacterial gastroenteritis (ABG) in the European Union, with greater incidence in children under five years old. Most patients present complete recovery within days of infection, with no associated comorbidities. Antibiotic therapy should be reserved for severe cases.

Objectives: The aim of this study was to investigate the epidemiology, symptoms, treatment, and complications of *Campylobacter* spp. infection in pediatric patients with ABG.

Material and methods: Case-by-case review of the clinical records of patients evaluated in the Pediatric Emergency Department of a level II hospital with a diagnosis of ABG and *Campylobacter* spp. isolated from stool samples over a five-year period (2013-2017).

Results: Of the 1990 stool tests performed, 637 (32%) were positive for the presence of bacteria. *Campylobacter* spp. was identified in the samples of 459 patients (72%). Eighteen patients were excluded for insufficient data, making up a final sample of 441 patients, with a mean age of three years old. Clinically, patients presented with aqueous diarrhea (59.6%), bloody diarrhea (43.8%), bloody and mucus diarrhea (15.4%), mucus diarrhea (3.9%), vomiting (36.3%), abdominal pain (24.3%), fever (63%), seizures (0.9%), and rash (0.2%). Eighty-nine patients were hospitalized. Eleven patients received antibiotic therapy.

Discussion: This study represents the largest national case-by-case review of ABG by *Campylobacter* spp. in the pediatric population. *Campylobacter* was the main bacteria identified, mostly associated with self-limited disease.

Conclusion: A judicious use of stool tests allows etiological identification in ABG. The growing number of cases of ABG by *Campylobacter* spp. reinforces the need for better hygiene procedures.

Keywords: *Campylobacter*; child; gastroenteritis; hygiene

RESUMO

Introdução: *Campylobacter* spp. é a causa principal de gastroenterite aguda bacteriana (GAB) pediátrica na União Europeia, com maior incidência em crianças com idade inferior a cinco anos. A maioria dos doentes tem uma recuperação completa num período de dias da data de infeção, sem comorbilidades associadas. A antibioterapia deve ser reservada para casos mais graves.

Objetivo: O objetivo deste estudo foi avaliar a epidemiologia, sintomas, tratamento e complicações associadas à infeção por *Campylobacter* spp. em doentes pediátricos com GAB.

Material e métodos: Revisão dos casos clínicos de doentes avaliados no Serviço de Urgência Pediátrica de um hospital de nível II por um

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período de cinco anos (2013-2017) com diagnóstico de GAB e isolamento de *Campylobacter* spp. nas fezes.

Resultados: Dos 1990 testes coprológicos efetuados, 637 (32%) foram positivos para a presença de bactérias. *Campylobacter* spp. foi identificada em 459 doentes (72%). Dezoito doentes foram excluídos por falta de informação, constituindo uma amostra final de 441 doentes, com uma idade média de três anos. Clinicamente, os doentes apresentavam diarreia aquosa (59,6%), diarreia sanguinolenta (43,8%), diarreia mucosanguinolenta (15,4%), diarreia mucosa (3,9%), vómitos (36,3%), dor abdominal (24,3%), febre (63%), convulsões (0,9%) e exantema cutâneo (0,2%). Oitenta e nove doentes foram internados. Onze doentes receberam antibioterapia.

Discussão: Este estudo representa a maior revisão nacional até à data de casos de GAB por *Campylobacter* spp. na população pediátrica. *Campylobacter* foi a principal bactéria identificada, maioritariamente associada a doença autolimitada.

Conclusão: O uso racional de testes coprológicos permite a identificação etiológica na GAB. O aumento dos casos de GAB por *Campylobacter* spp. reforça a necessidade de melhor cuidados de higiene.

Palavras-chave: *Campylobacter*; criança; gastroenterite; higiene

INTRODUCTION

Infection by *Campylobacter* spp., in particular *C. jejuni* and *C. coli*, is the main cause of acute bacterial gastroenteritis (ABG) in Europe,[1] with a higher prevalence than reported for infections caused by *Salmonella* spp., *Shigella* spp., and enteropathogenic *Escherichia coli*.[2,3] According to the latest report of the European Centre for Disease Prevention and Control, campylobacteriosis is the most frequently notified zoonotic disease in humans, with a growing incidence in recent years and the largest number of cases occurring in male children under five years old.[4] In Portugal, recent data also shows an increasing prevalence of the disease, with *C. jejuni* being the most frequently identified etiological agent. Human campylobacteriosis is a compulsory notifiable disease since 2014.[5]

It is generally believed that *Campylobacter* acts by direct invasion of the intestinal epithelial cells, inducing an inflammatory process and producing a toxin.[1,6,7] *C. jejuni* infection in humans is usually sporadic and more frequent during the Summer months. Most etiological agents come from animal reservoirs (birds, cattle, goats, and sheep) and are transmitted by ingestion of poorly cooked meat (mainly poultry), unpasteurized milk and milk derivatives, and untreated water, with human-to-human transmission being very rare.[8,9]

C. jejuni causes aqueous diarrhea or diarrhea with mucus and/or blood in about half of cases. Other relatively frequent symptoms include fever, abdominal pain, nausea or vomiting, headache, and myalgia. The disease usually occurs 24-72 hours after ingestion of contaminated food or water and has an average duration of seven to ten days, although recurrences are not rare (25% of cases).[9,10]

The diagnosis is usually established by isolation of the bacteria in stools and identification of the etiological organism through mass spectrometry or biochemical and molecular methods. It can also be accomplished by direct microscopy/dark-field microscopy, specific antigen detection, identification of the bacterium DNA through polymerase chain reaction, and serology through ELISA technique.[1,7,8]

Treatment consists of restoration of the fluid and electrolyte balance. Antimicrobial therapy is only recommended in cases of high risk of severe disease, namely presence of dysentery, high fever, extraintestinal disease, symptom worsening or recurrence, symptoms lasting more than one week, concomitant chronic conditions, immunodeficiency, or pregnancy, and in outbreak situations. Macrolides are the first-line treatment.[1,10]

Campylobacteriosis is a self-limiting disease in most cases, particularly in healthy children, although complications have been reported, such as reactive arthritis, sepsis, Guillain-Barré syndrome, and hemolytic anemia.[2,5]

The aims of this study were to estimate the prevalence of *Campylobacter* spp. in the stools of pediatric patients with ABG, and characterize cases regarding clinical and epidemiological features, therapeutic approach, and associated complications.

MATERIAL AND METHODS

A case-by-case review of the clinical records of patients evaluated in the Pediatric Emergency Department (ED) of a level II hospital between January 2013 and December 2017 was conducted. All patients with diagnosis of ABG by *Campylobacter* spp. were included. The diagnosis was established using a selective medium for isolation of *Campylobacter* spp. from stool samples and subsequent identification from a gallery of biochemical tests (API Campy).

Although the criteria for performing stool tests have some degree of individual variability, in the study hospital they are indicated in cases where the following signs/symptoms are present: frequent/intense abdominal cramps, high fever, prolonged diarrhea or diarrhea with mucus and/or blood, concomitant chronic conditions, immunodeficiency, and admission to the Pediatric Department with a diagnosis of ABG.

The following patient data were retrieved for clinical records: age, gender, date of Pediatric ED evaluation, area of residence, history of recent food intake, epidemiological context, clinical features (stool characteristics, presence of other symptoms), treatment, reason for admission, and disease progression.

Data were analyzed using the Statistical Package for the Social Sciences Program® (SPSS Inc., Chicago. IL) version 23, through measures of central tendency and dispersion for quantitative variables and absolute and relative frequencies for qualitative variables.

RESULTS

During the study period, 1990 stool tests were carried out in the Pediatric ED, 637 (32%) of which were positive for the presence of bacteria. *Campylobacter spp*. was identified in 459 cases (72%), followed by *Salmonella* spp. in 144 (22.6%), *Yersinia enterocolitica* in 37 (5.8%), and *Shigella* spp. in only one case (0.2%). No cases of *Aeromonas* spp. or *Escherichia coli* 0157 were detected. Bacterial coinfection was identified in four cases, one by *Campylobacter* spp. and *Yersinia enterocolitica*, one by *Yersinia enterocolitica* and *Shigella* spp., one by *Campylobacter* spp., *Yersinia enterocolitica*, and *Salmonella*, and one by *Campylobacter* spp. and *Salmonella*.

In addition to stool tests, virological stool examination was performed in 90.7% of patients with *Campylobacter* spp. isolated in stools, being positive in 7%: 4.1% for rotavirus, 0.7% for adenovirus, and 1.8% for both viruses.

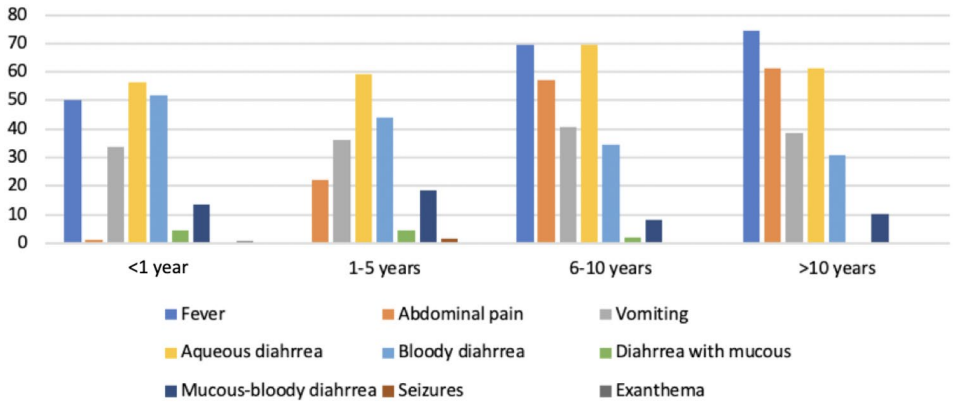
From the 459 *Campylobacter*-positive stool tests, 18 were excluded for lack of data, making up a final sample of 441 patients, with a mean age of 3.2 years (standard deviation ± 4.2; range 1 month–17 years) and male predominance (57.8%).

The infection was predominant in the months of Spring to Autumn, with 11.1% of cases occurring in May, 10.9% in August, and 10% in October. *C. jejuni* was the main species identified (372 cases; 85.3%), followed by *C. coli* (21 cases; 4.8%), and *C. upsaliensis* (2 cases; 0.5%). No newborn was admitted to the Pediatric ED with ABG due to *Campylobacter* spp. infection.

Children included in the study were stratified by age group into infants (<1 year old), one-to-five-year-olds, six-to-10-year-olds, and older than 10 years old. The highest incidence of infection was observed in children aged one to five years (n=243, 55.1%), followed by infants (n=110, 24.9%) and children aged six to 10 years (n=49, 11.1%), and the lowest incidence was seen in children older than 10 years (n=39, 8.8%). Differences in incidence rates were statistically significant (p=0.042). Infants were further stratified according to age group into one-to-three-month-olds and four-to-twelve-month-olds, with the highest incidence reported in the latter (n=86, 78.2%).

Most patients had no data about consumption of suspicious food (n=367, 83.2%), and 39 denied its intake (8.8%). In cases with identification of a possible bacteria food source, untreated water was the most frequent (3.6%). Epidemiological causes were identified in 12.7% of cases, through reports of concomitant cases of diarrhea in the family, with no data available for 55.1% of cases.

The forms of presentation included aqueous diarrhea (n=263, 59.6%), bloody diarrhea (n=193, 43.8%), mucous-bloody diarrhea (n=68, 15.4%), diarrhea with mucous (n=17, 3.9%), vomiting (n=160, 36.3%), abdominal pain (n=107, 24.3%), fever (n=278, 63.0%), seizures (n=4, 0.9%; all in the context of fever), and exanthema (n=1, 0.2%). Clinical presentation according to age group is depicted in **Figure 1**.



ABG, acute bacterial gastroenteritis

Figure 1 - Clinical presentation of patients with ABG, according to age group

No statistically significant differences were found in clinical presentation across age groups, except for seizures, which mostly occurred in feverish context in children between one and five years old.

Among children observed in the Pediatric ED, 108 required a short hospital stay, and 104 were admitted to the Pediatric Department (PD; **Figure 2**). Admissions occurred mostly among infants younger than three months.

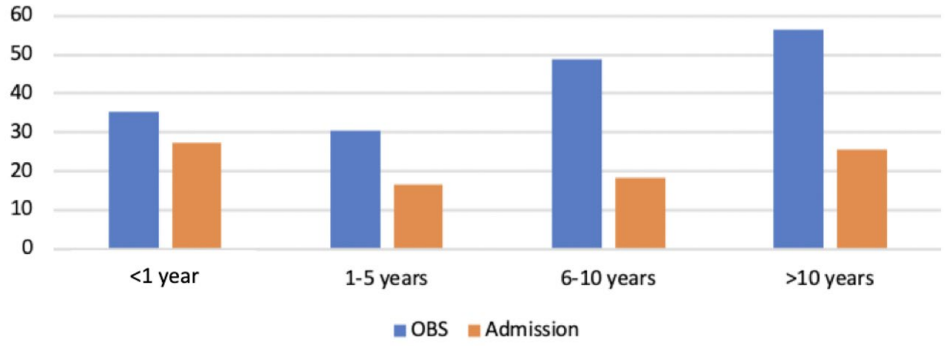
A total of 125 children (28.3%) were readmitted to the Pediatric ED for persistence or worsening of symptoms, 27 of whom (21.6%) were hospitalized (**Figure 3**).

Of all patients admitted to the PD, 28.8% (n=30) were younger than 12 months. The average duration of hospital stay was 3.2 days (range 1–10 days). During hospital stay, 94.4% received some form of treatment, including intravenous fluids in 92% (n=82) and antibiotic therapy in 12.4% (n=11; azithromycin in nine and clarithromycin in two). Four patients received antibiotic therapy directed at other coinfections.

A total of 143 samples were randomly selected for the study of antibiotic resistance patterns in the reference laboratory, with results showing resistance to quinolones in 93.7%, to tetracyclines in 83.2%, to macrolides in 11.9%, and to aminoglycosides in 0.7%.

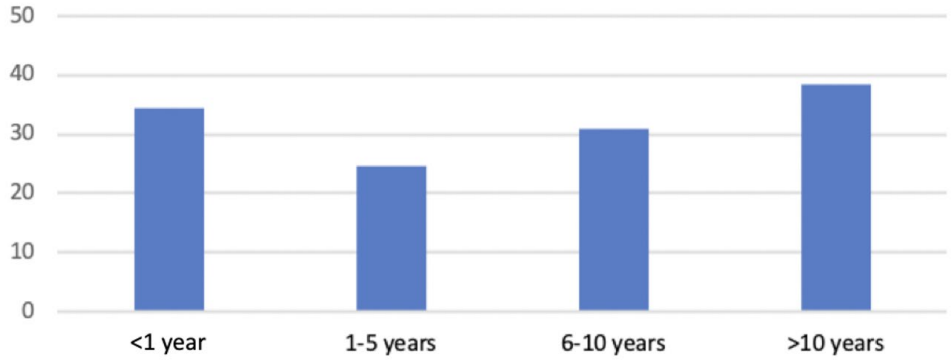
A total of 156 children (37.9%) developed complications, mostly dehydration (n=120, 67.4%), but also food refusal (n=44, 24.7%; **Figure 4**).

After hospital discharge, 280 children (63.5%) were revaluated in outpatient setting. Control stool tests were carried out in 43.5%, with negative stool test results in 85.6% of these cases. A total of 15 children (3.4%) had more than one episode of ABG by *Campylobacter* spp. in the considered study period.



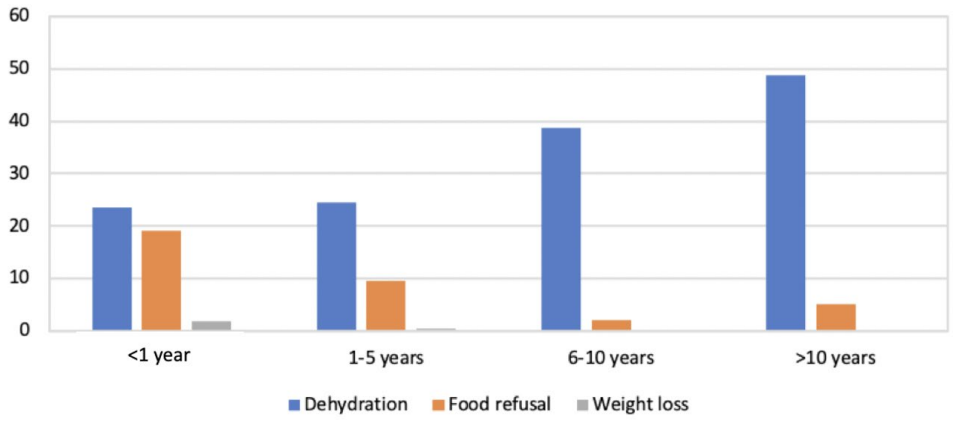
ABG, acute bacterial gastroenteritis; ED, Emergency Department; OBS, observation

Figure 2 - Destination of patients with ABG after observation in the ED, according to age group



ABG, acute bacterial gastroenteritis; ED, Emergency Department

Figure 3 - Readmission of patients with ABG to the ED, according to age group



ABG, acute bacterial gastroenteritis

Figure 4 - Complications of patients with ABG, according to age group

DISCUSSION

Acute diarrhea remains a very common cause of ED admission, making ABG a condition with relevant epidemiological, economic, and social impact in pediatric age. Acute gastroenteritis usually has a benign and self-limited progression and viral origin. However, the prevalence of bacterial infection is significant.[3,11,12]

Campylobacter spp. was the main bacteria isolated in the present study, accounting for 72% of positive stool tests, followed by *Salmonella* spp. (22.6%). The higher prevalence of *Campylobacter* spp. compared to other bacteria has been reported in national and international studies.[8,13,14,16]

Four studies focusing on acute gastroenteritis in pediatric age in Portugal with a similar methodology to the present one have been previously published. Three of these had comparable findings to this study: a multicenter study carried out in the north of Portugal in 2005, a study carried out in Lisbon and Tagus Valley in 2016, and a study carried out in the central region of Portugal in 2014.[8,9,13-16] In the fourth study, *Salmonella* spp. was the most frequent etiological agent (found in 54% of positive co-cultures), followed by *Campylobacter* spp. (23%).[9] In another study assessing only hospitalized patients, *Escherichia coli* was the most frequent etiological agent (43%), followed by *Campylobacter* spp. (37%).[15] However, this study had a different methodology from the current one, precluding the comparison of results.[15] Regarding *Campylobacter* species, *C. jejuni* was the most frequently associated with ABG, with an increase in the number of cases diagnosed over the years, in agreement with other studies.[2,5,8,13]

The percentage of viruses and bacteria coinfection in this study was 7%, a value similar to the one found in the literature.[13] A higher number of cases was found in children aged between one and five years, but also a high number of cases in children under one year, in agreement with the recently published national report[5] and three of the above-mentioned national studies.[9,13,14] In the study conducted only in patients admitted to the PD,[15] *Campylobacter* spp. was the most frequent pathogen detected in patients aged 12 months and older, and particularly in those over five years. However, this study included a small sample size and hospitalized patients, a population with different clinical characteristics from the one included in the present study. Regarding gender distribution, this study found a predominance of *Campylobacter* spp. in males, also verified in two national studies.[8,13]

This study has as main limitations its retrospective nature, the use of clinical criteria for performing stool tests, and the scarcity of data available in some clinical records, which hindered the identification of the probable source of infection in some cases and the presence of family cases in others.

Clinical manifestations at presentation were similar between this study and two of the national studies available in the literature.[9,14] The presentation during the first year of life was similar to other age groups, but seizures were only present in children aged one to five years. According to the literature, aqueous diarrhea is found in about half of cases, which was also observed in this study.[2,7] The high frequency of cases of diarrhea with blood or mucous in this sample likely represents a data bias related to the fact that stool tests are much more often required in presence of this type of presentation.

Although undeniably relevant from an epidemiological point of view, etiological study is recommended in cases where targeted therapy is indicated or to aid in the differential diagnosis.[3] The isolation rate of pathogens in stools in the present study was 32%, similar to that registered in other studies.[8,9,15]

Importantly, 89 patients (20.2%) were hospitalized in the PD, on

average for 3.2 days, 82 of whom required intravenous hydration. Other studies reported hospitalization rates between 10% and 55%.[8,9,13,14] As per recommendations, antimicrobial treatment was prescribed in selected cases. Only 11 patients (12.4%) received directed antibiotic therapy (nine azithromycin and two clarithromycin). The very low prescription rate of antibiotics is justified by the fact that treatment of this enteritis is unspecific, and the evolution of bacterial diarrhea is generally self-limited. The choice of medication was mostly empiric, taking into account the most frequently isolated pathogens and their susceptibility. In the group of samples submitted to antibiotic sensitivity test (AST), a pattern of antibiotic resistance similar to the one described in the literature was found, although with a higher rate of quinolone resistance.[17,18]

At the time of ED discharge, caregivers were educated about warning signs that should be monitored and those requiring prompt medical reassessment. The clinical course was generally favorable, with a low rate of complications and PD admission.

CONCLUSION

ABG in children remains one of the most common causes of hospital admission and a major public health concern in Portugal. *Campylobacter* spp. is currently the most frequent cause of acute bacterial diarrhea in developed countries. An increase in the number of new diagnoses has been reported in recent years for reasons yet to be clarified. Although ABG is mostly a self-limited disease with favorable clinical course, the occurrence of associated complications and/or other forms of more serious and potentially fatal infections should be considered. Stool test enables the etiological identification, which is crucial in cases requiring directed therapy.

The increase in the number of cases diagnosed over the years suggests the need to raise awareness of professionals in primary health care for appropriate hygiene measures in the manipulation and preparation of meals to be conveyed to their patients.

AUTHORSHIP

Liliana Sá – Conceptualization; Formal Analysis; Visualization; Writing – original draft; Writing – review & editing

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REFERENCES

1. Heresi GP, Murphy JR, Cleary TG. Campylobacter jejuni. In: Feigin RD, Cherry JD, Demmler-Harrioson GJ, Kaplan SL, editors. Feigin and Cherry´s textbook of pediatric infectious diseases. Philadelphia: Saunders Elsevier; 2009. p. 1612-8.
2. EFSA (European Food Safety Authority), ECDC (European Centre for Disease Prevention and Control). The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2011. EFSA J 2013;11:3129-250.
3. Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R, *et al*. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence- based guidelines for the management of acute gastroenteritis in children in Europe. J Pediatr Gastroenterol Nutr 2008;46:S81-122.
4. European Centre for Disease Prevention and Control. Annual epidemiological report: Campybacteriosis. 2016. (Accessed on April 25, 2018). Available in: https://www.ecdc.europa.eu/en/publications-data/campylobacteriosis-annual-epidemiological-report-2016-2014-data.
5. Duarte A, Santos A, Benoliel J, Domingues F, Oleastro M. A infeção humana por Campylobacter em Portugal: alguns dados epidemiológicos. Instituto Nacional de Saúde Doutor Ricardo Jorge. Infeções Gastrointestinais. Artigos breves nº7. 2013.
6. Ketley JM. Pathogenesis of enteric infection by Campylobacter. Microbiology 1997;143:5-21.
7. Murray PR, Rosenthal KS, Pfaller, MA. Medical microbiology. 5th. Philadelphia: Mosby Elsevier; 2005. p.14.
8. Borges AC, Pedrosa C, Santos A, Vitorino M, Costa M, Godinho C. *Campylobacter jejuni*: gastrenterites agudas e infecções extra-intestinais. Acta Pediatr Port 2005;36:191-3.
9. Rodrigues F, Calvino J, Alves AF, Lemos L. Diarreia aguda por *Campylobacter* spp. Acta Pediatr Port 2006;37:91-4.
10. Ban M Allos. Clinical manifestations, diagnosis, and treatment of Campylobacter infection. 2019. (Accessed on August 20, 2018). Available in: http://www.uptodate.com.
11. Paiva M, Santos F, Amaral JMV. Gastroenterite aguda. In: Amaral JV, editor. Tratado de Clínica Pediátrica. Lisboa: Abbott Lda; 2008. p. 532-6.
12. Bhutta ZA. Acute gastroenteritis in children. In: Kliegman RM, Stanton BF, Schor NF, Geme JW, Behrman RE, editors. Nelson Textbook of Pediatrics. Philadelphia: Elsevier Saunders; 2011. p. 1323-38.
13. Peixoto AMM, Brett ACO, Rodrigues FMP. Gastroenterite Aguda Bacteriana num Serviço de Urgência Pediátrico. Faculdade de Medicina da Universidade de Coimbra. 2016.
14. Soares AT, Couto C, Romão P, Melo IS, Braga M, Diogo J, *et al*. Gastroenterite aguda por *Campylobacter spp: casuística de uma urgência pediátrica. Acta Me*d Port 2014;27:556-60.

15. Escobar C, Silva T, Costa B, Oliveira M, Correia P, Ferreira GC, *et al. Gastroenterite aguda em crianças internadas na área de Lisboa. Acta Pediatr Port 2013; 44:148-55.*
16. Tam CC, O'Brien SJ, Tompkins DS, Bolton FJ, Berry L, Dodds J, *et al*. Changes in causes of acute gastroenteritis in the United Kingdom over 15 years: microbiologic findings from 2 prospective, population-based studies of infectious intestinal disease. Clin Infect Dis 2012;54:1275-86.
17. Lengerh A, Moges F, Unakal C, Anagaw B. Prevalence, associated risk factors and antimicrobial susceptibility pattern of *Campylobacter* species among under five diarrheic children at Gondar University Hospital, Northwest Ethiopia. BMC Ped 2013;13:82.
18. Adedayo O, Kirkpatrick BD. Campylobacter jejuni infections: update on presentation, diagnosis, and management. Hosp Physician 2008;44:9-15.

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Received for publication: 18.09.2020
Accepted in revised form:27.04.2021

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):16-24. doi:10.25753/BirthGrowthMJ.v31.i1.21113

ORIGINAL ARTICLES

Characterization of play, sleep, and behavior in preschool-aged children

Caracterização dos hábitos de brincar, sono e comportamento em crianças em idade pré-escolar

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ABSTRACT

Introduction: Playing is a fundamental activity of childhood. The primary goal of this study was to characterize the playing habits of Portuguese children aged between three and five years old. The secondary goals were to investigate children's sleeping habits, audiovisual media exposure, and behavior, as well as caregivers´ perception of these.

Material and methods: Observational study based on the application of an online questionnaire to parents and caregivers about children's sociodemographic features, playing habits, exposure to screens, sleep, and behavior.

Results: A total of 240 questionnaires were retrieved, 58.3% (n=140) of which regarding male children. Overall, 93.9% (n=225) of children attended or had previously attended kindergarten, 56.9% (n=137) practiced at least one extracurricular activity, 64.4% (n=155) played outdoors in most days, and 80.9% (n=194) played with their peers. Most caregivers (68.3%, n=164) daily played with their children, but 95% (n=228) would like to do it more often. Free play was preferred among children (64%, n=154). Most children (77.4%, n=186) had contacted with audiovisual media before the age of 18 months. Most caregivers (89.6%, n=215) considered that their children slept well, with 27.4% (n=66) acknowledging that they threw frequent tantrums and 21.3% (n=51) that they were impulsive or aggressive. Most caregivers recognized the importance of playing for children. Regarding sleep habits and behavior, lower focus in quiet activities (odds ratio [OR] 4.638, 95% confidence interval [CI] 1.902-11.314) and more regular tantrums (OR 2.317, 95% CI 1.022-5.250) were independent predictors of sleeping problems.

Conclusion: Free playing, frequent outdoor playing, and playing with other children stood out as protective factors of children's physical and mental health. However, inadequate screen exposure and schedule overload with structured activities represent concerns that should be addressed in Pediatric appointments. Family-centered playful learning should be encouraged.

Keywords: behavior; children; development; Pediatrics; play; sleep

RESUMO

Introdução: Brincar é uma atividade essencial da infância. O objetivo principal deste estudo foi caracterizar os hábitos de brincar de crianças portuguesas com idades compreendidas entre os três e cinco anos. Como objetivos secundários, pretendeu avaliar-se os hábitos de sono, exposição a meios audiovisuais e comportamento das crianças, bem como a perceção dos cuidadores sobre estes estes assuntos.

Material e métodos: Estudo observacional baseado na aplicação de um questionário online a pais e cuidadores sobre aspetos sociodemográficos, hábitos de jogo, exposição a ecrãs, sono e comportamento das crianças.

Resultados: Foram recolhidos 240 questionários, 58,3% (n=140) dos quais relativos a crianças do género masculino. No total, 93,9%

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(n=225) das crianças frequentavam ou já tinham frequentado o jardim de infância, 56,9% (n=137) praticavam pelo menos uma atividade extracurricular, 64,4% (n=155) brincavam ao ar livre quase todos os dias e 80,9% (n=194) brincavam com pares. A maioria (68,3%, n=164) dos cuidadores brincava com as crianças diariamente, mas 95% (n=228) gostaria de o fazer mais frequentemente. A brincadeira livre foi a preferida entre as crianças (64%, n=154). A maioria das crianças (77,4%, n=186) tinha contactado com meios audiovisuais antes dos 18 meses de idade. Relativamente aos cuidadores, 89,6% (n=215) consideraram que as crianças dormiam bem, com 27,4% (n=66) a afirmar que as crianças faziam birras frequentes e 21,3% (n=51) que estas eram impulsivas ou agressivas. A maioria dos cuidadores reconheceu a importância do ato de brincar para a criança. Relativamente aos hábitos de sono, o menor foco em atividades calmas (*odds ratio* [OR] 4.638, intervalo de confiança [IC] 95% 1.902-11.314) e birras frequentes (OR 2.317, IC 95% 1.022-5.250) foram preditores independentes de problemas do sono.

Conclusão: A brincadeira livre, brincar frequentemente ao ar livre e brincar com outras crianças destacaram-se como fatores protetores da saúde física e mental das crianças. Contudo, a exposição inadequada a ecrãs e a sobrecarga horária com atividades estruturadas constituem uma preocupação, devendo ser abordados nas consultas de Pediatria. A aprendizagem lúdica centrada na família deve ser incentivada.

Palavras-chave: brincar; comportamento; criança; desenvolvimento; Pediatria; sono

INTRODUCTION

Playing is a child's right and an essential activity for his/her development, thus representing the key verb of childhood.[1,2] Today's society, marked by technological development and growing demand for children's performance in various areas, determines several barriers to child participation in playing. Increasingly early exposure to audiovisual media, a great amount of time spent at school or in extracurricular activities, and lower parental availability are acknowledged threats to play.[2]

Understanding how children play and how caregivers understand play is key for defining intervention areas and strategies. However, studies investigating the playing habits of children in Portugal are scarce.

The primary goal of this study was to characterize the playing habits of Portuguese children aged three to five years. Secondary goals were to characterize their sleeping habits, exposure to screens, and behavior, as well as caregivers´ perception of these aspects.

MATERIAL AND METHODS

This was an observational, cross-sectional study based on the application of an online questionnaire to parents and main caregivers of children aged between three and five years. A convenience sample was retrieved through inclusion of all caregivers who accessed the online survey and correctly completed it. Those who were not the main caregivers of children in the referred age range were excluded. Study participants provided informed consent to participate, and the study was approved by the Ethics Committee of the participating hospital. Data were collected during July 2018. The questionnaire was subdivided into the following sections: sociodemographic characterization of caregivers and characterization of their interaction with children; sociodemographic characterization of children and characterization of their playing habits, screen exposure, sleep, and behavior; and questions of opinion, with closed answer (from "totally agree" to "totally disagree").

Categorical variables were expressed as frequencies and percentages. Comparisons between categorical variables were performed using the χ^2 test. Binary logistic regression was used to calculate odds ratios [OR] in multivariate analysis. The inclusion of variables into multivariable model was tested using the forward stepwise selection method. Statistical significance was accepted for P values <0.05, and statistical analysis was performed using IBM SPSS Statistics, version 22 (IBM, Armonk, New York).

RESULTS

A total of 240 valid online questionnaires was retrieved. **Table 1** depicts the study population, which comprised 58.3% (n=140) of male children and had the following age distribution: 36% (n=86) of three-year-olds, 31.6% (n=76) of four-year-olds, and 32.4%(n=78) of five-year-olds. Regarding caregivers, the population included had a median of 36 years (range 21-71) and was mostly composed of mothers (79.6%; n=191), followed by fathers (10.4%; n=25), grandparents (4%; n=10), and others (6%; n=14). Concerning education level, 68.8% (n=165) of caregivers had a university degree and 17.7% (n=42) had completed high school. Additionally, 82.9% (n=199) were employed.

Although 68.3% (n=164) of caregivers said they played with their children daily, 95% (n=228) would like to do it more often. Lack of time was the main limiting factor (77.9%; n=187), although 3.3% (n=8) claimed not knowing "how to play with the child". A minority (5%, n=12) admitted playing with children only on weekends or holidays. As for the daily amount of time spent playing with children, 24.2% (n=58) did it for up to 30 minutes, 36.3% (n=87) between 30-60 minutes, and 39.6% (n=95) for more than one hour.

Table 1 - Characterization of the population of children and caregivers included in this study

Children (n=240)	**Frequency (%)**
Age (years)	
3	86 (35.8%)
4	76 (31.7%)
5	78 (32.5%)
Gender, Male	140 (58.3%)
Caregivers (n=240)	
Age (media of years, range)	39 (21-71)
Gender, Female	197 (82.1%)
Degrees of kinship with the child	
Mother	191 (79.6%)
Father	25 (10.4%)
Grandparent	10 (4.2%)
Other	14 (5.8%)
Education level	
University degree	165 (68.8%)
Highschool degree	42 (17.6%)
Employment status	
Employed	199 (82.9%)

Most children (93.8%, n=225) attended kindergarten, 80.8% (n=194) for six or more hours a day, and 57.1% (n=137) attended at least one extracurricular activity (**Figure 1**). The majority (64.2%; n=154) played outdoors in most days, with 32.9% (n=79) doing it only on weekends and 2.5% (n=6) rarely. A significant percentage of children (80.8%, n=194) daily interacted with other children, including brothers, cousins, and neighbors.

Regarding playing options, free play (e.g., make-believe and pretend play) was the preferred by children (64.2%, n=154), followed by sports (10%; n=24), plastic arts (7.9%; n=19), and video games (3.8%; n=9; **Table 2**). Approximately a third (34.2%, n=82) of caregivers acknowledged often influencing their children on what to do or how to play.

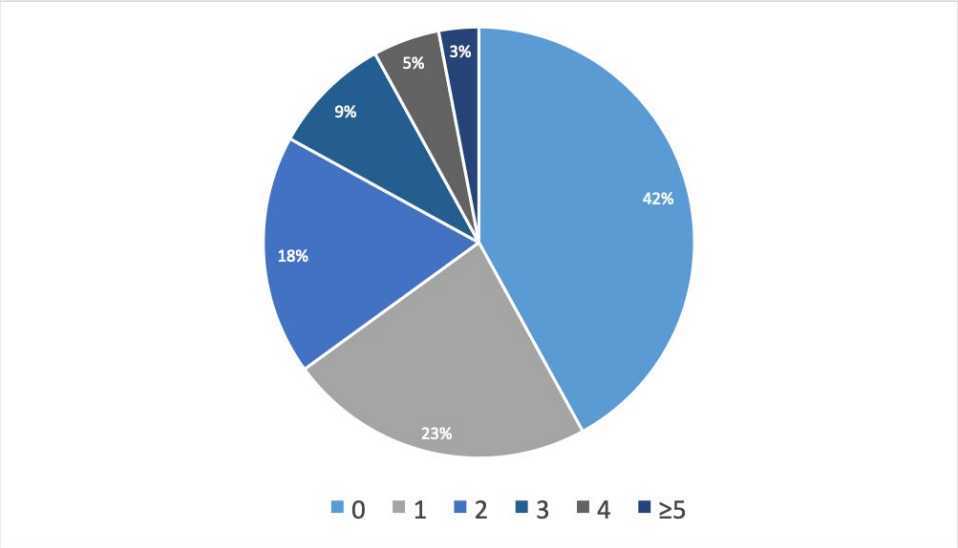

Figure 1 - Number of hours spent in extracurricular activities per week, including weekends

Table 2 - Playing preferences of children, according to caregivers

Playing preference	**n (%)**
Free play (e.g., make believe; pretend play)	154 (64.2%)
Sports activities (e.g., playing ball; cycling; skates)	24 (10%)
Plastic arts (e.g., plasticine; colleges; paintings)	19 (7.9%)
Structured games (e.g., board games; cards)	16 (6.7%)
Traditional games (e.g., tag; hide-and-seek; hopscotch; jumping rope)	13 (5.4%)
Videogames	9 (3.8%)
Mix of the referred activities	5 (2.1%)

Most children (77.5%, n=186) had contacted with audiovisual media (TV, tablet, mobile phone, computer, or console) before the age of 18 months, with 44.6% (n=107) using these devices daily for one to three hours and for more than three hours in 6.5% (n=16) of cases. Most children (77.4%, n=186) did not have these devices in the room. The first contact with books was before the age of 12 months for 75.2% (n=180) of children.

When asked about their children's sleeping habits, 89.6% (n=214) of caregivers considered that they slept well. Most children had their own room (88.3%; n=212) and their own bed (93.9%; n=225). About 52.8% (n=127) of children always or almost always required the presence of an adult to fall asleep, and 37.4% (n=90) always or almost always called for an adult to fall asleep if waking up at night. Most children (86.3%, n=207) slept eight to 13 hours, 7.5% (n=18) eight to 10 hours, 5.4% (n=13) less than eight hours, and 0.83% (n=2) more than 13 hours per day.

Concerning children's behavior, 85.8% (n=206) of caregivers considered that they were able to remain seated and concentrated on quiet activities, 27.5% (n=66) stated that they had frequent tantrums, and 21.3% (n=51) acknowledged that they were impulsive or aggressive. A small percentage (7.5%, n=18) frequently suffered from headaches or abdominal pain, and 1.3% (n=3) were regularly

tired, unmotivated, or uninterested. Children who did not sleep well (i.e., at least 10-13 hours a day or have other sleeping problems in the caregiver's perception) were more often impulsive or aggressive and less focused on quiet activities and had more regular tantrums (p<0.05) (**Table 3**). In multivariate analysis, the focus on quiet activities (less focused vs. focused, OR 4.638, 95% CI 1.902-11.314) and frequent tantrums (frequent vs. infrequent tantrums, OR 2.317, 95% CI 1.022-5.250) were independent predictors of sleeping problems, but not impulsive/aggressive behavior.

Answers to questions of opinion revealed that 99.6% (n=239) of caregivers completely agreed that "playing is a fundamental activity for learning", and the majority (79.2%, n=190) agreed that "children learn more while playing with other children than with adults" (**Table 4**). A little less than half of caregivers (47.1%; n=113) partially or totally agreed that "children learn more while playing with their parents or primary caregivers than with kindergarten educators". Finally, it was mostly unanimous that "exposure to violence in audiovisual media can influence children's behavior" and that "the preference for sedentary activities can increase the risk of obesity/overweight".

Table 3 - Relation between children´s behavior and sleeping habits

Child behavior	Total	Sleeps well	Does not sleep well	P
Remains seated/focused on quiet activities	197 (86.0%)	178 (89.9%)	19 (61.3%)	**<0.001**
Has frequent tantrums	63 (27.4%)	49 (24.6%)	14 (45.2%)	**0.017**
Is impulsive/aggressive	49 (21.4%)	38 (19.1%)	11 (36.7%)	**0.029**
Has headaches/abdominal pain	17 (7.4%)	14 (7.0%)	3 (9.7%)	0.601
Is usually tired, unmotivated, or uninterested	3 (1.3%)	2 (1.0%)	1 (3.2%)	0.311

"Sleeps well" – considering the caregiver's subjective opinion and that the child sleeps 10-13 hours per day.

Table 4 - Caregivers answers to questions of opinion

	Opinion N (%)				
Statement	**I totally agree**	**I partially agree**	**I partially desagree**	**I totally disagree**	**I do not know**
Playing is a fundamental activity for children learning	239 (99.6%)	0%	0%	0%	1 (0.4%)
Children learn more playing with other children than with adults	55 (22.9%)	134 (55.8%)	19 (7.9%)	5 (2.1%)	27 (11.3%)
Children learn more playing with parents or caregivers than with kindergarten educators	50 (20.8%)	17 (7.1%)	58 (24.2%)	19 (7.9%)	96 (40%)
Exposure to violent content and programs in audiovisual media can influence children's behavior (by being more violent, impulsive, or aggressive)	165 (68.8%)	63 (26.3%)	2 (0.8%)	1 (0.4%)	9 (3.8%)
Preference for sedentary activities can increase children's risk of being overweight or obese	206 (85.8%)	23 (9.6%)	7 (2.9%)	0%	4 (1.7%)

DISCUSSION

The importance of playtime in children's development is largely acknowledged in the literature and was also recognized by most caregivers in this study.[1,2] It represents a key action for multiple functional and structural brain processes, namely behavior modulation, socio-emotional skills, language, mathematical reasoning, creativity, and imagination, all of which are fundamental aspects of learning.[3-7] It is also an important way of regulating stress, impulsivity, and aggressiveness, improving self-regulation, and stimulating parental independence.[8,9]

Although most caregivers in the present study stated that daily played with their children, most would like to do it for longer, with lack of time being the main obstacle for not doing so. This agrees with results from another Portuguese study, according to which 63.3% of parents spent one to three hours a day playing with their children and 26.2% up to one hour a day.[10] Spending time playing with children intensifies emotional bonds, which is crucial to foster the exploration of the unknown by the child. Children learn in a continuous way, not only in formal settings such as school but also through caregivers and daily experiences, and this informal process is crucial and should be reinforced.[9] Everyday activities, such as housework, going to the supermarket, or car trips, are examples of opportunities for interaction, playing, and learning.[8,9]

Most children in this study spent at least six hours daily in kindergarten and had at least one extracurricular activity. Caregivers' demanding working schedules are preponderant factors in such use of children's time, but other factors may also play a part. Nowadays, social focus on academic success leads to an excessive encouragement of structured activities at the expense of free play time, as it is commonly believed that they are crucial for children's development.[9,10] However, too many scheduled hours, associated with the lack of free time for playing and spending quality time with the family, is highly limiting of creativity and may relate to anxiety and depression later.[9] School preparation should encompass a holistic perspective (including socio-emotional, behavioral, and cognitive aspects),[11] and the importance of playing in the acquisition of functional and executive competencies and in adult life has been largely recognized.[12] The false dichotomy between playing and formal learning has been replaced by the value of "playful learning", through the active and happy discovery of contents, achieved through innate curiosity and motivation and associated with content memorization.[13-17]

Most children in this study played outside in most days, in contradiction with the tendency of disregarding outdoor playtime for being unsafe and for lack of playgrounds and green spaces in urban settings, leading to a "nature deficit".[18,19] Excessive concerns about getting dirty, self-injuring, getting wet, etc., may be an exaggerated tendency of modernity and an obstacle for resilience construction.[20]

The fact that most caregivers in this study recognized the importance of promoting playtime between their children and other children is a positive aspect, as playtime with peers is the cornerstone of the development of social capacities, namely cooperation, negotiation, teamwork, conflict resolution, leadership capacity, and self-defense capacity.[21,22]

Free play was identified as the preferred playing option in this study. A systematic review from 2015 consistently showed that free play contributed to children's physical and mental health.[23] Importantly, a study in animal models explored the consequences of free play deprivation and showed underdevelopment of pre-frontal cortex areas, limiting the individuals' ability for problem resolution, sociability, and maturity.[10] In role-play playing, children make up and establish rules, which is important for creativity development, promotion of self-regulation, and capacity of abstract reasoning in hypothetical scenarios.[5,6] All forms of play have benefits: sports are important for the development of motor skills and learning to cooperate, plastic arts stimulate creativity, and structured gaming teaches how to follow rules and accept defeat.[9] Only a small percentage of children (3,8%) indicated videogames as the main play activity. Multimedia exposure predisposes to passivity and sedentarism, discourages curiosity and language, and takes away time from active play and interaction with others.[9]

Most parents said they did not interfere with the way their children played. This is relevant, as curiosity, independence, and language development are constrained when adults are intrusive and directive in children´s playing.[9]

Most children in this study were exposed to audiovisual media before the age of 18 months, contrary to recommendations of the American Academy of Pediatrics (AAP) for limiting exposure to videoconferences with the close family in this age group.[24] Screen time also seemed to be excessive in about half of cases. Both AAP and the World Health Organization (WHO) recommend that children between two and five years old should only watch programs of high educational value, for up to one hour daily, and under supervision.[24,25] The present study did not account for the type of screen or program used. A study from 2017 by the Regulating Entity for Social Communication reported that television was the predominant audiovisual media in Portuguese children aged between three and eight years, and 94% of children watched television every day, on average for one hour and 41 minutes,[26] which is consistent with this study's results. While well-designed television programs can improve cognitive, literacy, and social outcomes in children between three and five years old, skills and executive functions for school success are best acquired through social play and parent-child interaction.[27] Exposure of children to violent content and programs in the media concerned most caregivers inquired, highlighting that those should be carefully selected.

WHO recommends that children spend at least 180 minutes daily in physical activities of varying intensity and at least 60 minutes daily in moderate to vigorous activities, which can and should encompass different ways of playing and gaming.[25] Most caregivers in this study were aware that sedentary activity increases obesity risk. Childhood

is a critical period for the development of motor competencies and acquisition of healthy lifestyles. Active playing is associated with prevention of cardiovascular diseases, stress, and depression, and with improvement of agility, coordination, balance, and flexibility.[9] WHO recommends that part of sedentary activities include reading,[25] and three-quarters of children in this study had contacted with books before the age of 12 months, which represents a positive study finding.

Regarding sleeping habits, most parents considered that their children slept well, but around 50% of children required parental involvement to fall asleep, and around one-third had night awakenings. Studies indicate that direct parental intervention in children's falling asleep should gradually decrease and that they should fall asleep on their own and independently of the caregiver.[28] Night awakenings in small children are frequent and can be related to separation anxiety and poor sleep quality.[29] Most children in this study slept the recommended daily time (10-13 hours), but previous data had shown that most children in Portugal do not get adequate sleep.[28] A child aged three to five years old should sleep between 10 to 13 hours a day, including a one-to-three-hour nap, which is not always foreseen in preschool institutions.[28] In fact, sleeping problems in children are mostly undervalued.[29] Sleep deprivation in children is associated with poor mental and physical health, including attentional and behavioral problems, increased impulsivity, and mood and memory changes, compromising the learning ability. Results of this study, showing a high prevalence of children with adequate sleep time (**Table 3**), are consistent with the evidence in the literature.[28,29]

About half of children in this study presented behavior changes (tantrums, impulsiveness/aggressiveness), with a minority showing physical symptoms. These represent normal features in the development process and were predicted. Tantrums peak between two and three years of age, a period when the child is acquiring autonomy and trying to dominate the environment. At this age, 20% of children have tantrums at least once a day, and 50-80% at least once a week. Explosive temper persists during childhood in only 5% of children. However, excessive tantrums, both in frequency and intensity, may constitute warning signs for neurodevelopment and behavior disorders.[30]

This study has several limitations that should be acknowledged, starting with its convenience sampling and online data retrieval, which precluded the inclusion of individuals without an internet connection. On the other hand, the fact that data retrieved was based on the subjective report of caregivers, added to their high education level, may have influenced the results obtained. The use of non-validated questionnaires or scales, namely for the assessment of mental health, behavior, and sleep, are also relevant study limitations. Importantly, since this study was conducted before the pandemic outburst, a comparative study in the post-pandemic setting will be predictably interesting.

CONCLUSION

The great changes that society underwent over the past years led to modifications in the way children play and in their leisure experiences. Most parents and caregivers recognize the importance of playing, and most children choose "free play" as the preferred activity. In addition, the preference for playing outdoors and with other children were positive findings of this study. On the other hand, inadequate screen exposure, time overload in structured activities, and lack of caregiver availability seem to be the main challenges for children and caregivers nowadays and should be discussed during pediatric consultations as part of a global health assessment.

Playing should be taken very seriously in children's development process, and providing conditions for playing should be a priority for professionals, caregivers, and decision-makers.

More studies should be conducted on this subject, namely investigating the association between playing habits and health indicators, encouraging reflection and social-political decision to defend this fundamental child's right.

ACKNOWLEDGEMENTS

To Dr. Fátima Ferreira, who believed in playful learning and encouraged this work.

AUTHORSHIP

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REFERENCES

1. Milteer RM, Ginsburg KR; Council On Communications And Media; Committee On Psychosocial Aspects Of Child And Family Health. The Importance of play in promoting healthy child development and maintaining strong parent-child bond: focus on children in poverty. Pediatrics. 2012;129(1):e204-13.
2. Póvoas M, Castro T, Mateus AM, Costa M, Escária A, Miranda C. O brincar da criança em idade pré-escolar. Acta Pediatr Port. 2013;44(3):108-12.
3. Hirsh-Pasek K, Golinkoff RM, Berk L, Singer DG. A Mandate for Playful Learning in Preschool. New York, NY: Oxford University Press; 2009.1ªedição. pp. 17-42

4. Bodrova E, Germeroth C, Leong DJ. Play and self-regulation: lessons from Vygotsky. Am J Play. 2013;6(1):111-23.
5. Walker CM, Gopnik A. Pretense and possibility–a theoretical proposal about the effects of pretend play on development: comment on Lillard et al. (2013). Psychol Bull. 2013;139(1):40-4.
6. Pellis S, Pellis V. In The Playful Brain: Venturing to the Limits of Neuroscience. Oxford, United Kingdom: Oneworld; 2009. 1ªed. pp. 62-90; 161 -6.
7. Lewis V, Boucher J, Lupton L, Watson S. Relationships between symbolic play, functional play, verbal and non-verbal ability in young children. Int J Lang Commun Disord. 2000;35(1):117-27.
8. Galinsky E. In: Mind in the Making: the seven essential life skills every child needs. 1st ed. New York: Harper Collins; Harperstudio. 2010. pp. 43-4.
9. Yogman M, Garner A, Hutchinson J, Hirsh-Pasek K, Golinkoff RM; Committee on Psychosocial Aspects of Child and Family Health; Council on Communications and Media. The power of play: a Pediatric Role in Enhancing Development in Young Children. Pediatrics. 2018;142(3).pii:e20182058.
10. Conselho Nacional de Educação. "A EDUCAÇÃO DAS CRIANÇAS DOS 0 AOS 12 ANOS". Lisboa: Conselho Nacional de Educação; 2008 Available at: https://www.cnedu.pt/content/antigo/files/1_A_Educacao.pdf; acedido a 06/06/19
11. High PC; Committee on Early Childhood, Adoption, and Dependent Care and Council on School Health. Pediatrics. 2008;121(4).
12. Walker SP, Chang SM, Vera-Hernández M, Grantham-McGregor S. Early childhood stimulation benefits adult competence and reduces violent behavior. Pediatrics. 2011;127(5):849-57.
13. Golinkoff RM, Hirsh-Pasek K. Becoming Brilliant: What Science Tells us About Raising Successful Children. 1st ed. Washington, DC: American Psychological Association (APA); 2016.pp. 34-48.
14. Lubans DR, Morgan PJ, Cliff DP, Barnett LM, Okely AD. Fundamental movement skills in children and adolescents: review of associated health benefits. Sports Med. 2010;40(12):1019-35. Review.
15. Hirsh-Pasek K, Golinkoff RM, Eyer D. Einstein Never Used Flash Cards: How Our Children Really Learn—and Why They Need to Play More and Memorize Less. Pleasant Valley, NY: Rodale; 2003. pp. 205-43.
16. Sobel DM, Sommerville JA. The importance of discovery in children's causal learning from interventions. Front Psychol. 2010;1:176.
17. Gruber MJ, Gelman BD, Ranganath C. States of curiosity modulate hippocampus-dependent learning via the dopaminergic circuit. Neuron. 2014;84(2):486-96.
18. Child Trends. Neighborhood safety [Internet]. Bethesda; 2019 [cited 2019 Jul 10]. Available from: https://www.childtrends.org/indicators/neighborhood-safety/.
19. Louv R. In: Last Child in the Woods: Saving Our Children From Nature-Deficit Disorder. Chapel Hill, NC: Algonquin Books; 2008. p.99-114.
20. Barry E. In British playgrounds, bringing in risk to build resilience [Internet]. New York Times 2018 [cited 2019 Jul 7]. Available at: https://www.nytimes.com/2018/03/10/world/europe/britain-playgrounds- risk.html.
21. Pellegrini AD, Smith PK. Physical activity play: the nature and function of a neglected aspect of playing. Child Dev.1998;69(3):577-98. Review.
22. Lieber R. Think Seriously About Spending for Play. 2016;(January 2):B1 [Internet]. New York Times 2018 [cited 2019 Jul 7]. Available at: https://www.nytimes.com/2016/01/02/your-money/think-seriously-about-spending-for-play.html.
23. Brussoni M, Gibbons R, Gray C, Ishikawa T, Sandseter EB, Bienenstock A, *et al*. What is the Relationship between Risky Outdoor Play and Health in Children? A Systematic Review. Int J Environ Res Public Health. 2015;12(6):6423-54. Review.
24. American Academy of Pediatrics (AAP). American Academy of Pediatrics Announces New Recommendations for Children's Media Use [Internet]. AAP; 2016 [cited 2019 Feb 1]. Available at: https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/american-academy-of-pediatrics-announces-new-recommendations-for-childrens-media-use.aspx
25. World Health Organization. (2019). Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age. World Health Organization. https://apps.who.int/iris/handle/10665/311664.
26. Entidade Reguladora para a Comunicação Social (ERC). CRESCENDO ENTRE ECRÃS: Usos de meios eletrónicos por crianças (3-8 Anos) [Internet]. Lisboa: ERC; 2017 [citado 2020 Jan 28]. Available at:https://www.internetsegura.pt/sites/default/files/crescendo-entre-ecras.pdf
27. Council on communications and media. Media and Young Minds. Pediatrics. 2016 Nov;138(5):e20162591. doi: 10.1542/peds.2016-2591. PMID: 27940793.
28. Sociedade Portuguesa de Pediatria – Secção de Pediatria Social. Recomendações SPS-SPP: Prática da sesta da criança nas creches e infantários, públicos ou privados. Published online in June 2017.URL:https://www.spp.pt/UserFiles/file/Noticias_2017/VERSAO%20PROFISSIONAIS%20DE%20SAUDE_RECOMENDACOES%20SPS-SPP%20SESTA%20NA%20CRIANCA.pdf [03.02.2021].
29. Bhargava S. Diagnosis and Management of Common Sleep Problems in Children. Pediatrics in Review. 2011,32(3)91-99. DOI: https://doi.org/10.1542/pir.32-3-91
30. Gouveia R. As birras na criança. Rev Port Clín Geral. 2009;25(6):702-5.

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Received for publication: 03.10.2020
Accepted in revised form: 19.07.2021

ORIGINAL ARTICLES

Measles, Mumps, and Rubella vaccination in children with egg allergy

Vacinação Anti-Sarampo, Parotidite e Rubéola na criança com alergia ao ovo

Leonor Cunha[1], Diana Oliveira Almeida[2], Filipa Rodrigues dos Santos[1], Helena Falcão[1]

ABSTRACT

Introduction: Egg allergy is one of the most common food allergies in childhood. Administration of the measles, mumps, and rubella (MMR) vaccine is recommended in pediatric age. Despite the presence of traces of egg protein in its composition, the literature recommends MMR vaccine administration regardless of the patient's past egg allergy history, identifying cases in which the administration should occur in hospital setting.

Purpose: To characterize the pediatric population referred to the Allergy and Clinical Immunology Department of Centro Hospitalar Universitário do Porto for MMR vaccine administration and investigate vaccination safety in children with egg allergy or sensitization.

Methods: This was a retrospective observational study of clinical records of children with confirmed or suspected egg allergy referred to the Allergy and Clinical Immunology Department for administration of the MMR vaccine between January 1, 2013 and December 31, 2019.

Results: Among 60 children studied, 90% presented symptoms upon egg intake, with cutaneous reactions being the most prevalent (67%) and four reported cases of anaphylaxis. Allergy to cow's milk protein (55%), followed by allergy to other foods (45%) were the most frequent personal histories of allergic diseases. Asthma was identified in 10% of patients and was controlled in all cases. Among children referred for vaccination booster dose, one had had a reaction to the previous MMR vaccine dose. Three children developed late local skin reactions, and one had a late systemic reaction after vaccination. All children had negative oral food challenge.

Conclusion: MMR vaccine administration is safe and recommended in pediatric age, regardless of egg allergy history. However, immunization should be performed in hospital setting in children with a history of anaphylaxis due to egg allergy, previous anaphylactic reaction to MMR vaccine or one of its constituents, uncontrolled asthma with documented egg allergy, and uncontrolled asthma with allergy to a previous MMR vaccine dose.

Keywords: egg allergy; measles, parotitis and rubella vaccine

RESUMO

Introdução: A alergia ao ovo representa uma das alergias alimentares mais frequentes na infância. A administração da vacina anti-sarampo, parotidite e rubéola (VASPR) é recomendada em idade pediátrica. Apesar da presença de vestígios de ovalbumina na composição da vacina, a literatura recomenda a sua administração independentemente da história de alergia, advertindo para os casos em que a mesma deve ocorrer em ambiente hospitalar.

Objetivo: Caracterizar a população pediátrica referenciada para a consulta de Imunoalergologia do Centro Hospitalar Universitário do Porto para administração da VASPR, bem como a segurança da mesma em crianças com alergia ou sensibilização ao ovo.

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Métodos: Estudo observacional retrospetivo dos processos clínicos de crianças referenciadas para a consulta de Imunoalergologia para administração da VASPR com alergia suspeita ou confirmado a ovo entre 1 de janeiro de 2013 e 31 de dezembro de 2019.

Resultados: Das 60 crianças estudadas, 90% apresentaram sintomas mediante ingestão de ovo, predominantemente cutâneos (67%) mas também anafilaxia em quatro casos. Alergia à proteína do leite de vaca (55%), seguida da alergia a outros alimentos (45%) foram os antecedentes pessoais de doença alérgica mais frequentes. Foi identificada asma em 10% dos casos, encontrando-se controlada em todos. Das crianças referenciadas para administração de reforço vacinal, uma tinha apresentado reação à dose prévia da VASPR. Três crianças desenvolveram reação cutânea local tardia e uma desenvolveu reação sistémica tardia após administração da VASPR. Todas tiveram prova de provocação oral negativa.

Conclusão: A administração da VASPR é segura e a sua recomendação mantém-se mesmo em crianças com alergia ao ovo. Contudo, a inoculação deve ser realizada em ambiente hospitalar em crianças com reação anafilática ao ovo, reação anafilática a uma dose prévia da vacina ou seus componentes, asma não controlada e alergia ao ovo, ou asma não controlada e alergia a uma dose prévia da vacina.

Palavras-chave: alergia ao ovo; vacina anti-sarampo, parotidite e rubéola

INTRODUCTION

Egg allergy represents the second most common cause of food allergy in childhood. Its prevalence in children is estimated to range between 0.5–3.5%,[1-5] with most children acquiring tolerance between the ages of two and five years.[4,6]

Measles, mumps, and rubella (MMR) vaccination is pivotal for the primary prevention of those infectious diseases, diminishing the probability of infection and mortality. MMR vaccine contains in its formulation live attenuated viruses grown in cultured chick embryo fibroblasts, raising concerns about the presence of ovalbumin, the most abundant (>50%) allergenic protein in the egg white. However, because it is only partially stable to cooking and unstable to digestive enzymes, ovalbumin is little allergenic. The amount of ovalbumin present in the vaccine is considered insufficient to cause an allergic reaction, and other vaccine constituents are believed to be responsible for the adverse reactions seen after administration.[2,4,6-13]

Although the incidence of anaphylactic reactions to MMR vaccine is very low and studies show its safety in children allergic to egg, physicians still have concerns regarding its inoculation, which often results in delays in vaccine administration, with associated risks.[2,4]

The aim of this study was to characterize the pediatric population referred to the Allergy and Clinical Immunology Department for administration of the MMR vaccine and its safety in children with egg allergy or egg sensitization.

MATERIAL AND METHODS

This was a retrospective study of all patients with a history of egg allergy or egg sensitization requiring MMR vaccination attended at the Allergy and Clinical Immunology Department between January 1, 2013 and December 31, 2019.

The following data were retrieved from patients' clinical records: demographics; age of MMR immunization; egg allergy symptoms; history of atopy; results of skin prick tests (SPT) with egg extract; total immunoglobulin E (IgE) titers; titer of serum-specific IgE against egg white, egg yolk, ovalbumin, and ovomucoid; result of oral food challenge (OFC) with egg; adverse reactions after MMR vaccine administration; setting where immunization took place (hospital or primary health care center).

The study sample was divided into two groups: Group A, including all patients who received the first dose of MMR vaccine, and Group B, including all patients who received the second dose of MMR vaccine.

Data was analyzed through descriptive statistics, using mean and standard deviation for quantitative data and frequency expressed as percentage for qualitative data.

RESULTS

A total of 60 children were included during the considered time period, 46 (76.7%) male. Vaccination occurred in hospital setting in all cases. Forty-eight children had received the first administration of the MMR vaccine.

Most children (90%) presented clinical history suggestive of egg allergy, with 40 children presenting with cutaneous symptoms, seven with gastrointestinal symptoms, three with respiratory symptoms, and four with egg anaphylaxis history. Among the remaining six children (10%), five had never ingested egg at the time of referral, and one had an unknown

time of egg introduction in the diet.

In the five children who had never ingested egg, the motive for referral was cow's milk protein allergy and parental refusal of immunization in the primary care setting. However, these children had egg introduced in their diet during follow-up, developing cutaneous symptoms upon egg ingestion. One of them had total serum IgE and specific IgE within the normal range, negative SPT, and negative OFC with egg, excluding the diagnosis of egg allergy. The other four patients showed high total serum IgE and positive IgEs specific for egg white, egg yolk, ovalbumin, or ovomucoid, as well as positive OFC with egg. The child with unknown timing of egg introduction in the diet had been referred due to a reaction following MMR immunization at the age of 15 months. After medical history assessment (local cutaneous reaction), an allergic reaction to MMR vaccine was excluded. The child showed total serum IgE within the normal range, specific IgEs for egg yolk, egg white, ovomucoid, and ovalbumin, and negative OFC, excluding egg allergy.

Regarding clinical history, 33 children (55%) had cow's milk protein allergy, and 16 (27%) allergy to other foods (**Table 1**).

SPT was performed in 46.7% of children, with most being positive for egg white (**Table 2**). Most children (95%) were tested for egg yolk- and egg white-specific IgE, being positive for both in most cases. Specific IgE for ovalbumin and ovomucoid was registered in 36 and 33 children, respectively, with most cases positive for ovomucoid. Of the 33 children who performed OFC, 29 were positive.

After the first MMR vaccine dose, three cases of local cutaneous reaction were identified, including pruritic erythematous maculopapular skin rash, and one case of late systemic reaction with periorbital angioedema and urticaria in a child with house dust mite allergy and atopic eczema. The previous allergy study in these children is depicted in **Table 3**.

In children with egg anaphylaxis, SPT was positive for egg white and egg yolk; total IgE was elevated, and specific IgE was positive for ovomucoid, with no record of specific IgE for egg yolk, egg white, or ovalbumin. However, these children showed no allergic reactions to MMR immunization.

Group A included 42 children who had received the first MMR vaccine dose. In these children, the MMR vaccine had been administered with a mean delay of 2.38 months (standard deviation ± 3.0). Of note, in 2012 the Portuguese National Vaccination Plan guidelines were updated, anticipating the first MMR vaccine dose from the age of 15 to 12 months.

Group B included 18 children who received the second immunization dose under the recommended vaccination period, except for two children who were six years old at the time of vaccination. Only one case of a local adverse reaction to a previous MMR vaccine dose was reported in this group.

Table 1 - Characterization of patients with allergy history

Allergy History	Number of children (n)	Percentage (%)
Cow's milk protein allergy	33	55.0
Allergy to other foods	16	26.7
Asthma (controled)	6	10.0
Rhinitis	5	8.3
Atopic Dermatitis	5	8.3

Table 2 - Skin prick test, specific IgE, and OFC test results

			Number of children (n)	Percentage (%)
SPT (mm)	Egg yolk	Positive	8	34.8
		Negative	15	65.2
	Egg white	Positive	17	60.7
		Negative	11	39.3
Specific IgE (KU/L)	Egg yolk	Positive	33	61.1
		Negative	15	27.8
	Egg white	Positive	45	79
		Negative	7	12.3
	Ovalbumin	Positive	21	58.3
		Negative	15	41.7
	Ovomucoid	Positive	11	33.3
		Negative	22	66.7
OFC to egg	Positive		29	80.6
	Negative		7	19.4

IgE, immunoglobulin E; OFC, oral food challenge; SPT, skin prick test

Table 3 - Characterization of patients developing reactions after MMR vaccination

Case		1	2	3	4
Gender		F	M	M	M
Symptoms upon egg ingestion		Eczema	Eczema	Eczema	-
SPT (mm)	Egg yolk	-	-	Negative	-
	Egg white	-	-	Negative	-
Specific IgE (KU/L)	Egg yolk	0.21	1.63	0.02	0.05
	Egg white	1.6	4.47	0.06	0.18
	Ovalbumin		-	-	0.21
	Ovomucoid	-	-	-	0.12
OFC to egg		Negative	Negative	Negative	Negative
Reaction after vaccination		Late systemic	Late local	Late local	Late local

F, female; IgE, immunoglobulin E; M, male; MMR, measles, mumps, and rubella; OFC, oral food challenge; SPT, skin prick test

DISCUSSION

Many studies have shown the safety of MMR immunization in children with or without documented egg allergy.[1,2,5-7,9,12-14] Severe adverse reactions to MMR vaccination are very rare, with most reactions being local and transitory and generally occurring due to vaccination adjuvants.

Of the 60 children receiving MMR vaccines in this study, three developed mild local adverse reactions and one developed a late systemic reaction. According to the World Health Organization, local reactions are common and include pain, redness, and/or swelling at the injection site.[15] These reactions are caused by non-specific inflammation attributed to the injection itself and to the inoculation of foreign materials and do not constitute a contraindication to immunization.[15,16] Delayed urticaria, skin rash, and/or angioedema may occur a few hours after immunization, with immune system activation potentially due to nonspecific degranulation of mast cells.[17]

In this study, the patient with a previous history of egg anaphylaxis had no allergic reactions after vaccination. This finding is consistent with other studies showing that almost all children, including those with severe egg allergy, tolerate MMR immunization.[18-20]

In several European countries, MMR vaccination in egg-allergic patients is not a concern anymore. Several studies indicate that these vaccines may contain traces of egg protein in picogram levels, which do not represent a sufficient quantity to cause an allergic reaction.[1-3,7,8,10,11,18,21,22] Furthermore, additional studies demonstrate a substantial decrease of anaphylactic reactions since vaccines have stopped including gelatin in their constituents.[4,9,23-24] Therefore, MMR vaccination is recommended in all eligible children, independent of egg allergy.[3]

Although egg allergy is not a contraindication for MMR vaccination, there are still some concerns in the medical community when it comes to MMR immunization in egg-allergic patients, which can lead to delays in the vaccination schedule.[2,4,11] In line with this, a mean delay of 2.4 months was observed in the present study in the vaccination calendar of children in Group A.

The fact that this study included a reduced sample size represents a limitation and precludes generalizing the results obtained. Moreover, the retrospective nature of the analysis does not allow to determine the time between hospital referral and MMR immunization. Still, the results retrieved indicate that a history of egg allergy is not a contraindication for MMR vaccine administration. Suspicion of egg allergy should warrant prompt referral to the immunoallergologist, but should not delay MMR immunization.[12]

The British Society for Allergy and Clinical Immunology (BSACI) and the European Academy of Allergy and Clinical Immunology (EAACI) position paper on vaccination and allergy recommend that infants and children with egg allergy should be vaccinated in the primary care setting as a routine procedure.[16,18-25] Further allergic investigations are not recommended before vaccine administration. However, in the present study, many children had performed SPT to egg, specific IgE, or OFC for purposes of diagnosis and treatment of egg allergy itself.

The Portuguese Directorate-General of Health (DGS) published in 2012 a recommendation for the administration of MMR vaccine in all eligible children, independent of previous egg ingestion. Children with egg allergy should receive MMR vaccination in regular vaccination centers without requiring hospital referral despite allergy severity. The guidelines recommend MMR vaccine administration in hospital setting for patients with a history of anaphylaxis due to egg allergy, previous anaphylactic reaction to MMR vaccine or one of its constituents, uncontrolled asthma with documented egg allergy, or uncontrolled asthma with allergy to a previous MMR vaccine dose.[26]

MMR immunization in patients with suspected or documented egg allergy is still a major reason for hospital referral. However, in this study and according to DGS recommendations, only five cases had true indication for hospital referral. This burden of hospital referrals may lead to unnecessary delays in the vaccination schedule and should be avoided.

AUTHORSHIP

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REFERENCES

1. Cuabet JC, Wang J. Current understanding of egg allergy. Pediatr Clin N Am 2011; 58(2): 427-43.
2. Can C, Kural B. Reassessing the Risks of MMR Vaccination for Egg-Allergic Patients Referred by Healthcare Workers; a Clinical Paradigm. Iran Red Crescent Med J 2019; 21(6): 1-5.
3. Avilés F, Martí MC, Gómez XM, Pendás JAR, Lushchenkova O, Tella LP, *et al*. Vacuna triple vírica y alergia a huevo. Experiencia em una unidad de vacinación hospitalária. An Pediatr (Barc)

2007; 66(4):362-7.
4. Rosa S, Ribeira F, Pinto PL. Vacinação antisarampo, parotidite e rubéola em crianças com suspeita de alergia ao ovo. Rev Port Med Geral Fam 2015; 31(6):406-9.
5. Clark AT, Skypala I, Leech SC, Ewan PW, Dugué P, Brathwaite N, *et al*. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. Clinical et Experimental Allergy 2010; 40:1116-29.
6. See TM, Jin TE, Peng HC, Chiee AYA. Measles-Mumps-Rubella vaccine for children with egg allergy: Is admission for patient vaccionation necessary? Med J Malaysi 2016; 71(4): 157-60.
7. Cronin J, Scorr A, Russell S, McCoy S, Walsh S, O'Sullivan R. A review of a paediatric emergency department vaccination programme for patients at risk of allergy⁄anaphylaxis. Acta Pædiatrica 2012; 101(9):941–5.
8. Elitok GK, Çelikboya E, Bulbul L, Kaya A, Toraman T, Bulbul A, *et al*. Does Food Allergy Require Any Change in Measles-Mumps-Rubella Vaccination? The Indian Journal of Pediatrics 2019; 86(10): 915-20.
9. James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of measles vaccine to children allergic to eggs. The New England Journal of Medicine 1995; 332(19): 1262-6.
10. Carballo C, Pastor MCD, Zavala BB, Cano MS, Caballer BH. Safety of measles-mumps-rubeulla (MMR) vaccine in patients allergic to eggs. Allergol et Immunopathol 2007; 35(3): 105-9.
11. Sánchez J, Ramírez R, Cardona R. Frecuencia de las reacciones alérgicas a la vacuna triple viral em pacientes com alergia al huevo. Biomédica 2018; 38(4):514-20.
12. Khakoo GA, Lack G. Guidelines for measles vaccination in egg-allergic children. Clinical and Experimental Allergy 2000; 30(2):288-93.
13. Services USDoHaH. Guidelines for the Diagnosis and Management of Food Allergy in the United States - Summary for Patients, Families, and Caregivers 2011; S1-58.
14. Alves RP, Gaspar A, Ferreira MB. Reações alérgicas a vacinas. Revista Portuguesa de Imunoalergologia 2007; 15(6):465-83.
15. WHO. Immunization Safety Surveillance Guidelines for immunization programme managers on surveillance of adverse events following immunization.2013. 2nd edn. http://www.wpro.who.int/topics/immunization_safety/ImmunizationSafetySurveillance.pdf.
16. Lennart N, Brockow K, Alm J, Cardona V, Caubet JC, Gomes E, *et al*. Vaccination and allergu: EACCI position paper, practical aspects. Pediat Allergy Immunol. 2017; 28(7):628-40.
17. Siegrist CA. Mechanisms underlying adverse reactions to vaccines, J Comp Pathol 2007; 137(Suppl 1):S46-50.
18. Fox AT, Swan KE, Perkin M, Toit G, Lack G. The changing pattern of measles, mumps and rubella vaccine uptake in egg-allergic children. Clinical et Experimental Allergy 2014; 44(7):999-1002.
19. Aickin R, Hill D, Kemp A. Measles immunisation in children with allergy to egg. BMJ 1994; 309(6949): 223–5.
20. James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. N Engl J Med 1995; 332:1262–6.
21. Nokleby H. Vaccination and anaphylaxis. Curr Allergy Asthma Rep 2006; 6(1):9–13.
22. Anderson DV, Jorgensen IM. MMR vaccination of children with egg allergy is safe. Dan Med J. 2013; 60(2):A4573.
23. Carapetis JR, Curtis N, Royle J. MMR immunization. True anaphylaxis to MMR vaccine is extremely rare. BMJ. 2001; 323(7317):869.
24. Kuno-Sakai H, Kimura M. Removal of gelatin from live vaccines and DTaP-an ultimate solution for vaccine-related gelatin allergy. Biologicals. 2003;31(4):245-9.
25. Clark AT, Skypala I, Leech SC, Ewan PW, Dugué P, Brathwaite N, *et al.* British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. Clin Exp Allergy. 2010; 40(8):1116-29.
26. Saúde DGd. Programa Nacional de Vacinação - PNV 2012: VASPR (Vacina combinada contra o sarampo, a parotidite epidémica e a rubéola) e a alergia ao ovo 2012.

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Received for publication: 09.03.2021
Accepted in revised form: 28.07.2021

REVIEW ARTICLES

Cross-allergy between penicillins and cephalosporins: a paradigm shift

Reatividade cruzada entre penicilinas e cefalosporinas: mudança de paradigma

Liliana Dias[1], Cláudia Pedrosa[2]

ABSTRACT

Allergic reactions to beta-lactam antibiotics are the most common cause of allergic drug reactions. The incorrect diagnosis prevents patients from receiving a highly effective therapy.

The potential cross-reactivity between penicillin and cephalosporin has very significant therapeutic implications. Penicillins and cephalosporins share a common beta-lactam ring and side chains. A number of studies indicate that the R1 side chain, rather than the ring itself, is the determining factor for cross-reactivity.

Herein is presented a review of the immunologic mechanisms implicated in penicillin and cephalosporin cross-reactivity and a practical approach to the use of cephalosporins in patients allergic to penicillin.

Keywords: cephalosporin; cross-reactivity; penicillin; side chain

RESUMO

A alergia aos antibióticos beta-lactâmicos é a causa mais frequente de alergia secundária a fármacos. O diagnóstico incorreto impede os doentes de receber uma opção terapêutica altamente efetiva.

A reatividade cruzada entre penicilina e cefalosporina tem importantes implicações terapêuticas. A estrutura das penicilinas e cefalosporinas partilha o anel beta-lactâmico e as cadeias laterais. Vários estudos implicam a cadeia lateral R1 e não o anel beta-lactâmico como fator determinante para a reatividade cruzada.

O presente artigo faz uma revisão dos mecanismos imunológicos envolvidos na reatividade cruzada e apresenta uma abordagem prática ao uso de cefalosporinas em doentes alérgicos a penicilina.

Palavras-chave: cadeia lateral; cefalosporina; penicilina; reatividade cruzada

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INTRODUCTION

β-lactams (BL) are the first-line therapy for community- and hospital-acquired bacterial infections.[1] The vast knowledge of its pharmacokinetics, associated with a broad spectrum of activity and low toxicity, makes them the most used group of antimicrobials.[2]

The BL family includes penicillins, cephalosporins, carbapenems, monobactams, and beta-lactamase inhibitors. They are the antibiotic class most commonly reported to cause allergic reactions.[3] However, after appropriate assessment, more than 90% of subjects reporting allergy can tolerate penicillin.[4] This mislabel occurs because most reported reactions can be related to intolerance, benign viral rash, or drug-infection interactions.[4]

An incorrect penicillin allergy diagnosis excludes a highly effective therapeutic option, with a potential increase of side effects, microbial resistance, and risk of infection recurrence.[5,6] Using the tools available for a correct diagnosis allows to safely use these antibiotics.[7]

TYPES OF HYPERSENSITIVITY REACTIONS TO ANTIBIOTICS

BL can originate any of the four types of hypersensitivity reactions proposed by Gell and Coombs (**Table 1**), which account for the most frequent immune-related adverse drugs reactions.[8-11]

Table 1 - Immunologic aspects of hypersensitivity reactions according to Gell and Coombs classification. (Adapted from Regateiro F. and Faria E).

TYPE	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Description	Allergy	Cytotoxic	Imune complex disease	Delayed or celular hypersensitivity			
Time of Onset	Immediate 15 min-1 hour	Delayed (days, >72 hours)	Delayed (1-3 weeks)	Delayed (days to weeks)			
Immune Mechanism	IgE	IgG (and IgM)	IgG and IgM	IFN-γ, TNF-α (Th1 cells)	IL-5, IL-4, IL-13 (Th2 cells)	Perforin/ Granzyme B (CTL)	CXCL-8, IL-17, GM-CSF (T cells)
Antigen	Soluble Antigen	Antigen associated with the cell or matrix	Soluble Antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell-associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effector Mechanism	Activation of mast cells and basophils	Complement, FcR+ cells (phagocytes, NK cells)	Imune complex Complement, FcR+ cells activation	Activation of macrophages	Eosinophils	T cells	Neutrophils
Examples of hypersensitivity reactions	Rhinitis Urticaria Anaphylaxis	Hemolytic anemia Thrombocytopenia	Vasculitis, glomerulonephritis, arthritis, serum sickness	Contact dermatitis (with IVc)	Maculopapular exanthema with eosinophilia DHIS/DRESS	Contact dermatitis, Maculopapular and bullous exanthema (SJS, TEN) DILI Interstitisl nephritis	AGEP

AGEP, acute generalized exanthematous pustulosis; DILI, drug-induced liver injury; DRESS/DiHS, drug-induced hypersensitivity syndrome/ drug reaction with eosinophilia and systemic symptoms; FcR: Fc receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN-g, interferon-gamma; Ig, Immunoglobulin; IL, interleukin; NK, Natural Killer; SSJ, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF-a, Tumour necrosis factor alpha;

Immunoglobulin (Ig) E-mediated hypersensitivity reactions (Gell and Coombs type I) generally occur within one hour after drug administration. The drug or drug-protein complex is recognized by IgE antibodies bound to their high-affinity receptor on the surface of mast cells and basophils. Crosslinking of IgE leads to degranulation and release of a variety of pre-formed (histamine, triptase) and newly synthesized (leukotrienes, TNF-α) mediators. Mediators are responsible for clinical manifestations, namely cutaneous (itching, hives, angioedema, generalized erythema), respiratory (rhinitis, laryngeal angioedema, wheezing), gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), cardiovascular (tachycardia, hypotension), and in most severe cases, anaphylaxis with or without shock.[10,12]

Delayed hypersensitivity reactions are mostly mediated by T cells.[10,12] Antibody-mediated reactions (Gell and Coombs types II and III) are uncommon. T-cell-mediated reactions (Gell and Coombs type IV) commonly occur after several days of treatment. The most common manifestations are maculopapular exanthema and delayed urticaria, and the most serious include severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms syndrome, and acute generalized exanthematous pustulosis.[10,12,13]

PENICILLINS AND CEPHALOSPORINS: MOLECULAR STRUCTURE

Penicillins and cephalosporins have similarities in their chemical structure.[14,15] Both share a common β-lactam ring, but penicillins have a 5-membered thiazolidine ring, and cephalosporins a 6-membered dihydrothiazine ring attached to the BL nucleus.[16] The type and position of side chains differentiate penicillins and cephalosporins (**Figure 1**).[17]

The side chain is an important site of immunological recognition and hence of allergic cross-reactivity.[17,18]

Penicillins have low molecular weight; hence they must covalently bind to transport macromolecules to form a hapten-carrier complex in order to induce an immune response.[12] Under physiological conditions, the penicillin central nucleus spontaneously opens, without defragmenting, binds to transport proteins, and forms the *major* antigenic determinant (penicilloyl polylysine).[18-20]

But the major antigenic determinant alone is insufficient to explain all penicillin-specific immune responses.[18-20] A small proportion of penicillins (approximately 5%) are metabolized by other paths, and the resulting antigens are known as *minor* determinants (benzyl penicillin, penicilloate, and peniloate).[18,20]

Regarding cephalosporins, the process by which a hapten-protein complex is formed is unknown.[21,22] Unlike penicillins, the central nucleus is extremely unstable and undergoes rapid fragmentation, resulting in unstable metabolites that do not enable protein haptenization. The haptenic determinants in cephalosporins are thus unknown.[16,23]

Apart from the central structure, side chains are important inductors of immunologic response.[24] The R1 side chain remains intact and is the major responsible for cross-reactivity, while the R2 side chain makes little contribution to cephalosporin hypersensitivity.[25]

In both compounds, the reactivity of the native molecule must be investigated. However, in the case of penicillins, it is also important to investigate the immunogenicity of *major* and *minor* antigenic determinants resulting from their metabolism.[26]

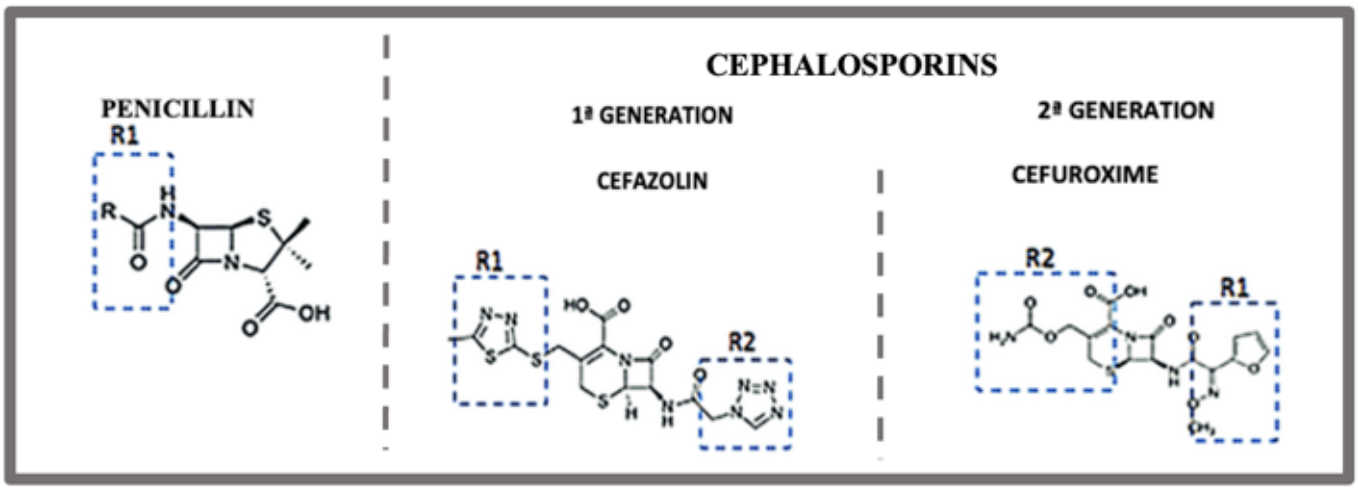


Figure 1. Molecular structure of penicillins and cephalosporins

EPIDEMIOLOGY

The most common side effects of BL in children are skin manifestations. Nevertheless, only a small number of these reactions are due to hypersensitivity mechanisms. Other probable causes are the coexistence of viral infections or reactions associated with other non-immunological mechanisms.[27,28]

The prevalence of self-reported reactions to BL in pediatric age varies from 1.7% to 5.2%,[29-31] with amoxicillin (1.4%), other penicillins (1.2%), and cephalosporins (0.7%) being the most implicated drugs.[29-31] Although IgE-mediated reactions are not uncommon, anaphylaxis is rare (approximately 0.015–0.004% for penicillins and 0.1–0.0001% for cephalosporins).[4,32]

Allergy to cephalosporins is generally managed in the context of patients with penicillin allergy.[27] A 2012 literature review reported a 2.5% prevalence of cross-reactivity between penicillins and cephalosporins with similar side chains.[33]

CROSS-REACTIVITY

The cross allergy between penicillins and cephalosporins was assigned to the BL ring for decades, whereas side chains were associated with less relevant allergies.[16] With the increasing knowledge of their molecular structure and metabolism and absence of cross-reactivity between antibiotics with the same ring, attention for the role of side chains in allergic reactions was raised.[22] Nowadays, it is generally accepted that cross-reactivity is primarily determined by the R1 side chain.[24,34,35]

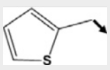
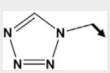
Regardless of the knowledge about the role of side chains, the risk of cross-reactivity between these agents has been overestimated in older studies. Before 1980, first-generation cephalosporins were produced by chemical modification of the penicillin structure, resulting in high levels of contamination.[14] Additionally, some patients treated with penicillin developed IgG and IgM antibodies against cephalosporins with no clinical significance.[33,36]

Pichichero *et al.* conducted a metanalysis showing that patients allergic to penicillin had an increased risk of allergic reactions to first-generation cephalosporins, but cross-allergy was negligible with second- and third-generation counterparts.[23] A prospective observational study in a pediatric population (n=664) with positive skin test for penicillin revealed cross-reactivity among molecules dependent on cephalosporin generation. A total of 23.9% of the allergic population in this study developed reactions to first- and second-generation cephalosporins, while only 0.3% presented manifestations to third- and fourth-generation molecules.[37] In a meta-analysis of articles published between January 1980 and March 2019 estimating the risk of cross-reactivity to cephalosporins in patients with a proven IgE- or T-cell-mediated penicillin allergy, the rate of cross-reactivity varied with the degree of similarity between R1 side chains.[38] This set of studies associated differences in cross-reactivity to a higher similarity between R1 side chains of the respective agents.[23,37,38]

Cross-reactivity between agents whose side chains are similar but not identical is also possible and has been documented, being presumably attributed to similar three-dimensional structure and physicochemical properties.[18,24,39] **Table 2** depicts the pharmacological groups exhibiting cross-reactivity due to identical and similar side chains, respectively.[14,18,27,40]

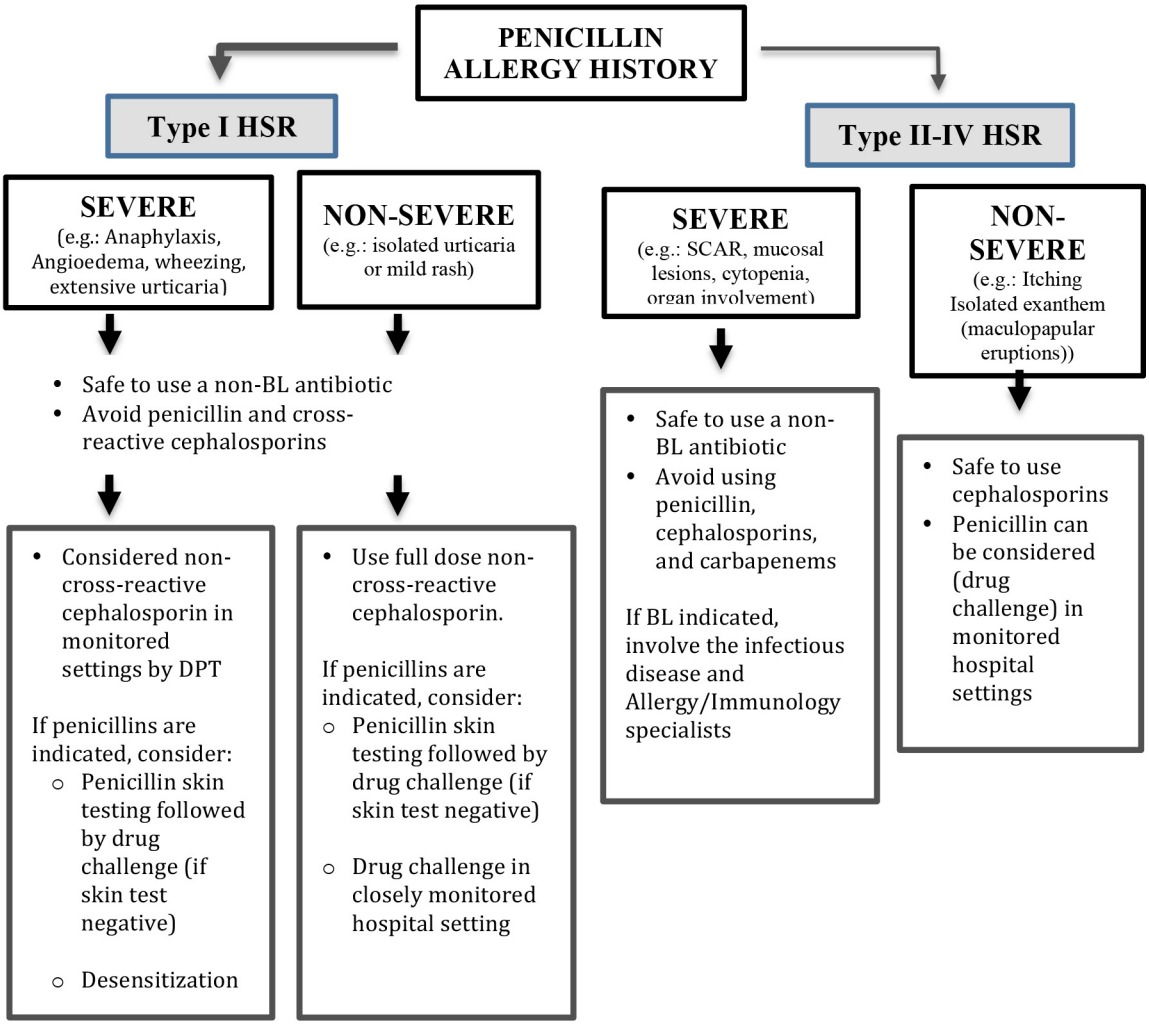
In patients allergic to penicillin, recent studies recommend the use of cephalosporins depending on the development and severity of clinical manifestations (**Figure 2**).[4,11] While the use of first-generation cephalosporins should be avoided in patients allergic to penicillin, the risk of cross-reactivity to third- or fourth-generation cephalosporins is limited.[11,27,41]

Table 2 - Penicillins and cephalosporins with identical or similar side chain (Adapted from Min-Hye Kim *et al.*)

Groups with identical R1 side-chain structures						
I	II	III	IV	V	VI	VII
						
Amoxicillin Cefadroxil[1stG] Cefprozil[2nsG] Cefatrizine[2ndG]	Ampicillin Cefaclor[2ndG] Cephalexin[1stG] Cephradine[1stG]	Ceftriaxone[3rdG] Cefotaxime[3rdG] Cefpodoxime[3rdG] Ceftizoxime[3rdG] Cefmenoxime[3rdG]	Cefoxitin[2ndG] Cephaloridine[1ndG] Cephalothin[1stG]	Cefamandole[2ndG] Cefonicid[2ndG]	Ceftazidime[3rdG] Aztreonam	Cefepime[4thG] Cefotaxime[3rdG] Ceftriaxone[3rdG]

Groups with similar R1 side-chain structures					
Penicillin Cephalothin[1stG] Cephaloridine[1stG] Cefoxitin[2ndG]	Cefaclor[2ndG] Cefadroxil[1stG]	Cefuroxime[2ndG] Cefotaxime[3rdG]	Ceftazidime[3rdG] Ceftriaxone[3rdG]	Ceftazidime[3rdG] Cefotaxime[3rdG]	Ceftazidime[3rdG] Cefepime[4thG]

G, generation



BL, Beta-lactam; DPT, Drug provocation test; HSR, Hypersensitivity reactions; SCAR, Severe cutaneous adverse reaction.

Figure 2 - Clinical recommendations for patients with a history of penicillin allergy[4,11]

DIAGNOSIS

The evaluation of patients with antibiotic allergy begins with a careful history, including clinical manifestations, treatment of the allergic reaction, timing of the reaction, and details of the drugs used.[42,43]

The study should be conducted within a period of at least four to six weeks after the suspected allergic reaction.[22] Assessment of IgE-mediated penicillin allergy should start with skin testing.[44]

For immediate reactions, a skin prick test and intradermal test with immediate reading can be considered.[4] Penicillin skin testing is usually performed with major antigenic determinants (penicilloyl polylysine), minor determinant mixture, ampicillin or amoxicillin, and benzylpenicillin.[26] Drug tests are compared with positive (histamine) and negative (usually glycerinated saline) controls.[4]

In patients with a negative penicillin skin test, the absence of immediate allergy should be confirmed by an oral drug provocation test (DPT, also named graded challenge) with the culprit drug.[26,42] DPT consists of administering the drug in a graduated manner under close surveillance. The starting dose is usually 1/100 or 1/10 of the single therapeutic dose,[43] after which the patient is observed for at least 30–60 minutes. If no adverse reaction is observed, increasing doses are administered until the full therapeutic dose.[4,22,43]

Skin test and DPT together have a negative predictive value for excluding IgE-mediated penicillin allergy of more than 99%.[44]

Patients with a history of severe allergic reactions, positive penicillin skin test, or DPT may cross-react with cephalosporin. Due to structural and molecular differences in these drug classes, skin test to penicillin does not predict cephalosporin allergy. Nonetheless, if the

cephalosporin has a similar side chain, skin test may have diagnostic value.[20,45] Therefore, some clinicians additionally perform skin test using a cephalosporin with a different side chain.[44] Patients with negative cephalosporin skin test can perform a cephalosporin graded challenge.[22]

Testing for non-immediate reactions is not standard. Delayed intradermal or patch test reading can be used but is associated with low sensitivity and poor negative predictive value.[43] If negative, DPT can be considered for non-SCAR T-cell-mediated hypersensitivity. In delayed reactions, DPT can be continuously used, being contraindicated for severe T-cell-mediated reactions.[11,44]

CONCLUSION

BL represent the first-line treatment of several bacterial infections and are the most frequent cause of hypersensitivity drug reactions.[1] Clinical manifestations are heterogeneous, ranging from mild to severe and from immediate to delayed.[10,12]

When investigating the potential for cross-reactivity, the drugs' molecular structure and metabolism under physiological conditions should be considered. The current evidence indicates that similarity between R1 side chains is the main cross-reactivity inducer, advising against the use of first-generation cephalosporins with similar side chains in patients with a history of allergic reaction to penicillin. Limited cross-reactivity is reported to third- or fourth-generation cephalosporins.

AUTHORSHIP

Liliana Dias - Conceptualization; Data curation; Investigation; Resources; Methodology; Writing - original draft; Writing review & editing

Cláudia Pedrosa - Investigation; Methodology; Resources; Writing - review & editing

REFERENCES

1. Hermanides J, Lemkes BA, Prins JM, Hollmann MW, Terreehorst I. Presumed β-lactam allergy and cross-reactivity in the operating theater: A practical approach. Anesthesiology. 2018;129(2):335-42.
2. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: A review. JAMA 2019; 321(2): 188-99.
3. Bush K, Bradford PA. B-lactams and β-lactamase inhibitors: An overview. Cold Spring Harbor perspectives in medicine. 2016;6(8): a025247.
4. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. The Lancet. 2019;393(10167):183-98.
5. Yates AB. Management of patients with a history of allergy to beta-lactam antibiotics. The American Journal of Medicine 2008; 121(7): 572-6.
6. Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clinical & Experimental Allergy 2003; 33(4): 501-6.
7. Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation?. Journal of Allergy and Clinical Immunology: In Practice 2018; 6(1): 82-9.
8. Coombs PR, Gell PG. Classification of Allergic Reactions Responsible for Clinical Hypersensitivity and Disease. Clinical Aspects of Immunology, Oxford University Press 1968; 575-96.
9. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, *et al*. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy 2003; 58(10): 961-72.
10. Regateiro F, Faria E. Mecanismos imunopatológicos das reações de hipersensibilidade a fármacos. Revista Portuguesa Imunoalergologia 2016;24(2): 63-78.
11. Blumenthal KG, Shenoy ES, Wolfson AR, Berkowitz DN, Carballo VA, Balekian DS, *et al*. Addressing inpatient beta-lactam allergies: A multi-hospital implementation. The journal of allergy and clinical immunology: In practice 2017; 5(3): 616-25.
12. Oliver Hausmann, Drug Allergy. Middleton's allergy essentials. 1st ed. Elsevier Health Sciences 2017; 225-46.
13. Caruso C, Valluzzi RL, Colantuono S, Gaeta F, Romano A. B-lactam allergy and cross-reactivity: A clinician's guide to selecting an alternative antibiotic. *JAA*. 2021; 14(31): 31-46.
14. Barber MS, Giesecke U, Reichert A, Minas W. Industrial enzymatic production of cephalosporin-based beta-lactams. Advances in biochemical engineering, biotechnology 2004; 88: 179-15.
15. Girard JP. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in men. International Archives of Allergy and Immunology 1968; 33(5): 428-38.
16. Pichichero ME. Use of selected cephalosporins in penicillin-allergic patients: A paradigm shift. Diagnostic Microbiology & Infectious Disease 2007; 57(3): S13-S18.
17. Romano A, Gaeta F, Poves M, Valluzzi R. Cross-reactivity among beta-lactams. Current Allergy and Asthma Reports 2016; 16(3): 1-12.
18. Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. Annals of Allergy, Asthma & Immunology 2014; 112(5): 404-12.
19. Khan F, Weiss M. Skin testing for beta-lactam antibiotics: Impact of the availability of a major determinant. Current Allergy Asthma Reports 2013; 13(1): 64-70.
20. Rosário NA, Grumach AS. Allergy to beta-lactams in pediatrics: A practical approach. Jornal de pediatria 2006; 82(5 Suppl): S181.
21. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, *et al*. Update on the evaluation of hypersensitivity

reactions to betalactams. Allergy. 2009;64(2):183-93.
22. Lee QU. Use of cephalosporins in patients with immediate penicillin hypersensitivity: Cross-reactivity revisited. Hong Kong medical journal 2014; 20(5):428-36.
23. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: A meta-analysis. Otolaryngology - Head and Neck Surgery 2007; 136(3): 340-7.
24. Zagursky RJ, Pichichero ME. Cross-reactivity in β-lactam allergy. The Journal of Allergy and Clinical Immunology: In Practice 2018; 6(1): 72-81.
25. Blanca M, Romano A, Torres MJ, Fernandez J, Mayorga C, Rodriguez J, *et al.* Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64(2):183-93.
26. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS*, et al.* BSACI guidelines for the management of drug allergy. Clinical & Experimental Allergy 2009; 39(1): 43-61.
27. Pichichero ME. A review of evidence supporting the american academy of pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics 2005; 115(4): 1048-57.
28. Caubet J, Kaiser L, Lemaître B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: A prospective study based on drug rechallenge. The Journal of Allergy and Clinical Immunology 2010; 127(1): 218-22.
29. Orhan F, Karakas T, Cakir M, Akkol N, Bahat E, Mujgan F, *et al*. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. Pediatric Allergy and Immunology 2008; 19(1): 82-5.
30. Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in german children. Pediatric Allergy and Immunology 2008; 19(7): 634-8.
31. Rebelo GE, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: From self-reporting to confirmed diagnosis. Clinical & Experimental Allergy 2008; 38(1): 191-8.
32. Lee P, Shanson D. Results of a UK survey of fatal anaphylaxis after oral amoxicillin. Journal of antimicrobial chemotherapy. 2007;60(5):1172-3.
33. Campagna JD, Bond MC, Schabelman E, Hayes BD. The use of cephalosporins in penicillin-allergic patients: A Literature review. Journal of Emergency Medicine 2012; 42(5): 612-20.
34. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C, Rodriguez J, *et al.* Update on the evaluation of hypersensitivity reactions to betalactams. Allergy 2009; 64(2): 183-93.
35. Miranda A, Blanca M, Vega JM, Segurado E, Justicia JL, Juarez C. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. The Journal of Allergy and Clinical Immunology 1996; 98(3): 671-7.
36. Levine BB, Fellner MJ, Levytska V, Franklin EC, Alisberg N. Benzylpenicilloyl-specific serum antibodies to penicillin in man. II. sensitivity of the hemagglutination assay method, molecular classes of the antibodies detected, and antibody titers of randomly selected patients. The Journal of immunology 1966; 96(4): 719.
37. Atanasković-Marković M, Veličković TĆ, Gavrović-Jankulović M, Vučković O, Nestorović B. Immediate allergic reactions to cephalosporins and penicillins and their cross-reactivity in children. Pediatric allergy and immunology. 2005;16(4):341-7.
38. Picard M, Robitaille G, Karam F. Cross-reactivity to cephalosporins and carbapenems in penicillin-allergic patients: Two systematic reviews and meta-analyses. The journal of allergy and clinical immunology in practice. 2019;7(8):2722-38.
39. Farinha S, Cardoso B, Tomaz E, Inácio F. Profiles of sensitization to cephalosporins in clinical practice. Revista Portuguesa Imunoalergologia 2018; 26(4): 263-71.
40. Kim M, Lee J. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. Allergy, asthma & immunology research. 2014; 6(6): 485-95.
41. Infarmed. Boletim de fármaco-vigilância. Novos Cadernos NAEA 2010; 14(1): 4.
42. Mirakian R, Leech SC, Krishna MT, Richter AG, Huber PA, Farooque S, *et al.* Management of allergy to penicillins and other beta-lactams. Clinical & Experimental Allergy 2015; 45(2): 300-27.
43. Blanca LN, Atanaskovic MM, Gomes ER, Kidon M, Kuyucu S, Mori F, *et al*. An EAACI task force report on allergy to beta-lactams in children: Clinical entities and diagnostic procedures. Pediatric allergy and immunology. 2021;32(7):1426-36.
44. Joint Task Force on Practice Parameter, American Academy of Allergy Asthma and Immunology and American College of Allergy Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010; 105: 259–73.
45. Félix MM, Kuschnir FC. Penicillin allergy: current aspects. Adolescência e Saúde 2011; 8(3): 43-53.

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Received for publication: 26.11.2020
Accepted in revised form: 20.01.2022

NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2022, vol 31, n.º 1

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):38-54. doi:10.25753/BirthGrowthMJ.v31.i1.26341

CASE REPORTS

Congenital disorders of glycosylation

Defeitos congénitos da glicosilação

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ABSTRACT

Congenital disorders of glycosylation are a highly variable, rapidly expanding family of genetic diseases that result from defects in the synthesis of glycans. The vast majority of these monogenic diseases are inherited in an autosomal recessive way, but some types follow an autosomal dominant or X-linked inheritance.

The present work aimed to review the state of the art of congenital disorders of glycosylation, including available therapeutic options, and present a simplified diagnostic approach to this group of diseases.

Congenital disorders of glycosylation can be classified into four categories: N-linked glycosylation defects, O-linked glycosylation defects, combined glycosylation defects, and glycosphingolipid and glycosylphosphatidylinositol anchor synthesis defects. The phenotype may range from mild to severe, depending on disease severity. Clinical features include dysmorphic features, neurologic, dermatologic, cardiac, endocrine, immunologic, hematologic, gastrointestinal and liver involvement, and skeletal muscle abnormalities. As there is no universal or pathognomonic sign or symptom and no sensitive diagnostic test, it is of foremost importance to keep a high index of suspicion of these diseases. When a congenital disorder of glycosylation is suspected, the first step in screening is to perform serum transferrin isoelectric focusing. Molecular genetic testing is the most specific diagnostic test. Treatment is usually symptomatic, with specific treatment only available for some of these disorders.

Since congenital defects of glycosylation may affect any organ at any age and have variable clinical presentation, they should be considered in the differential diagnosis of any patient with multiorgan involvement.

Keywords: congenital disorders of glycosylation; MPI-CDG; multisystemic disease; oral mannose; PMM2-CDG; serum transferrin isoelectric focusing

RESUMO

Os defeitos congénitos da glicosilação são um grupo variável de doenças genéticas em rápida expansão, resultantes de defeitos na síntese de glicanos. A grande maioria destas doenças monogénicas é transmitida de forma autossómica recessiva, mas algumas têm transmissão autossómica dominante ou ligada ao cromossoma X.

Neste trabalho, os autores pretenderam rever o atual estado da arte sobre este grupo de doenças, incluindo opções terapêuticas disponíveis

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e apresentar uma abordagem de diagnóstico simplificada para as mesmas.

Os defeitos congénitos da glicosilação podem ser classificados em quatro categorias: defeitos da N-glicosilação, defeitos da O-glicosilação, defeitos combinados da glicosilação, e defeitos na biossíntese dos lípidos e da âncora glicosilfosfatidilinositol. O fenótipo pode variar entre ligeiro a grave, dependendo da gravidade da doença. As manifestações clínicas incluem dismorfias, envolvimento neurológico, dermatológico, cardíaco, endócrino, imunológico, hematológico, gastrointestinal e hepático, e anomalias músculo-esqueléticas. Devido à ausência de sinais ou sintomas universais ou patognomónicos e de biomarcadores, é fundamental manter um elevado índice de suspeição para o diagnóstico deste grupo de doenças. Mediante suspeita clínica, o primeiro passo no rastreio deve ser a focagem isoelétrica da transferrina sérica. O teste genético molecular é o teste de diagnóstico mais específico. O tratamento é geralmente sintomático, só estando disponível tratamento específico para alguns subtipos destas doenças.

Como os defeitos congénitos da glicosilação podem atingir qualquer órgão em qualquer idade e ter uma apresentação clínica variável, este grupo de doenças deve fazer parte do diagnóstico diferencial de todos os doentes com envolvimento multiorgânico.

Palavras-chave: defeitos congénitos da glicosilação; doença multissistémica; focagem isoelétrica da transferrina sérica; manose oral; MPI-CDG; PMM2-CDG

INTRODUCTION

Congenital disorders of glycosylation (CDGs) are a highly variable, rapidly expanding family of genetic diseases resulting from defects in the synthesis of glycans that either lead to underglycosylation or misglycosylation of glycoconjugates.[1] Although the vast majority of these monogenic diseases are inherited in an autosomal recessive way, about 15 CDGs show an autosomal dominant or X-linked inheritance. Some show either one or the other form of inheritance depending on the variant(s).[2,3]

The first patients with CDGs were reported in 1980 by Jaeken et al., being currently identified more than 140 forms of the disease.[2,4] The exact prevalence and incidence of CDGs as a group have not been established. Estimates point to a prevalence of 1/10,000 in Europeans and African- Americans based on carrier frequencies of known pathogenic variants in 53 genes. However, most CDG types have less than 100 cases reported worldwide.[2] Due to the difficulties in diagnosing this type of genetic diseases, their true prevalence is probably underestimated.

Oligosaccharides, or glycans, are multisugar structures attached to proteins or lipids. Glycosylation is an extremely variable and ubiquitous process that refers to the attachment of glycans to proteins and lipids to form glycoproteins and glycolipids. It is a crucial step in the processing of these enzymes, as it is required for folding, transport, self-recognition and function. Hypoglycosylation of glycoproteins acting as hormones, enzymes or transporters leads to its malfunctioning, decreased activity and rapid degradation.[1,5] Given the universal nature of glycosylation in human biology, it is not surprising that disorders in this pathway can manifest as severe, usually multisystemic diseases.[6]

OBJECTIVES

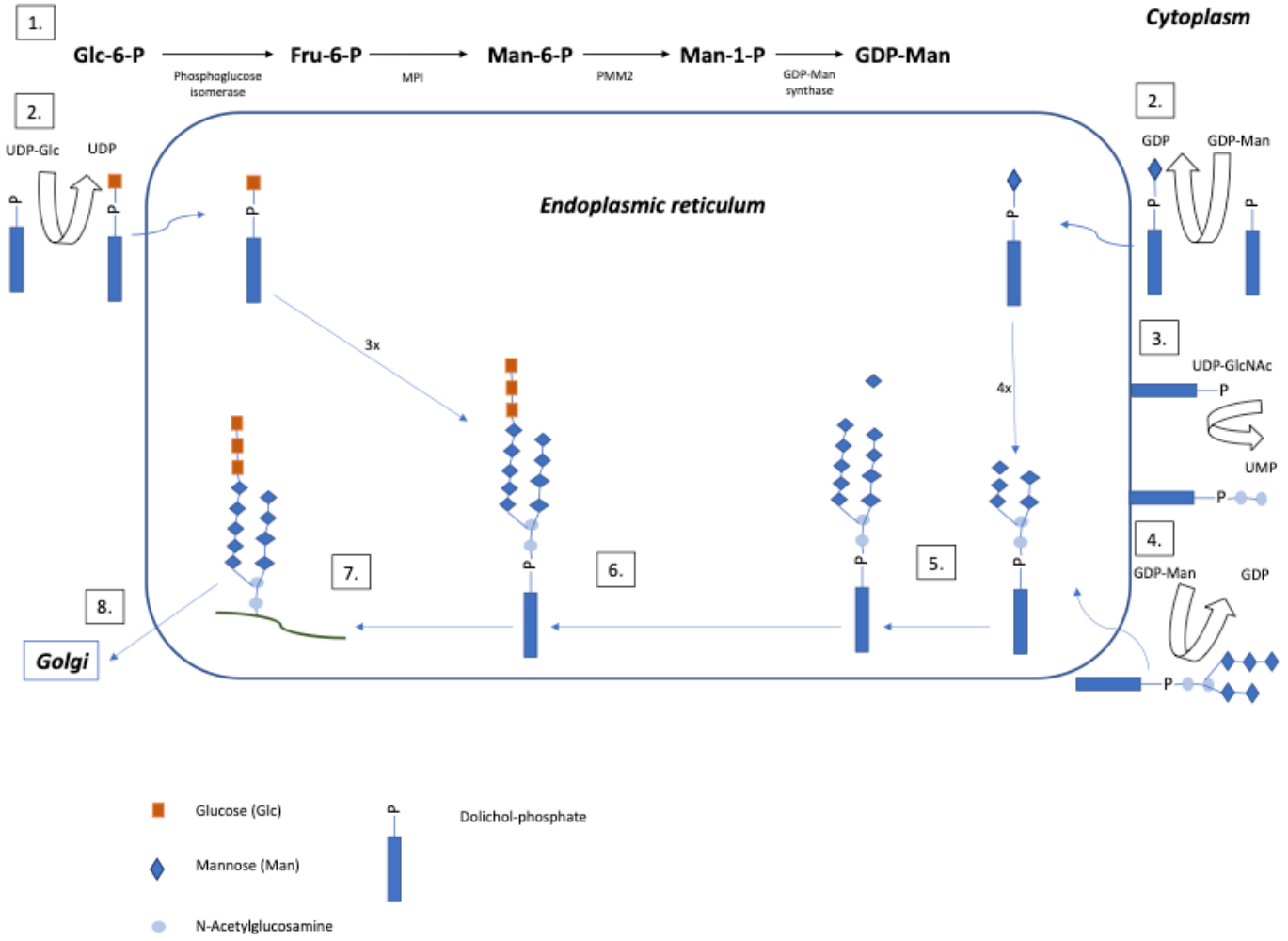
The aim of this study was to review the current state of the art, namely regarding available therapeutic options of CDGs and present a simplified diagnostic approach to this group of disorders.

ETIOLOGY

Attachment of glycans to proteins can be of two types: N-linked glycosylation (attachment to the amide group of asparagine via an N-acetylglucosamine residue [GlcNAc]) or O-linked glycosylation (attachment to the hydroxyl group of serine or threonine via an N-acetylgalactosamine [GalNAc] or another monosaccharide residue). The synthesis of N-glycans requires a much longer and more complex pathway than that of O-glycans, which includes N-glycosylation and a processing pathway that is absent in O-glycosylation. N-glycosylation occurs in three cellular compartments: cytosol, endoplasmic reticulum (ER) and Golgi apparatus. **Figure 1** depicts a schematic view of the initial steps of the N-glycosylation pathway.[1,7,8]

The biosynthesis of O-glycans usually starts in the Golgi apparatus with the attachment of GalNAc (or xylose in the case of glycosaminoglycans) to the hydroxyl group of serine or threonine residues.[1] Contrary to N-glycan synthesis, no processing is involved.[7]

Lipid-based glycosylation pathways may also be affected in CDGs. The disorders that disturb the glycosylphosphatidylinositol (GPI) anchor biosynthesis pathway are a major group of glycosylation disorders that affect glycolipid production.[8]



Frut: fructose, GalNAc: N-acetylgalactosamine, GDP: guanosine diphosphate, GDP-Man: guanosine diphosphate- mannose, Glc: glucose, GlcNAc: N-acetylglucosamine, Man: mannose, MPI: mannose phosphate isomerase, P: phosphate, PMM: phosphomannomutase, UDP: uridine diphosphate, UMP: uridine monophosphate

Figure 1 - Simplified view of the initial steps of the N-glycosylation pathway (Adapted from Vilarinho L *et al.*[1] and Grünewald S *et al.*[4]

1. The first step consists of the synthesis of the activated GDP-Man sugar from glucose in the cytoplasm. Various enzymes take part in this process, such as phosphoglucose isomerase, MPI, PMM and GDP-Man-synthase. 2. GDP-Man and UDP-Glc serve as substrates for dolichol phosphate mannose and dolichol phosphate glucose synthesis, which also occurs in the cytoplasmic side of the endoplasmic reticulum. These two precursors are then transferred to the luminal side of the endoplasmic reticulum. 3. One GlcNAc molecule is transferred from UDP-GlcNAc to dolichol phosphate to form dolichol pyrophosphate GlcNAc on the endoplasmic side of the endoplasmic reticulum. A second GlcNAc molecule is added to form dolichol pyrophosphate $(GlcNAc)_{2.}$ 4. Five mannose GDP-Man residues are attached to dolichol pyrophosphate $(GlcNAc)_{2,}$ forming dolichol pyrophosphate $(GlcNAc)_2(Man)_5$. 5. This substrate is then transferred to the luminal side of the endoplasmic reticulum, receiving four Man residues from dolichol phosphate mannose. 6. Three Glc residues from dolichol phosphate glucose are further added. 7. The Glc3Man9GlcNAc2 oligosaccharide is finally transferred from dolichol pyrophosphate to an asparagine residue of the growing glycoprotein to initiate protein N-glycosylation. 8. The three Glc residues are removed by glycosidases and the protein is transported to the Golgi apparatus for further processing.

PHYSIOPATHOLOGY

Disorders can either be caused by abnormal assembly and transfer of oligosaccharides onto growing proteins, usually in the ER, or by abnormal processing of bound oligosaccharides in the Golgi apparatus.[5] The multisystemic manifestations of CDGs can be explained by the fact that N-linked glycoproteins represent more than 10% of all proteins. The importance of O-glycosylation is best exemplified by the O-mannosylation of dystroglycan, which is required for normal muscular scaffolding formation, and by the O-xylosylation of glycosaminoglycans for proteoglycans, which plays a role in connective tissue.[1,8,9]

GPI anchoring is crucial for signal transduction, cell adhesion, and antigen presentation.[8]

The signs and symptoms associated with CDGs are either due to substrate accumulation, decrease of a final reaction product, or a combination of both. Glycosylation of proteins and lipids is a ubiquitous and extremely diversified process that modifies the intrinsic properties of these molecules, accounting for the different physiopathological mechanisms that give rise to the clinical manifestations of CDGs.[1]

NOMENCLATURE

Historically, CDGs were named according to the patterns of transferrin isoelectric focusing (type I vs. type II) and alphanumerically according to their first description. Type I N-linked disorders were termed CDG-I "x" and type II disorders were termed CDG-II

"x", with the "x" being alphabetically assigned according to the discovery order (e.g., CDG-Ia, CDG Ib).[5] The N-linked protein glycosylation defect PMM2-CDG, previously known as CDG type Ia, was the first CDG to be described by Jaak Jaeken in 1980. With the widespread use of next-generation sequencing (NGS) in diagnosis, CDG nomenclature was updated in 2009 to specify the molecular etiology of the diseases. Presently, the disorders are denoted by the name of the affected gene (non-italicized), followed by the designation CDG (e.g., PMM2-CDG).[2,5,10]

CLASSIFICATION

CDGs are broadly classified into four categories: [11]

(I) N-linked glycosylation defects
(II) O-linked glycosylation defects
(III) Combined glycosylation defects (multiple pathway involvement)
(IV) Glycosphingolipid and glycosylphosphatidylinisotol (GPI) anchor synthesis defects

CLINICAL MANIFESTATIONS

Due to the diversity of glycosylation pathways and targeted proteins, CDGs are usually multisystem diseases. Like in other inborn errors of metabolism, the phenotype may range from mild to severe, depending on the disease severity.[8,12] Some clinical features may present at birth and remain unchanged or improve over the course of time, while others are progressive and may not be evident during infancy.[8]

Table 1 presents a summary of selected CDG subtypes.[13]

Table 1 - Overview of selected congenital disorders of glycosylation types of CDG. (Adapted from Ferreira CR *et al.*[18])

Disease	*Defective gene*	*Defective protein*	*Defect location*	*Inheritance*	*Phenotype*
MPI-CDG	MPI	Phosphomannose isomerase	Cytosol	AR	- Liver disease (hepatomegaly, hepatopathy, cirrhosis) - Coagulopathy - Hyperinsulinemic hypoglycemia - Gastrointestinal symptoms (chronic diarrhea, protein-losing enteropathy) - normal intellectual development

PMM2-CDG	PMM2	Phosphomannose isomerase	Cytosol	AR	- Strabismus - Large ears, thin upper lip, inverted nipples, abnormal fat distribution - developmental delay (intellectual disability) - Coagulation abnormalities, thrombotic events, stroke-like episodes -Hepatopathy - Endocrine abnormalities - Cerebellar hypoplasia
GFPT1-CDG (= CMS12) DPAGT1-CDG (=CMS13) ALG14-CDG (=CMS15) ALG2-CDG (CMS14)	GFPT1, DPAGT1 ALG14 ALG2	Glutamine: F69 amidotransferase GlcNAc-1-P transferase UDP-GlcNAc transferase α1–3/6 Man-transferase	Cytosol ER (cytosolic side) ER (cytosolic side) ER (cytosolic side)	AR	- Myasthenia - DPAGT1-CDG and ALG2-CDG: may present with multisystemic disorder
RFT1-CDG ALG11-CDG	RFT1 ALG11	Man5GlcNAc2-PP-Dol flippase α1–2 Man-transferase	ER ER (cytosolic side)	AR	- Developmental delay - Seizures - Intellectual disability - Sensorineural hearing loss

ALG6-CDG ALG8-CDG*	ALG6 ALG8	α1–3 Glc-transferase α1–3 Glc-transferase	ER (luminal side) ER (luminal side)	AR	- Developmental delay - Proximal muscle weakness - Seizures - Ataxia in most cases - *Brachydactyly, intellectual disability, dysmorphic features (low-set ears, hypertelorism and macroglossia)
ALG3-CDG ALG9-CDG (severe form: Gillessen-Kaesbach-Mishimura syndrome) ALG12-CDG	ALG3 ALG9 ALG-12	α1–3 Man-transferase α1–2 Man-transferase α1–6 Man-transferase	ER (luminal side) ER (luminal side) ER (luminal side)	AR	ALG9-CDG: - polycystic kidneys - hepatic fibrosis - congenital heart disease - characteristic skeletal changes (mesomelia, round pelvis, shortened sacrosciatic notch, ovoid ischia, hypomineralization of skull, cervical vertebral bodies, pubic rami, thick occipital bone) -similar skeletal anomalies in ALG3-CDG and ALG12-CDG
MGAT2-CDG	MGAT2	β1–2 GlcNAc-transferase II	Medial Golgi	AR	- Long eyelashes, prominent nasal bridge, underdeveloped alae nasi, low-hanging columella, thin vermillion of the upper lip - Severe growth delay - Mental disability with absent speech - Radio-ulnar synostosis

MAN1B1-CDG (MRT15)	MAN1B1	α1–2 mannosidase I	ER	AR	- Intellectual disability - Facial dysmorphism (widely spaced eyes, down-slanting palpebral fissures, long ears, underdeveloped naso-labial fold, thin vermillion of the upper lip) - Truncal obesity
SRD5A3-CDG	SRD5A3	Polyprenol reductase	ER	AR	- Eye malformations (cataract, retinal anomalies, glaucoma, visual loss) - Cerebellar ataxia - Ichthyosiform skin anomalies (one third of the cases) - Mostly severe developmental disability
DOLK-CDG	DOLK	Dolichol kinase	ER	AR	- Multisystemic phenotype (neurologic, endocrine and coagulation abnormalities) - Dilated cardiomyopathy
DPM1-CDG DPM2-CDG DPM3-CDG	DPM1 DPM2 DPM3	Dol-P-Man synthase Dol-P-Man synthase Dol-P-Man synthase	ER (cytosolic side) ER ER	AR	- muscle dystrophy
COG1-CDG	COG1	Conserved oligomeric Golgi complex subunit 1	Vesicular membrane/ Cytosol	AR	- Variable phenotypic features and variable severity - Costo-cerebro-mandibular-like syndrome

COG7-CDG	COG7	Conserved oligomeric Golgi complex subunit 7	Vesicular membrane/ Cytosol	AR	- Microcephaly - Growth impairment - Adducted thumbs - Ventricular septal defect - Episodes of hyperthermia
SLC35C1-CDG	SLC35C1	GDP-Fuc transport	Golgi	AR	- Frequent infections - Neutrophilia - Brachycephaly, low insertion of the anterior hairline coarse features, puffy eyelids, flat nasal bridge, large tongue, long upper lip with everted lower lips - Bombay blood group
ATP6V0A2-CDG (autosomal recessive cutis laxa type IIA- wrinkly skin syndrome)	ATP6V0A2	Subunit of vacuolar ATPase	Vacuolar membrane	AR	- Generalized congenital sagging skin, cutis laxa, abnormal fat distribution - Motor developmental disability - Skeletal abnormalities - Short stature - Joint luxation - Cobblestone-like brain - Dysgenesis and seizures
ATP6V1A-CDG (=autossomal recessive cutis laxa type IID) ATP6V1E1-CDG (=autossomal recessive cútis laxa type IIC)	ATP6V1A ATP6V1E1	Subunit of vacuolar ATPase Subunit of vacuolar ATPase	Vacuolar membrane Vacuolar membrane	AR	- Generalized cutis laxa - Motor and intellectual developmental disability - Cardiac involvement - Hypercholesterolemia

ATP6AP1-CDG (=immunodeficiency 47) ATP6AP2-CDG (=-linked mental retardation, Hedera type; X-linked parkinsonism with spasticity)	ATP6AP1 ATP6AP2	Subunit of vacuolar ATPase Subunit of vacuolar ATPase	Vacuolar membrane Vacuolar membrane	XL XL	- Early liver disease (cholestasis, fibrosis, cirrhosis) - Frequent infections (hypogammaglobulinemia) - Cutis laxa
TMEM199-CDG CCDC115-CDG	TMEM199	Assembly factor for vacuolar ATPase Assembly factor for vacuolar ATPase	Vacuolar membrane Vacuolar membrane	AR AR	- Early liver disease (cholestasis, fibrosis, cirrhosis) - Hypercholesterolemia - Low serum ceruloplasmin - Developmental disability
TMEM165-CDG	TMEM165	Ca2+/H+ antiporter	Golgi	AR	- Spondyloepimetaphysea skeletal dysplasia with extreme osteopenia - Short stature, - Hyperinsulinism - Growth hormone deficiency - Variable intellectual disability
SLC39A8-CDG	SLC39A8	Cation transporter	Plasma membrane	AR	- Multisystem disorder with seizures - Skeletal dysplasia with rhizomelic shortening and dwarfism - Low blood manganese and zinc concentrations - Increased urinary concentration from renal wasting

PGM1-CDG	PGM1	Phospho glucomutase	Cytosol	AR	- Midline malformations (Pierre-Robin sequence, bifid uvula, cleft palate) - Hepatopathy - Muscle weakness - Cardiomyopathy - Hypoglycemia
GMPPA-CDG (=lacrima, achalasia, and mental retardation syndrome)	GMPPA	GDP-mannose pyrophosphoryla se α subunit	Cytosol	AR	- Alacrima - Achalasia - Intellectual disability
PIGL-CDG (= **CHIME** syndrome)	PIGL	GlcNAc-PI de-N-acetylase	ER (cytosolic side)	AR	- ocular **C**olobomas - congenital **H**eart Disease, early-onset **I**chthyosis - **M**ental Retardation - **E**ar anomalies (conductive hearing loss)
PIGM-CDG (=GPIBD1)	PIGM	Man-transferase 1	ER (luminal side)	AR	- Portal vein thrombosis - Seizures

Dysmorphic features

Although CDGs usually carry no complications during pregnancy or birth, the association with nonimmune hydrops fetalis has been reported.[14] Newborns may present with facial dysmorphism (prominent cheeks, large and dysplastic ears), abnormal subcutaneous adipose tissue distribution (orange peel skin, fat pouches, inverted nipples), skeletal abnormalities, or dystrophic limbs. Children with PMM2-CDG typically present abnormal fat distribution and inverted nipples, but other forms of CDGs (ALG12-CDG, DPAGT1-CDG, MGAT2-CDG, MOGS-CDG) have also been associated with dysmorphic features. Dysmorphic facial features associated with PMM2-CDG have been described in large series and include prominent forehead, large ears and ear lobules, almond-shaped eyes, thin upper lip, prominent jaw, and long and slender fingers and toes.[13] It is reasonable to consider the diagnosis of CDGs in patients with dysmorphic features and no clear diagnosis.[1,5]

Neurologic involvement

Due to the high biosynthetic demand of the central nervous system, neurologic manifestations are present in almost all CDGs.[8] Deficient glycosylation in neural development may be relevant for the development and maintenance of normal cognitive functions.[16] While some CDGs have been associated with a purely neurologic phenotype, others show neurologic involvement as part of a multisystemic presentation. MPI-CDG, one of the few treatable forms of CDGs, is a notable exception, as it does not present with neurologic involvement.[5] The most common symptoms are psychomotor retardation/intellectual disability, hypotonia with frequent hyporeflexia, microcephaly, epileptic seizures, ataxia/cerebellar syndrome, peripheral neuropathy, spasticity, nystagmus, retinitis pigmentosa, strabismus, and stroke-like episodes.[11,12,16] Apart from cerebellar and cerebral atrophy, most CDG patients with epilepsy have no characteristic brain malformations. Nevertheless, O-glycosylation disorders are associated with features such as lissencephaly, polymicrogyria, schizencephaly and neuronal heterotopia. The cerebellum is often affected in PMM2-CDG, dystroglycanopathies, and SRD5A3-CDG, although the course of cerebellar ataxia is not progressive.[12,16] Cerebellar vermian hypoplasia is considered a highly specific sign of CDGs, but rarely present in the neonatal period.

Mutations affecting O-linked glycosylation result in congenital muscular dystrophy-dystroglycanopathies, including Walker-Warburg syndrome and muscle-eye-brain disease. This spectrum of diseases encompasses structural brain defects, such as lissencephaly, midline defects, cerebellar hypoplasia, hypotonia/myopathy and a spectrum of ocular and retinal conditions.[5,8]

GPI anchoring biogenesis defects can present as multiple congenital anomaly syndromes, with severe neurologic involvement and early death.[8]

Musculoskeletal involvement

Because collagen is a glycoprotein, CDGs can present with connective tissue or skeletal abnormalities. Several CDGs have skeletal dysplasia as the most prominent feature, including ALG12-CDG, TMEM165CDG and COG7-CDG.[5] CDGs with well-defined skeletal dysplasia include ALG3-CDG, ALG6-CDG, ALG9-CDG, PGM3-CDG, CSGALNACT1-CDG and SLC35D1-CDG. Some skeletal abnormalities are also unique to particular CDG subtypes such as Schneckenbecken dysplasia in SLC35D1-CDG, brachytelephalangy in PIGV-CDG and PIGO-CDG, pseudodiastrophic dysplasia in ALG12-CDG, Gillessen-Kaesbach and Nishimura skeletal dysplasia in ALG9-CDG and Desbuquois dysplasia in PGM3-CDG.[12] Ehlers-Danlos syndrome, progeroid type characterized by joint hypermobility, loose skin, short stature, osteopenia, and poor wound healing, is now classified as a CDG. Hereditary multiple osteochondroma syndromes, which are inherited in an autosomal dominant manner and can present with osteochondromas at birth in 5% of cases, are also included in the group of CDGs.[5]

Dermatologic involvement

Various skin abnormalities can be found in CDGs, including the characteristic “orange peel”, fat pads, ichthyosis, increased skin laxity, tumoral calcinosis, hypo/hyperpigmentation, aplasia cutis congenita and hypohidrosis/hyperthermia. Cutis laxa type IIA is now recognized as a CDG.[5,15]

Gastrointestinal and liver involvement

A common feature of many CDGs is failure to thrive, which has a probable multifactorial etiology comprising orofacial motor dysfunction secondary to hypotonia, malabsorption, neurologic impairment and alterations in the highly glycosylated gastrointestinal mucosa. Lymph circulation may also be abnormal in some patients. Reflux and vomiting are commonly found in CDG patients, and chronic diarrhea can also be found in several CDG types.[11] Protein-losing enteropathy is a specific feature commonly found in MPI-CDG, but occasionally also present in other forms, such as ALG6-CDG and PMM2-CDG. Ascites is a critical CDG manifestation, with hypoalbuminemia being a potentially significant complication of these conditions, often linked to poor prognosis in severe infantile cases.[5,11]

The liver is a major site of glycosylation in the body, as it produces most glycosylated proteins. Therefore, glycosylation disorders are expected to affect not only liver development but also its structure and function. Liver involvement is associated with one of two main

pathophysiological patterns: developmental abnormalities (ductal plate malformation or congenital hepatic fibrosis, as in MPI-CDG), or a combination of elevated liver transaminases (more common), hepatomegaly (less common), and steatosis in early infancy/childhood, as in PMM2-CDG. While the former is only treatable with liver transplantation, the second may spontaneously resolve over time. The most severe form of liver disease (acute liver failure) can arise in the setting of multiorgan failure (COG7-CDG, ALG3-CDG) or severe multisystemic disease. No typical histologic pattern of liver disease is described in CDGs. Liver fibrosis and cirrhosis have been reported in PMM2-CDG, MPI-CDG, and TMEM199-CDG setting.[11,12,17]

Liver involvement has been estimated in about 22% of CDG types and can be debilitating or even life-threatening with progression to liver cirrhosis or liver failure. CDGs with predominant or isolated liver involvement include MPI-CDG, CCDC115-CDG, TMEM199-CDG, and ATP6AP1, all of which include the V-type ATPase complex in Golgi apparatus and are classified as type II CDGs. Other CDGs associated with liver disease include six N-glycosylation diseases (including PMM2-CDG) and seven CDG types with defects in multiple glycosylation pathways.[11,17]

Cardiac involvement

Cardiovascular manifestations are not typical features in most CDGs. Nonetheless, congenital heart defects or anomalies (specifically conotruncal defects) have been described in PMM2-CDG, SRD5A3-CDG and COG1-CDG. Cardiomyopathy (hypertrophic and dilated) and pericardial effusion have been reported in association with several forms of CDGs, particularly PMM2-CDG, with the latter ranging from mild and asymptomatic to more severe and with worse prognosis.[5]

Hematologic involvement

Although primary and secondary dysfunction due to liver disease can be difficult to distinguish, the most serious cause of morbidity and mortality in CDGs is hematologic dysfunction.[5] This dysfunction arises from abnormal glycosylation of coagulation factors and platelet membrane glycoproteins, with an increase in the risk of thrombotic and bleeding complications, especially in PMM2-CDG, MPI-CDG, and ALG1-CDG. An imbalance between procoagulant and anticoagulant factors and nonspecific or dysfunctional platelet interactions accounts for coagulation abnormalities in CDGs. Low levels of factors IX and XI, antithrombin, protein C, and protein S, deficiency of factors II, V, VII, VIII, and X, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and elevated D-dimer are common findings. Hematologic complications include arterial and venous thrombosis, mucosal and visceral hemorrhage, and stroke-like episodes of so far unclear etiology.[5,11] Still, coagulation parameters can improve and even normalize over time, lowering the risk of clotting and bleeding events in adults. While decreased antithrombin, protein C, and protein S levels are associated with increased risk of thrombosis, the correlation between PT, aPTT, and levels of factors IX and XI is less clear.[11]

Endocrine involvement

CDGs can affect multiple endocrine pathways, including those involved in growth, thyroid function, glucose metabolism, and sexual development. Poor nutrition and/or dysfunction of the growth hormone/insulin-like growth factor I cascade may lead to growth failure, which is seen in most CDGs. Low normal to increased serum levels of growth hormone (GH), with decreased levels of insulin-like growth factor (IGF-1), suggest that CDG patients are often GH-resistant. Increased clearance of hypoglycosylated forms of insulin-like growth factor binding protein 3 (IGFBP-3) results in low levels of this hormone.[11] On the other hand, elevated thyroid-stimulating hormone levels are frequently found in young patients due to receptor glycosylation defects, especially in PMM2-CDG. Although thyroid-binding globulin and total T4 levels are often decreased in CDGs, patients are usually clinically euthyroid.[5,11] As adrenocorticotropic hormone is glycosylated, hypoglycemia, often associated with hyperinsulinism and adrenal insufficiency, may occur and present with lethargy, vomiting, or seizures. Female CDG patients often have elevated follicle-stimulating hormone (FSH) and luteinizing hormone levels but low estradiol, resulting in abnormal pubertal development, amenorrhea, and hypergonadotropic hypogonadism. Male CDG patients may present with small testes, elevated FSH, and cryptorchidism, with pubertal abnormalities being generally less common in males.[11]

Immunologic involvement

Normal functioning of cell-surface receptors, antibodies, and other critical components of the innate and adaptive immune systems depend on glycosylation. Therefore, immunologic dysfunction has been reported either as a major feature in several types of CDGs (ALG12-CDG, MAGT1-CDG, MOGS-CDG, PGM3-CDG, ATP6AP1-CDG/ATP6AP2-CDG, SLC35C1-CDG) or as a variable feature in more severe multisystemic presentations (PMM2-CDG).[5,11] Frequent or severe infections (bacterial, viral, fungal) and inadequate antibody response to vaccination and sinopulmonary,gastrointestinal and skin infections are common. Neutrophilia or neutropenia, lymphopenia, and low immunoglobulin (Ig)A and G, levels are the most common laboratory abnormalities. ALG12-CDG may cause lethal sepsis secondary to hypogammaglobulinemia and B-cell dysfunction in the neonatal period. SLC35C1-CDG, or leukocyte adhesion deficiency, type II courses with recurrent bacterial infections. MAGT1-CDG is caused by a deficiency in magnesium transporter 1 and results in a form of

X-linked primary combined immune deficiency (previously described as XMEN disease- X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia).[5,11]

DIAGNOSIS

The heterogeneity of CDGs makes their diagnosis a challenge. As there is no universal or pathognomonic sign or symptom and no sensitive diagnostic test for all CDGs, it is crucial to keep a high index of suspicion of these diseases. It is reasonable to suspect of CDGs in all patients with unexplained clinical story, especially those with unexplained neurologic or multisystem disease.[6] In general, patients presenting with one of the following clinical and biochemical features should undergo screening for glycosylation abnormalities: [5,12]

- nonimmune hydrops fetalis
- inverted nipples, abnormal fat distribution
- connective tissue involvement (such as cutis laxa)
- unexplained multisystemic phenotype, including neurologic manifestations
- non-progressive cerebellar ataxia
- severe epileptic encephalopathy
- elevated serum transaminases (especially if associated with decreased antithrombin/protein C and S activity)
- mixed coagulopathy and hypercoagulability
- hyperinsulinemic hypoglycemia
- liver steatosis/fibrosis/cirrhosis of unknown etiology
- recurrent pericardial effusion
- cardiomyopathy
- skeletal dysplasia (particularly pseudodiastrophic dysplasia, Gillessen-Kaesbach-Nishimura skeletal dysplasia, Desbuquois dysplasia, brachytelephlanagy)
- arthrogryposis with congenital myasthenia-like phenotype
- immunodeficiency

When a CDG is suspected, serum transferrin (Tf) isoelectric focusing (IEF) is the first step in screening.[12] Transferrin is a plasma iron transport protein with two asparagine N-glycosylation sites. The dominant isoform in healthy individuals is tetrasialo-Tf, while asialo- and monosialo-Tf isoforms are usually not detectable. Failure in N-glycan synthesis causes partial sialic acid deficiency, changing the charge of serum transferrin and causing it to migrate towards the cathode in an electrophoretic field. A type I pattern (CDG-I) indicates an assembly or transfer defect of the dolichol-linked glycan in the cytosol or ER. A type II pattern (CDG-II) indicates a processing defect after glycan transfer in the ER or during glycosylation in the Golgi apparatus. Some CDGs, such as PGM1-CDG, display features of both serum Tf IEF patterns (mixed type, CDG-I/CDG-II).[2,5,12,18]

During CDG diagnosis, secondary causes potentially associated with abnormal glycosylation patterns should be excluded. False- positive results may occur with moderate alcohol consumption in a dose-dependent manner, Tf gene polymorphisms, end-stage liver disease, pregnancy, estrogen replacement therapy, classic galactosemia and fructosemia. False-negative results may occur at young ages (< 2-6 months), with abnormal glycosylation normalizing later in life. Furthermore, Tf IEF only detects isolated in N-glycosylation or combined N-and O-glycosylation defects.[2,8,12]

It should be kept in mind that a normal serum Tf IEF profile does not exclude CDGs. In cases of strong clinical and biochemical suspicion, targeted NGS or whole-exome sequencing (WES) should be considered since PMM2-CDG due to promotor defect and other CDGs (SLC35A1-CDG, SLC35A3-CDG, SEC23B-CDG, PGM3-CDG) may present with normal N-glycosylation patterns, and Tf IEF may be normal or altered in several other CDGs (as ALG13-CDG, SLC35A2-CDG, RTF1-CDG, and SRD5A3-CDG).[12]

The next step when evaluating a potential CDG is to determine whether Tf IEF shows a type I or type II pattern. If a type I pattern is present, phosphomannomutase-2 (PMM2) or phosphomannose isomerase (PMI) deficiency are the first hypotheses, and if the proper clinical setting is present, their enzymatic activity should be measured in fibroblasts or leukocytes. PMM2-CDG is the most common CDG and with the best-defined clinical phenotype, while MPI-CDG is treatable and potentially fatal if left untreated. If the clinical phenotype is not typical of PMM2-CDG or MPI-CDG and PMM2 and PMI activity is normal, NGS, including targeted NGS (panel of genes known to be associated with CDG), or WES should be performed. Biallelic pathogenic variants in PMM2 or PMI confirm the diagnosis of PMM2-CDG or MPI-CDG.[2,12]

A type II serum transferrin CDG pattern suggests the presence of a Golgi defect, with IEF of serum apolipoprotein C-III (apoC-III) recommended in these cases. Apo-CIII isoform analysis is a complementary test for type II CDGs, as it usually undergoes O-glycosylation with a mucin core 1 glycan. It is useful to distinguish between an isolated N-glycosylation defect and a combined disorder of N- and O-glycosylation.[2,5,8,12]

Matrix-assisted laser desorption/ionization (MALDI) coupled with time-of-flight mass spectrometry (TOF MS) allows to simultaneously assess the glycan structure of all glycoproteins in the blood (N- and O-linked glycans). This test is more sensitive for type II CDGs and also better able to distinguish between specific subtypes of CDG. However, glycosylation processes may be tissue-specific (especially in muscle and central nervous system), rendering this test less sensitive.[2,5]

Dystroglycan immunohistochemistry can be performed on muscle biopsy specimens. This test is particularly useful for the congenital muscular dystrophy spectrum, as the deficient chemical pathways in these diseases are only expressed in either brain or muscle tissue.[5,8]

Flow cytometry of blood granulocytes is used when lipid glycosylation and GPI anchor biosynthesis defects are suspected. Flow cytometry analysis of white or red blood cells for certain GPI-anchored cell surface proteins is available as a test for paroxysmal nocturnal hemoglobinuria (PNH) due to acquired mutations in the PIGA gene. The PNH test may also reveal abnormalities in other GPI anchor deficiencies.[2]

Molecular genetic testing is the most specific diagnostic test, particularly given that no biochemical test can screen for all CDGs. Molecular gene panel testing or exome sequencing may be performed even in the presence of normal screening results in cases of strong clinical suspicion. Biochemical and functional confirmation of molecular genetic findings is crucial since the number of new genes associated with CDGs is exponentially increasing, and most patients with CDGs carry at least one mild and often novel missense mutation.[5,12]

Figure 2 depicts a proposal of a diagnostic algorithm for CDGs.

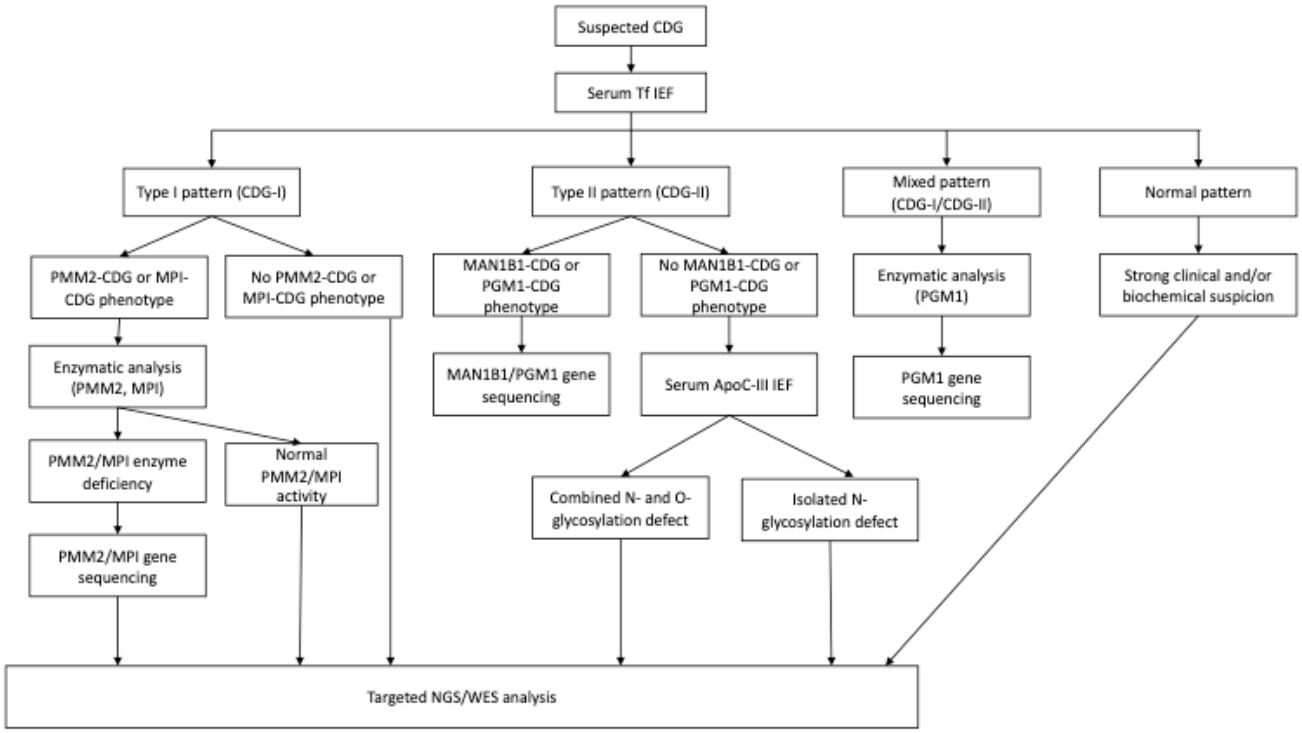


Figure 2 - Proposal of a diagnostic algorithm for congenital disorders of glycosylation (Adapted from Lipinski P, Tylki-Szymariska A,[13] Francisco R *et al.,* [21] and Quelhas D *et al.*[24])

THERAPEUTIC APPROACH

Specific treatment is only available for some types of CDGs, with symptomatic treatment being the only option for the majority. As most CDGs are multisystemic, a multidisciplinary approach is required to treat their several manifestations.[12]

Failure to thrive

The general approach consists of maximizing the tolerated caloric intake. Infants and children with CDGs can tolerate any type of formula, so no specific diet is required. Notwithstanding, elemental formulas may be better tolerated early in life. Feeding progression depends on the children´s oral motor function, with some requiring (transient) placement of a nasogastric tube or gastrostomy tube for nutritional support. However, failure to thrive often persists despite treatment.[11,20]

For patients with oral motor dysfunction and persistent vomiting and/or gastroesophageal reflux, postural measures, like maintenance of an upright position after eating and thickening of feeds, can be helpful. Speech and oral motor therapy support the transition to oral feeds and encourage speech when the child is ready.[20]

Protein-losing enteropathy

Regular albumin infusions, octreotide therapy, and diets rich in midchain fatty acids may be helpful in protein-losing enteropathy.[11,12,20]

Developmental delay

Case-by-case assessment should be performed to identify patients who may benefit from occupational therapy, physical therapy, or speech therapy.[20]

Ophthalmology

A consultation early in life with a pediatric ophthalmologist is important to identify potential eye abnormalities (strabismus, myopia, astigmatism, retinitis pigmentosa) and institute eye-preserving therapies (glasses, patching, or surgery), depending on the clinical situation.[20]

Hypothyroidism

Elevated thyroid-stimulating hormone (THS) levels are common, although CDG patients are usually euthyroid. Therefore, hypothyroidism should only be treated with levothyroxine in the presence of elevated TSH and low free thyroxine.[11,12,20]

Stroke-like episodes, coagulopathy and deep vein thrombosis

Supportive therapy for stroke-like episodes includes intravenous hydration, maintenance of normal blood glucose, and physical therapy during follow-up.[20]

Primary thrombosis prophylaxis is not recommended, but instead avoidance of potential triggers (elective surgery, oral contraceptives), adequate hydration, and early mobilization after invasive procedures.

Both unfractionated and low-molecular-weight heparin may be effectively used to treat thrombosis in the setting of CDGs. A reasonable alternative is factor Xa inhibitors. Vitamin K antagonists, such as warfarin, can be used for venous thrombosis secondary prophylaxis. [11]

If necessary, fresh frozen plasma may be employed to correct factor deficiency and clinical bleeding.[11,12,20]

Immunologic status

In infants and children with a history of recurrent or severe infections, leukocyte count with differential and serum immunoglobulin levels should be retrieved at the time of diagnosis and during acute infection episodes. Unless otherwise indicated, age-appropriate vaccination is recommended.[11,20]

Orthopedic issues

Thorax shortening and scoliosis/kyphosis are examples of orthopedic issues experienced by some CDG patients. Orthopedic and physical medicine care, use of wheelchairs and transfer devices for home, and physical therapy are part of the management plan. Surgical treatment of these issues may occasionally be necessary.[20]

Specific treatment

Only a few types of CDGs have a specific treatment, usually consisting of supplementation with simple sugars with the aim of improving hypoglycosylation.

MPI-CDG is the most effectively treatable CDG. Treatment consists of mannose supplementation at the dose of 1 g/kg/day divided into four to six doses. Although treatment can significantly improve protein-losing enteropathy, liver disease may persist and progress. Caution is required during pregnancy.[2,12,19]

Although treatment of PMM2-CDG is mainly supportive, mannose-1-phosphate substrate replacement therapy is being investigated in clinical trials. [2,12] Acetazolamide has been recently shown to be effective in the treatment of cerebellar motor syndrome and improve coagulation parameters, clinical severity, ataxia, epilepsy and lipodystrophy in patients with PMM2-CDG.[3,19] Some patients with SLC35C1-CDG respond to oral fucose supplementation, showing decreased incidence of recurrent infections with hyperleukocytosis but no neurodevelopment changes. D-galactose at a dose of 1.5-2.5 g/kg/day (until a maximum of 50 g/kg/day) has been shown to improve hypoglycemia, coagulopathy, and endocrinopathy in PGM-1-CDG. Galactose has also been suggested to improve endocrinopathy and coagulopathy in TMEM165-CDG and SLC39A8-CDG. Some patients respond to 15-20 mg/kg/day of manganese sulfate.[2,12]

Extended-release sialic acid and N-acetylmannosamine (ManCAc) are currently being investigated in GNE-CDG. Sodium butyrate has been shown to improve seizures in CAD-CDG and PIGM-CDG, and ketogenic diet has been shown to decrease seizure frequency in some PIGA-CDG patients.[2,11,12,19] Uridine supplementation led to cessation of seizures and improvement in development and anemia in CAD-CDG.[11,12,19]

Organ transplantation may be an option for CDGs in which the primary manifestation is limited to a specific organ and progressive neurologic disease is not a concern.[5,] Bone marrow transplantation and hematopoietic stem cell transplantation are therapeutic options in PGM3-CDG.[3]

Advances over the last few years have opened new therapeutic avenues in CDGs. The most promising new approaches include activated sugars, pharmacological chaperones, and gene therapy.[11]

The delivery of mannose-1-phosphate poses a challenge as the molecule is highly unstable. Liposomal targeting could be an option for efficient liver targeting, but technical difficulties limit this approach. Using a large complex molecule as a capsule around the

mannose-1-phosphate molecule could be an alternative, but its large size can potentially compromise an efficient cellular uptake. So far, none of these compounds have entered clinical trials.[11]

Proteins are present in the intracellular medium in folded or unfolded states. Point mutations may lead to a predominance of unfolded states, which lead to protein destabilization and aggregation. Pharmacological chaperones are small molecules that bind to specific proteins, stabilizing proteins in the folded state. PMM2-CDG has been classified as a misfolding disorder. In vitro testing has disclosed the possibility of uncovering ligands capable of stabilizing PMM2, suggesting that pharmacological chaperones may be a promising therapeutic option.[11,21] Gene therapy consists of the transfer and activation of a fully functional copy of an aberrant gene to the patient´s system. Being monogenic diseases, CDGs are potential candidates for this approach.[11,21] Apart from viral transgene delivery, such as adeno-associated virus vectors, other options include zinc-finger nucleases and transcription activator-like effector nucleases. Antisense therapy intends to restore transcript splicing after disruption by pathogenic splice variants. In vitro experiments have been conducted in PMM2-CDG patient-derived cells, and antisense therapy has shown promising results in TMEM165-CDG.[11]

MONITORING

The following laboratory tests and clinical assessments are recommended at the time of diagnosis (especially for PMM2-CDG) and subsequently on an annual basis:[20]

- liver function and serum albumin tests
- thyroid function tests (for TSH and elevated free thyroxine)
- protein C, protein S, antithrombin III, factor IX
- urinalysis
- serum gonadotropins in adolescent and adult women, to assess hypogonadotropic hypogonadism
- echocardiogram
- renal ultrasound to evaluate bilateral hyperechogenic kidneys, enlarged kidneys and renal cysts (PMM2-CDG)
- ophthalmologic examination
- orthopedic evaluation when scoliosis becomes evident

Of note, acetaminophen and other liver-metabolized drugs should be carefully used in patients with liver involvement.[20]

GENETIC COUNSELING

Assessment of genetic risk and carrier status and discussion of prenatal testing are recommended before pregnancy. In cases of known pathogenic variant(s), prenatal diagnosis and preimplantation genetic testing for N-linked or multiple-pathway CDGs are possible.[20]

ASSESSMENT OF RELATIVES

It is acceptable to evaluate apparently asymptomatic older and younger siblings of CDG patients to establish a potential CDG diagnosis as early as possible. Assessment may include molecular genetic testing if the pathogenic variant in the family is known or serum transferrin analysis if the pathogenic variant is unknown and transferrin is abnormal in the affected patient.[20]

PROGNOSIS

Despite multidisciplinary support, mortality from multiorgan failure or severe infections is reported in around 25% of CDG patients in the first years of life. Morbidity in these patients includes infections, seizures and hypoalbuminemia. Although there is no predictable life expectancy, the oldest living PMM2-CDG patients are currently in their 40s and 50s.[2, 22]

Early CDG diagnosis is desirable since identification of the pathogenic variant(s) enables prenatal diagnosis and preimplantation genetic diagnosis of congenital disorders of N-linked glycosylation or multiple pathways.[20]

TAKE-HOME MESSAGES

- CDGs are a vast group of heterogeneous diseases associated with elevated morbidity and mortality, especially in the first year of life. As defects may affect any organ at any age and elicit variable clinical presentations, their diagnosis poses a challenge.
- CDGs should be part of the differential diagnosis in patients with multiorgan involvement, especially in the presence of neurologic or hepatic disease or congenital anomalies.
- As there are no universally acknowledged signs or symptoms of CDGs, a high index of suspicion is crucial for diagnosis.

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REFERENCES

1. Vilarinho L, Quelhas D, Leão Teles E. Defectos congénitos de la glicosilación. In: Sanjurjo P, Baldellou A. editors. Diagnóstico y

Tratamiento de las enfermedadas metabólicas hereditárias. 3ª edicion. Majadahonda (Madrid): Ergon; 2010. p. 921-35.
2. Chang IJ, He M, Lam CT. Congenital disorders of glycosylation. Ann Transl Med 2018; 6(24): 477.
3. Jaeken, J. Congenital disorders of glycosylation: A multi-genetic disease family with multiple subcellular locations. Journal of Mother and Child 2020; 24(2): 14-20.
4. Grünewald S, Matthijs G, Jaeken J. Congenital Disorders of Glycosylation: A Review. *Pediatric Research* 2002; 52(5): 618-24.
5. Cuddapah S, Ganetzky R. Neonatal Presentation of Congenital Disorders of Glycosylation. NeoReviews 2017; 18(4): 234-9.
6. Schiff M, Roda C, Monin M-L, Arion A, Barth M, Bednarek N *et al*. Clinical, laboratory and molecular findings and long-term follow-up data in 96 French patients with PMM2-CDG (phosphomannomutase 2- congenital disorder of glycosylation) and review of the literature. J Med Genet 2017; 54(12): 843-51.
7. Jaeken J, Matthijs G. Congenital Disorders of Glycosylation: A Rapidly Expanding Disease Family. Annu. Rev. Genomics Hum. Genet. 2007; 8: 261-78.
8. Ganetzky R, Reynoso FJ, He M. Congenital disorders of glycosylation. December 2017. (Assessed November 13, 2021). Available at https://www.sciencedirect.com/science/article/pii/B9780128028964000146?via%3Dihub.
9. Schjoldager KT, Narimatsu Y, Joshi HJ, Clausen H. Global view of human protein glycosylation pathways and functions. Nature Reviews Molecular Cell Biology 2020; 21(12): 729–49.
10. Jaeken J, Hennet T, Matthijs G, Freeze HH. CDG nomenclature: time for a change! Biochim Biophys Acta 2009; 1792(9): 825-6.
11. Verheijen J, Tahata S, Kozicz T, Witters P, Morava E. Therapeutic approaches in Congenital Disorders of Glycosylation (CDG) involving N-linked glycosylation: an update. Genetics in Medicine 2020; 22(2): 268-279.
12. Lipinski P, Tylki-Szymariska A. Congenital Disorders of Glycosylation: What Clinicians Need to Know? Front. Pediatr. 2021: 3(9): 715-51.
13. Ferreira CR, Altassan R, Marques-Da-Silva D, Francisco R, Jaeken J, Morava E. Recognizable phenotypes in CDG. J Inherit Metab Dis. 2018; 41(3): 541-53.
14. Makhamreh MM, Cottingham N, Ferreira CR, Berger S, Al-Kouatly HB. Nonimmune hydrops fetalis and congenital disorders of glycosylation: A systematic literature review. J Inherit Metab Dis. 2020; 43(2): 223-33.
15. Rymen D, Jaeken J. Skin manifestations in CDG. J Inherit Metab Dis. 2014; 37(5): 699-708.
16. Paprocka J, Jezela-Stanek A, Tylki-Szymanska A, Grunewald S. Congenital Disorders of Glycosylation from a Neurological Perspective. Brain Sci. 2021; 1(11): 88.
17. Marques-da-Silva D, dos Reis Ferreira V, Monticelli M, Janeiro P, Videira PA, Witters P *et al*. Liver involvement in congenital disorders of glycosylation (CDG). A systematic review of the literature. J Inherit Metab Dis 2017; 40(2): 195-207.
18. Houdou M, Foulquier F. Anomalies congénitales de la glycosylation (CDG). Médecine/sciences 2020; 36(8): 735-46.
19. Sosicka P, Ng BG, Freeze HH. Chemical Therapies for Congenital Disorders of Glycosylation. ACS Chem Biol 2021.
20. Sparks SE, Krasnewich DM. Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview. January, 2017. (Assessed November 13, 2021). Available at: https://www.ncbi.nlm.nih.gov/books/NBK1332.
21. Brasil S, Pascoal C, Francisco R, Marques-da-Silva D, Andreotti G, Videira PA, *et al*. CDG Therapies: From Bench to Bedside. Int. J. Mol. Sci. 2018; 19(5): 1304.
22. Grünewald S. Congenital disorders of glycosylation: rapidly enlarging group of (neuro)metabolic disorders. Early Hum Dev 2007; 83(12): 825-30.
23. Francisco R, Marques-da-Silva D, Brasil S, Pascoal C, dos Reis Ferreira V, Morava E, Jaeken J. The challenge of CDG diagnosis. Mol Genet Metab. 2019; 126(1): 1-5.
24. Quelhas D, Martins E, Azevedo L, Bandeira A, Diogo L, Garcia P *et al*. Congenital Disorders of Glycosylation in Portugal- Two Decades of Experience. The Journal of Pediatrics 2021; 231: 148-56.

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Received for publication: 30.01.2022
Accepted in revised form: 10.02.2022

CASE REPORTS

Progressive back pain due to epidural cerebrospinal fluid collection: a rare complication of lumbar puncture in adolescents

Lombalgia progressiva secundária a coleção epidural de líquor: uma complicação rara da punção lombar em adolescentes

Ana Sofia Simões[1], Raquel Penteado[1], Leonor Carvalho[1], Andrea Dias[1,2]

ABSTRACT

Lumbar puncture is commonly performed in Pediatrics. Common complications include headache and mild pain at the puncture site. Uncommon complications after the procedure, such as epidural cerebrospinal fluid collection, have rarely been described in children and adolescents.

The authors present the clinical report of an adolescent with symptomatic epidural cerebrospinal fluid collection following a non-traumatic lumbar puncture.

Diagnosis (including magnetic resonance imaging findings), treatment, clinical course, and prognosis associated with epidural cerebrospinal fluid collection are reported.

Keywords: adolescent; complication; epidural; hygroma; lumbar puncture

RESUMO

A punção lombar é comumente realizada em Pediatria. Complicações frequentes associadas a este procedimento incluem cefaleia e dor ligeira no local da punção. Outras complicações, como coleção epidural de líquor, raramente são descritas em crianças e adolescentes.

Os autores apresentam o caso clínico de uma adolescente com coleção epidural de líquor sintomática após a realização de uma punção lombar não traumática.

É descrito o diagnóstico (incluindo achados na ressonância magnética), tratamento, curso clínico e prognóstico associado à coleção epidural de líquor.

Palavras-chave: adolescente; complicação; epidural; higroma; punção lombar

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INTRODUCTION

Lumbar puncture (LP) is one of the most frequently performed invasive diagnostic procedures in children and adolescents.[1]

Common LP complications include post-dural puncture headache (PDPH) and mild pain at the puncture site (5-10%).[2,3] Infrequent complications, such as cranial nerve palsy, meningitis, spinal epidermoid tumors, spinal hematoma, and cerebral herniation, have rarely been described in Pediatrics.[4]

Epidural cerebrospinal fluid (CSF) hygroma can occur after dura puncture due to CSF extravasation from the thecal sac. Although infrequent, the epidural collection can be large enough to cause neurological dysfunction.[5]

The authors present the clinical report of an adolescent with symptomatic epidural CSF collection following a non-traumatic LP.

CASE REPORT

An 11-year-old girl was admitted to a local hospital with a 24-hour history of fever, headache, and vomiting, without diarrhea. Family history and epidemiological data were unremarkable. On admission, she presented symptoms of confusion, but was clinically stable (temperature: 38.1°C, heart rate: 91 beats per minute, blood pressure: 120/60 mmHg, respiratory rate: 21 breaths per minute). On physical examination, the girl presented signs of meningeal irritation (positive Kernig and Brudzinski signs and nuchal rigidity), pharyngeal erythema, and tonsillar exudate. No skin rash was observed. Cardiovascular, respiratory, and abdominal examinations were unremarkable.

Laboratory results revealed increased white blood cell count (21000/mm^3) and positive C-reactive protein (14.6 mg/dL). A rapid strep throat test was collected, with negative result. Other standard laboratory findings were within the normal range. Blood culture was negative. Brain computed tomography (CT) scan showed signs of cerebral edema with global loss of grey-white matter differentiation, narrow ventricles and descent of the cerebellar tonsils, and left-sided frontal and maxillary sinusitis, with no signs of cerebral venous thrombosis. Medical management with head positioning, restrictive intravenous fluid therapy, adequate analgesia, and intravenous dexamethasone was started. Dexamethasone was maintained for 13 days. Intravenous antibiotic therapy (ceftriaxone and ciprofloxacin) and acyclovir were also initiated. The child was transferred to a main hospital.

On admission, within 24 hours after brain CT, brain magnetic resonance imaging (MRI) was performed, showing findings consistent with meningoencephalitis and no signs of hydrocephalus. Imaging revealed slight thickening of the left frontobasal cortex, with restricted diffusion of the left cortical-subcortical frontobasal region. It also showed a 3-mm-thick left frontotemporal subdural empyema, an 8-mm-thick small epidural abscess on the left anterior frontobasal region, and left-sided frontal, ethmoid, and maxillary sinusitis. Non-traumatic LP was performed, revealing cloudy CSF with high white blood cell count (895/mm^3, with 83% of polymorphonuclear cells), rare red blood cells/mm^3, CSF/serum glucose ratio of 0.55, and protein content of 94 mg/dL. CSF Gram stain, culture, and multiplex polymerase chain reaction were negative. Nine hours after the procedure, the patient complained of urinary retention and lower back pain.

On day two of hospital stay, antimicrobial therapy was changed to intravenous ceftriaxone, vancomycin, and metronidazole. Empiric therapy was initiated to provide antimicrobial coverage to the most commonly identified pathogens in sinusitis and subdural empyema (anaerobes, Gram-negative bacteria, *Staphylococcus aureus*). Surgical treatment was required for management of sinusitis and subdural empyema, with no significant complications. *Streptococcus viridans* (susceptible to penicillin, clindamycin, and vancomycin) was isolated from maxillary sinuses.

After surgery, the patient was admitted to the Pediatric Intensive Care Unit (PICU) for recovery. During PICU stay, she complained of severe headaches, progressive lower back pain, constipation, and urinary retention. On examination, she was conscious but became acutely agitated with tactile allodynia. She was hemodynamically stable, with no motor impairment.

Spinal MRI was performed, revealing extensive dorsal and lumbar spinal epidural fluid collection and anterior displacement of the thecal sac, with subarachnoid space reduction (**Figure 1**). Imaging findings were consistent with post-LP complication.

During the first 24 hours, pain was not responsive to medical management, including nonopioid analgesics (paracetamol, metamizole, ketorolac) and opioid therapy (morphine).

Due to severe refractory pain and psychomotor agitation, the patient received an intravenous morphine infusion (maximum 30 µg/kg/h), fentanyl (maximum 2.5 µg/kg/h), and midazolam (maximum 3.1 µg/kg/min), and was mechanically ventilated for two days. She also required a Foley catheter for three days.

During PICU stay, conservative measures with hydration and strict bed rest were enforced. Patient's symptoms improved within seven days, and she recovered without complications, being discharged forty days after admission. At three-month follow-up, the patient had complete resolution of clinical and imaging findings.

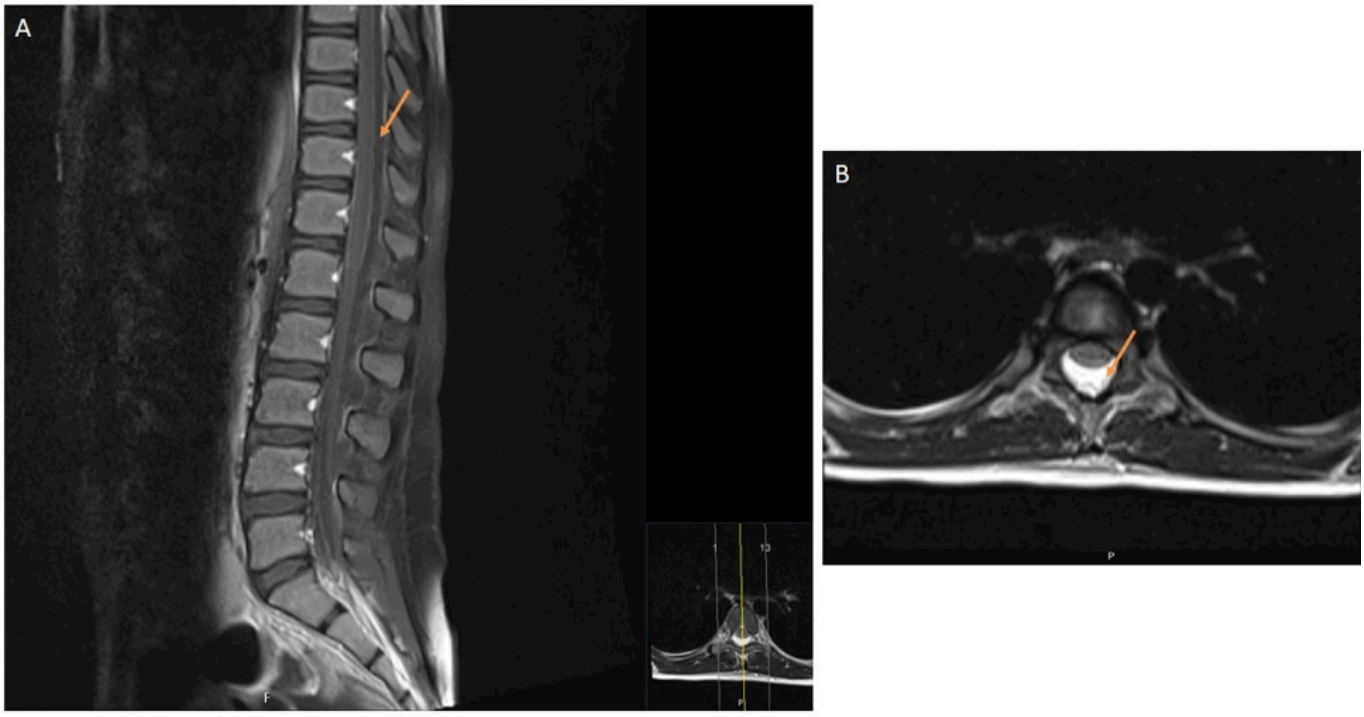

Figure 1 - Spinal MRI. (A) Sagittal view and (B) axial view showing an extensive dorsal and lumbar spinal epidural fluid collection and an anterior displacement of the thecal sac with reduction of the subarachnoid space.

DISCUSSION/CONCLUSIONS

LP is a procedure commonly performed in pediatric age,[6] mostly for the diagnosis of central nervous system infections. PDPH is its most frequent complication, potentially caused by transient intracranial hypotension due to the CSF leakage, although the exact underlying mechanism is still unknown.[7,8] Needle characteristics (diameter and type of spinal needle), puncture technique (needle orientation), number of attempted dural punctures, and patient's positioning after LP are factors influencing the occurrence of PDPH.[7]

Uncommon LP complications, such as epidural and subdural hematoma, symptomatic epidural CSF collection, subarachnoid haemorrhage, cranial nerve palsy, meningitis, and cerebral herniation, have rarely been reported in children.[2,5]

Although uncommon in infants and children, epidural CSF collection after LP has long been acknowledged among the Pediatric population, from neonates to adolescents.[5,9]

The incidence of post-LP epidural CSF collection is unknown, but it is believed to be higher than suspected. Koch *et al*. retrospectively analysed 25 MRIs performed in children with new symptoms following LP.[5] All MRI scans showed abnormal dorsal spinal epidural collection and exhibited significant anterior dura displacement.[2] Kiechl-Kohlendorfer *et al.* conducted a prospective study including 33 newborns who underwent ultrasound evaluation after LP to determine the occurrence of abnormal fluid collection. The authors demonstrated that CSF leakage is a frequent finding after LP, developing in 64% of all neonates enrolled in the study.[9]

Although predisposing risk factors and pathophysiology remain unknown, neonates and children with underdeveloped connective tissue in the epidural space may be at higher risk of this complication.[4]

These collections are usually dorsally located on MRI and extensive, and may compromise the thecal sac, resulting in transient cauda equina syndrome (CES).[2,10]

In the present case, typical MRI findings were identified. These included abnormal epidural CSF collection with anterior thecal sac displacement, resulting in decreased subarachnoid space.

Epidural CSF collection may be a misdiagnosed complication and only detected in the presence of significant symptoms, such as severe headache, lower back pain, constipation, and urinary retention, as occurred in this patient. Epidural CSF collection can be severe enough to result in CES. Amini A *et al.* reported a case of epidural CSF leak after LP causing CES in a four-year-old girl.[4]

CES is uncommon in pediatric age and results from compression or inflammation of nerve roots of cauda equina. This condition commonly comprises motor and sensory abnormalities of the lower limbs, along with bladder and bowel dysfunction. There are numerous CES classifications, based on location, disease type, and time of onset, and the condition is associated with various disorders, potentially occurring after LP.[4,11]

According to Koch *et al.*, the extent of epidural CSF collection does

not seem to be related to the number of LP attempts.[2] Typically, approximately 90% of symptoms start within the first 72 hours after LP and resolve within ten days, as observed in the present case.[12,13]

In Pediatric patients, conservative management with hydration, analgesia, and bed rest represents the first treatment choice, with patients usually recovering without neurological deficits.[4,5]

Epidural blood patch (EBP) therapy is indicated if conservative treatment is ineffective, as in patients with severe and persistent pain, with a reported success rate of 90%.[12,13] In EBP, a small volume of autologous blood is injected into the epidural space between the ligamentum flavum and dura.[14] The proposed mechanism is that clotted blood adheres to dura, resolving the leak and allowing CSF pressure to normalize.[14,15] In the present case, although the adolescent achieved complete recovery and symptomatic relief in the expected period, autologous EBP could have been considered to attain earlier recovery.

In conclusion, symptomatic epidural CSF collection can occur following LP and should be considered in the differential diagnosis in children if headache and back pain emerge after LP. Patients with persistent severe back pain and/or signs of spinal cord disease (backpain, urinary retention, loss of bowel and bladder control, weakness of lower limbs, sensory loss) after LP should undergo spine MRI. Close follow-up is required to ensure complete recovery.

AUTHORSHIP

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REFERENCES

1. Ebinger F, Kosel C, Pietz J, Rating D. Headache and backache after lumbar puncture in children and adolescents: A prospective study. Pediatrics. 2004;113(6 I):1588–92.
2. Koch BL, Moosbrugger EA, Egelhoff JC. Symptomatic spinal epidural collections after lumbar puncture in children. Am J Neuroradiol. 2007;28(9):1811–6.
3. Ylönen P, Kokki H. Management of postdural puncture headache with epidural blood patch in children. Paediatr Anaesth. 2002;12(6):526–9.
4. Amini A, Liu JK, Kan P, Brockmeyer DL. Cerebrospinal fluid dissecting into spinal epidural space after lumbar puncture causing cauda equina syndrome: Review of literature and illustrative case. Child's Nerv Syst. 2006;22(12):1639–41.
5. Ng WH, Drake JM. Symptomatic spinal epidural CSF collection after lumbar puncture in a young adult: Case report and review of literature. Child's Nerv Syst. 2010;26(2):259–62.
6. Nigrovic LE, Kuppermann N, Neuman MI. Risk Factors for Traumatic or Unsuccessful Lumbar Punctures in Children. Ann Emerg Med. 2007;49(6):762–71.
7. Janssens E, Aerssens P, Alliët P, Gillis P, Raes M. Post-dural puncture headaches in children. A literature review. Eur J Pediatr. 2003;162(3):117–21.
8. Hu B, Chen TM, Liu B, Chi W, Miao YQ, Nie XL, *et al*. Optimal management after paediatric lumbar puncture: A randomized controlled trial. BMC Neurol. 2019;19(1):1–7.
9. Kiechl-kohlendorfer U. Original Report Lumbar Puncture in Neonates : Incidence and Sonographic Appearance. AJR Am J Roentgenol. 2003;181(July):231–4.
10. Sinclair AJ, Carroll C, Davies B. Cauda equina syndrome following a lumbar puncture. J Clin Neurosci [Internet]. 2009;16(5):714–6. Available from: http://dx.doi.org/10.1016/j.jocn.2008.07.079.
11. Shi J, Jia L, Yuan W, Shi GD, Ma B, Wang B, *et al*. Clinical classification of cauda equina syndrome for proper treatment: A retrospective analysis of 39 patients. Acta Orthop. 2010;81(3):391–5.
12. Bezov D, Lipton RB, Ashina S. Post-dural puncture headache: Part i diagnosis, epidemiology, etiology, and pathophysiology. Headache. 2010;50(7):1144–52.
13. Rico-Santos M, Villafani J, Sáiz A, Nacarino PO. Progressive back pain due to epidural hygroma: An infrequent complication of lumbar puncture in adults. BMJ Case Rep. 2015;2015(C):1–2.
14. So Y, Park JM, Lee PM, Kim CL, Lee C, Kim JH. Epidural blood patch for the treatment of spontaneous and iatrogenic orthostatic headache. Pain Physician. 2016;19(8):E1115–22.
15. Birkholz SE, Patil AA, Chamczuk AJ. Treatment of postoperative recurrent cerebrospinal fluid leak with pseudo-meningocele formation using temporary epidural drain. Interdiscip Neurosurg Adv Tech Case Manag [Internet]. 2019;16(November 2018):25–8. Available from: https://doi.org/10.1016/j.inat.2018.11.006.

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Received for publication: 06.06.2020
Accepted in revised form: 08.03.2021

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):59-63. doi:10.25753/BirthGrowthMJ.v31.i1.19194

CASE REPORTS

Between Obsessive-Compulsive Disorder and Psychosis

Entre a Perturbação Obsessivo-Compulsiva e a Psicose

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ABSTRACT

Introduction: Obsessive-compulsive disorder is an heterogeneous condition in which periods of altered perception or delusions may arise. Similarly, individuals with psychotic disorders may have obsessive-compulsive symptoms.

Case report: A male adolescent presented to the Emergency Department (ED) with obsessive symptomatology with three months of evolution. Three weeks later, he returned to the ED showing symptom worsening and reporting delusions, being admitted to the inpatient unit to clarify the diagnosis. No positive symptoms were reported during hospitalization. During follow-up, the patient reported an episode of apparent delusional perception that he associated with the beginning of symptoms, again raising the question of whether a psychotic episode was present.

Discussion/Conclusions: The distinction between obsessive-compulsive disorder and psychosis is not always clear, with obsessive-compulsive disorder being a significant comorbidity in patients with a first psychotic episode. Close patient assessment is required for early diagnosis and appropriate intervention.

Keywords: adolescent; obsessive-compulsive disorder; psychosis

RESUMO

Introdução: A perturbação obsessivo-compulsiva é uma patologia heterogénea em que podem surgir períodos de perceção alterada ou ideias delirantes. De igual forma, indivíduos com perturbações psicóticas podem apresentar sintomas obsessivo-compulsivos.

Caso clínico: Um adolescente do sexo masculino recorreu ao Serviço de Urgência (SE) por sintomatologia obsessiva com três meses de evolução. Regressou ao SE após três semanas por agravamento do quadro e relato de ideias delirantes, tendo sido internado para clarificação do diagnóstico. Nunca foram objetivados sintomas positivos durante o internamento. Em consulta de seguimento, o jovem relatou um episódio de aparente perceção delirante que associou ao início da sintomatologia, levantando novamente a dúvida quanto à presença de um episódio psicótico.

Discussão/Conclusões: A distinção entre perturbação obsessivo-compulsiva e psicose nem sempre é clara, e a comorbilidade entre ambas é significativa. É necessária uma avaliação meticulosa do doente para um diagnóstico precoce e intervenção apropriada.

Palavras-chave: adolescência; perturbação obsessivo-compulsiva; psicose

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common, often chronic, disorder in children and adolescents, with significantly associated impairment across multiple functioning domains.[1]

According to Fontenelle *et al.*, OCD has been increasingly recognized as comorbid with different types of psychotic disorders. The prevalence of OCD in individuals with psychotic conditions ranges between 10% and 25%, which is more than eight times that reported for OCD in the general population.[2] Such comorbidity is clinically relevant, as OCD may modify the clinical expression of other disorders.[2]

OCD is characterized by the presence of obsessions and/or compulsions with varying severity. Patients recognize that those behaviors are excessive and unreasonable at some level, although this understanding is not required for OCD diagnosis in children and young people, who may present solely with compulsions. The usual onset of the full disorder takes place during adolescence or young adulthood, with slightly earlier onset in males compared to females.[3]

OCD as comorbidity represents an extra burden to patients suffering from psychotic disorders.[4] Patients with schizophrenia and OCD have been reported to have earlier-onset psychosis, an increased rate of depressive symptoms, and suicidal attempts compared to their non-OCD counterparts. However, these patterns have not been consistently reported.[4]

There are several possible explanations to why OCD and schizophrenia might be related, namely the hypotheses that one disorder may present as a prodrome of the other or one disorder may cause the other.[5]

The aim of this report was to describe the case of a 14-year-old male presenting with OCD and psychotic symptomatology with a yet unclear diagnosis and reflect on the difficulties in the management and treatment of these cases.

CASE REPORT

Chief complaint and history of present illness. A 14-year-old Caucasian male was admitted to the Pediatric Psychiatric Emergency Department (PPED) complaining of initial insomnia, obsessive thoughts, and repetitive behavior. He appeared to be very worried and reported persistent intrusive thoughts of self-criticism and fear of unintentionally insulting or hurting people. The boy reported rituals such as washing hands several times a day for fear of contamination and questioning his parents for reassuring his persistent doubt, and was very scared of dying. In addition, he showed progressive symptom worsening and declining school performance. Sertraline 50 mg and risperidone 0.5 mg were prescribed in the PPED, and a reassessment follow-up appointment was scheduled for four weeks later.

Three weeks later, the patient returned to the PPED with symptom worsening. He was fearful, increasingly unable to function independently, and unable to attend school. He presented alterations of thought content, verbalizing persistent doubts about being *"in another world"* and not being sure whether his parents *"were really themselves"*, and was becoming more socially isolated and distant from family and friends.

The boy had suffered a decline in overall functioning, particularly in school, over the past three months and was proposed a Child Psychiatry inpatient evaluation in the second PPED presentation, which he and his parents accepted.

Past medical, developmental, and family history. The patient's developmental history was described as expected for age. At four years, he had a two-month period of compulsive hand washing that resolved after a short period of psychotherapy. Both parents had a history of anxious symptomatology and were medicated. No history of major mental illness was identified in the close family. The boy denied smoking, taking any toxic drugs, and alcohol consumption.

Mental status. The patient presented with poor mood, anxiety, and easy crying. He engaged reasonably well in the evaluation, with fluent speech but not very organized thought, jumping back and forth in temporal events. It was unclear whether that was due to anxiety or general thought disorganization. He described persistent obsessive thoughts and doubts about family wellbeing and fear of unwittingly hurting family members, doing something illegal, or insulting someone. To prevent this, he completed rituals, like always drinking from the same side of the glass, counting steps, constantly praying, and avoiding situations he perceived as triggers (e.g., going to the church). These were interpreted as obsessive thoughts with compulsions. Additionally, he doubted whether his parents were really themselves, saying they could be aliens from another planet. These behaviors were interpreted as possible delusions. The boy also doubted about the possession of his thoughts: he had visited a psychologist some days earlier, who calmed him down with a head massage, after which he became afraid that the psychologist had *"stolen his mental capacities"*. This could also represent a psychotic symptom (abnormality of thought possession). He displayed no signs of aggressiveness but showed significant distress about having aggressive thoughts and potentially hurting others. He was partially aware of his situation. Auditory or visual hallucinations were ruled out, as well as suicidal ideation. In addition, he had initial or intermediate insomnia and diminished appetite.

Hospital presentation and differential diagnosis. On admission, the patient was very anxious, sad, and tearful. He had reasonable overall functioning and presented several long-lasting repetitive behaviors. He still mentioned doubts about his parents really being themselves and about the staff in the unit being real. He had some insight about his doubts, acknowledging that they did not "*make much sense*". At this point, OCD versus a psychotic disorder were the primary

differential diagnoses.

Delirium or an organic etiology was ruled out based on normal routine laboratory exams and magnetic resonance imaging. The presence of toxic substances was not investigated, as there was no history of use.

Targeting an OCD diagnosis, sertraline dose was optimized, risperidone was discontinued, and olanzapine and lorazepam were introduced to improve insomnia and anxiety.

The patient was submitted to psychological evaluation under the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which identified "several obsessions and compulsions, namely thoughts of aggression, violence, sexual and religious nature, verification, contamination/cleanliness, and a range of superstitious behaviors and intrusion of sounds (...)."

By the end of the second week, the patient was much less anxious, maintaining less frequent and intense rituals. His mood was brighter, and he seemed less worried and fearful. At that time, he showed no positive symptoms. The patient was discharged on day 16. He was diagnosed with F42.2. Obsessive-compulsive Disorder with mixed obsessional thoughts and acts (according to ICD-10).[6]

Discharge plans and follow-up. The patient was referred to the outpatient unit of the Pediatric Psychiatric Department within a week, maintaining the treatment plan. He was also referred to Psychology consultation for OCD treatment, using a cognitive-behavioral approach for symptom reduction. An ongoing care plan was established and agreed upon based on close collaboration among the outpatient provider, the patient, and the patient's family.

During follow-up, the boy reported an episode that he associated with the beginning of symptoms: he attributed the proof of the existence of a "*parallel reality*" to the triangle symbol. After this, he became very anxious when seeing a triangle, fearing that "*something bad would happen*", and tried to mitigate anxiety with repetitive behaviors. At the same time, he was afraid of "*doing something bad*" to others or being in contact with certain materials (like gasoline, bleach, etc.) for fear of contamination. He had partial insight but could not help performing those repetitive behaviors to calm down.

Subsequently, the boy expressed doubts about the existence of extraterrestrials and their ability to oversee the actions of humans, which were accompanied by marked anxiety. These bizarre and paranoid ideas again raised the question of whether a psychotic disorder could also be present. Doubts were also raised about whether the boy's inability to attend school was due to high anxiety or cognitive deterioration caused by a psychotic state.

With therapeutic adjustment, the boy started showing increasing insight. Symptoms still had an impact on functioning, mainly through difficulty in thinking and organizing tasks, but he was able to attend school and concentrate better.

Persistent pathological doubt is the landmark of OCD. However, the presence of bizarre and paranoid thoughts makes it unclear whether standing before an isolated case of OCD or also the beginning of a psychotic state.

DISCUSSION

OCD is a condition with several possible presentations, including occasionally a seemingly psychotic nature, in which periods of altered perception or delusions arise.[3] The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) encompasses the OCD diagnostic specifier "*without insight/with delusional beliefs*", which may be useful in these case presentations.[7] However, when an adolescent reports OCD symptoms, clinicians should fully explore the symptomatic picture, as subthreshold psychotic symptoms may be lingering underneath, thereby contributing to increased clinical and functional impairment.[5]

Regarding insight, Selles *et al.* studied an OCD youth sample in which almost 90% of patients reported excellent, good, and fair levels of insight.[8] A small group of patients (9.7%) was in the poor insight group, and very few (1.4%) were in the absent/delusional insight group. The poor/absent insight group was associated with higher OCD severity levels, specifically increased distress and avoidance and decreased symptom resistance.[8]

When differentiating between OCD and schizophrenia spectrum disorders (SSDs), Rodowski *et al.* suggested four areas of evidence that can help elucidate this distinction. The authors included prevalence data, past history and clinical presentation, presence/lack of insight of the connection between a thought and behavior, and long-term follow-up to assess the natural course of the disease.[3] In the present case, prevalence data suggested that OCD is the primary diagnosis, with past history also corroborating this hypothesis. The clinical presentation remained a confounding factor, and insight was compromised by delusional beliefs. The patient's long-term follow-up will be of utmost importance to determine the outcome.

One important aspect is how symptoms are phenomenologically interpreted. Oulis *et al.* put forward an approach suggesting a comparative assessment of major features of obsessions versus delusions and compulsions versus delusional repetitive behaviors to make an accurate differential diagnosis between OCD and SSDs when that is challenging.[9]

Despite efforts to distinguish OCD and schizophrenia, the conditions may indeed co-occur. This comorbidity has been explained by three main theories summarized by Rosli *et al.*: OCD can be a prodrome of schizophrenia; OCD can be a risk factor for schizophrenia; or both are to be taken as having a common risk factor (vulnerability genes).[10] This led to the term "schizo-obsessiveness", coined by Hwang and Opler in 1994 and proposed in some cases.[11] OCD-schizophrenia spectrum disorders include OCD, OCD with poor insight, OCD with schizotypal personality disorder, schizophrenia with obsessive-compulsive symptoms, schizophrenia with OCD, and pure schizophrenia.[12]

Faragian and colleagues reported that almost half of obsessive-compulsive symptoms (OCS) reported by schizo-obsessive patients

precede the first psychotic symptoms (PS), while OCS followed PS in only a quarter of patients, and OCS and PS co-occurred in 25% of patients.[13] These authors also reported that the presence of OCS was associated with earlier schizophrenia onset in schizo-obsessive patients and that men had an earlier onset of both sets of symptoms.[13]

In another study by Fontenelle *et al.*, patients presenting both PS and OCS were more likely to report a positive family history of anxiety disorders than those with psychotic but no OCD symptoms.[2] Faragian proposed that schizo-obsessive disorder had a marked neurodevelopmental origin and particularly early onset in men.[13]

A recent update on schizo-obsessive spectrum disorders showed that, despite the considerable amount of evidence in the literature showing the clinical relevance of schizo-obsessive disorder – which seems to have epidemiological, clinical, and phenomenological differences from the parental conditions –, little is known about neurobiology, genetic, and neurocognitive aspects or pharmacological treatment strategies for the condition.[11] Additionally, follow-up data about the clinical course of the disease is crucial. Extended follow-up is desirable to investigate whether there is further functioning decline or broadening of disordered thinking.[3]

CONCLUSION

The distinction between OCD and psychosis is not always clear.

One may present OCD with reduced insight/delusions or have OCS as prodrome of a psychotic disorder. Treatment and prognosis of both conditions differ and establishing a diagnosis warrants extensively exploring symptoms. In this case, a number of factors suggestive of psychotic disorder within OCD were present, namely male gender, early age of presentation, presence of delusions and some thought disorganization with periods of alteration of thought possession, and family history of anxiety disorders.

Time and follow-up are crucial for longitudinal analysis and further outcome clarification.

AUTHORSHIP

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REFERENCES

1. Porth R, Geller D. Atypical symptom presentations in children and adolescents with obsessive compulsive disorder. Comprehensive Psychiatry. 2018; 86, 25–30. PMID: 30048852.
2. Fontenelle LF, Lin A, Pantelis C, Wood SJ, Nelson B, Yung AR. Markers of vulnerability to obsessive-compulsive disorder in an ultra-high risk sample of patients who developed psychosis. Early Intervention in Psychiatry. 2012;6(2), 201–6. PMID: 22510335.
3. Rodowski MF, Cagande CC, Riddle MA. Childhood Obsessive-Compulsive Disorder Presenting as Schizophrenia Spectrum Disorders. Journal of Child and Adolescent Psychopharmacology. 2008;18(4), 395–401. PMID: 18759651.
4. Hagen K, Hansen B, Joa I, Larsen TK. Prevalence and clinical characteristics of patients with obsessive-compulsive disorder in first-episode psychosis. BMC Psychiatry. 2013;13(1). PMID: 23721089.
5. Niendam TA, Berzak J, Cannon TD, Bearden CE. Obsessive compulsive symptoms in the psychosis prodrome: Correlates of clinical and functional outcome. Schizophrenia Research. 2009;108(1-3), 170–5. PMID: 19097751.
6. World Health Organization. ICD-10: international statistical classification of diseases and related health problems: tenth revision, 2nd ed. World Health Organization. 2004.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. American Psychiatric Association. Washington D.C. 2013.
8. Selles RR et al. Symptom Insight in Pediatric Obsessive-Compulsive Disorder: Outcomes of an International Aggregated Cross-Sectional Sample. Journal of the American Academy of Child & Adolescent Psychiatry. 2018;57(8),615–9.e5. PMID: 30071984.
9. Oulis P, Konstantakopoulos G, Lykouras L, Michalopoulou P. Differential diagnosis of obsessive-compulsive symptoms from delusions in schizophrenia: A phenomenological approach. World Journal of Psychiatry. 2013; 3(3), 50. PMID: 24255875.
10. Rosli ANM, Wan Ismail WS. Comorbidity of Obsessive-Compulsive Disorder and Schizophrenia in an Adolescent. Case Reports in Psychiatry. 2015; 1–3. PMID: 26483984.
11. Hwang MY, Opler LA. Schizophrenia with obsessive-compulsive features: Assessment and treatment. Psychiatric Annals 1994;24(9), 468–72.
12. Scotti-Muzzi E, Saide OL. Schizo-obsessive spectrum disorders: an update. CNS Spectrums. 2016;22(03), 258–272. PMID: 27669819.
13. Faragian S, Fuchs C, Pashinian A, Weizman R, Weizman A, Poyurovsky M. Age-of-onset of schizophrenic and obsessive-compulsive symptoms in patients with schizo-obsessive disorder. Psychiatry Research. 2012;197(1-2), 19–2. PMID: 22436351.

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Received for publication: 08.01.2020
Accepted in revised form: 08.03.2021

NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2022, vol 31, n.º 1

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):64-67. doi:10.25753/BirthGrowthMJ.v31.i1.20729

CASE REPORTS

A rare cause of axillary swelling

Uma causa rara de tumefação axilar

Mafalda Moreira[1], Sónia Pinto Pereira[1], Ana Sofia Marinho[2], Berta Bonet[2], Sandra Teixeira[1]

ABSTRACT

Axillary swelling is a common condition in pediatric age. The most common diagnosis is lymph node swelling, but it can also be caused by soft tissue tumors, vascular lesions, or inflammation of sweat glands. In rare cases, it can be due to ectopic breast tissue (EBT).

A 14-year-old female presented with right axillary pain with one year of evolution and swelling for the past two months, gradually increasing in size, especially during menstruation. Sonography revealed EBT in both axillae, and further study showed duplication of the excretory system in both kidneys. The tissue on the right axilla was excised.

EBT should be considered in the differential diagnosis of axillary swelling in adolescents and young females. When the diagnosis is established, the presence of associated urologic anomalies should be investigated. Clinicians should be aware that EBT can undergo the same pathological changes as normally located breast tissue. Surgical removal should be considered for cosmetic and prophylactic treatment.

Keywords: axillary swelling; ectopic breast tissue; surgical excision; urologic anomaly

RESUMO

A tumefação axilar é um problema comum em idade pediátrica. O diagnóstico mais frequente é linfadenopatia, mas tumores dos tecidos moles, lesões vasculares, ou hidradenite são também diagnósticos possíveis. Em casos raros, a condição pode ser causada por tecido mamário ectópico (TME).

Uma adolescente de 14 anos foi avaliada por dor na região axilar direita durante o último ano e tumefação nos últimos dois meses, com aumento gradual de tamanho, especialmente durante a menstruação. A ecografia evidenciou TME em ambas as axilas e o estudo complementar revelou duplicação do sistema excretor renal bilateralmente. O tecido axilar direito foi excisado.

O TME deve ser considerado no diagnóstico diferencial de tumefações axilares em adolescentes e jovens adultas. Perante confirmação do diagnóstico, devem ser investigadas malformações nefro-urológicas associadas. Os clínicos devem ter presente que o TME pode estar sujeito às mesmas transformações que o tecido mamário corretamente localizado. A remoção cirúrgica deve ser equacionada por razões estéticas e profiláticas.

Palavras-chave: alteração urológica; excisão cirúrgica; tecido mamário ectópico; tumefação axilar

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INTRODUCTION

Axillary swelling is a usual cause of concern among children and adolescents and their parents, frequently requiring medical observation. The most common diagnosis is lymph node swelling, caused by lymphadenitis or lymphoma. Rarely, it can also be caused by soft tissue tumors (as rhabdomyosarcoma, lipoma, or fibroma), vascular lesions (as angiodysplasia or aneurysms), or inflammation of the sweat glands,[1-5] and by ectopic breast tissue (EBT), an undervalued diagnosis. EBT usually develops as a slowly growing mass and is most commonly identified in young women, with a few cases in the literature reported in adolescents.[1,6]

CASE DESCRIPTION

A healthy 14-year-old girl presented in consultation with pain in the right axilla with one year of evolution and swelling for the past two months, gradually increasing in size, especially during menstruation. She had the menarche at the age of ten years and used to razor-shave the axillae. The girl denied other associated symptoms and had no relevant family medical history. On examination, a 4 x 4-cm swelling without inflammatory signs, poorly marginated, freely mobile, and slightly painful on palpation was noted (**Figure 1**). No changes were identified in both breasts or left axilla. The initial differential diagnoses were hidradenitis and lymphadenitis. Further study through sonography of the region detected the presence of mammary tissue in both axillae **(Figure 2)** and allowed to establish the diagnosis of ectopic breast tissue (EBT). Given this diagnosis, an abdominal ultrasound was performed to search for associated nephron-urologic anomalies, which revealed a parenchymal septum dividing the two sinusal regions in both kidneys, compatible with duplication of the excretory systems. Due to associated pain and cosmetic reasons, excision of the ectopic tissue of the right axilla was performed, followed by macroscopic and histological confirmation of the diagnosis of EBT. The girl maintains regular clinical surveillance of the left axilla.

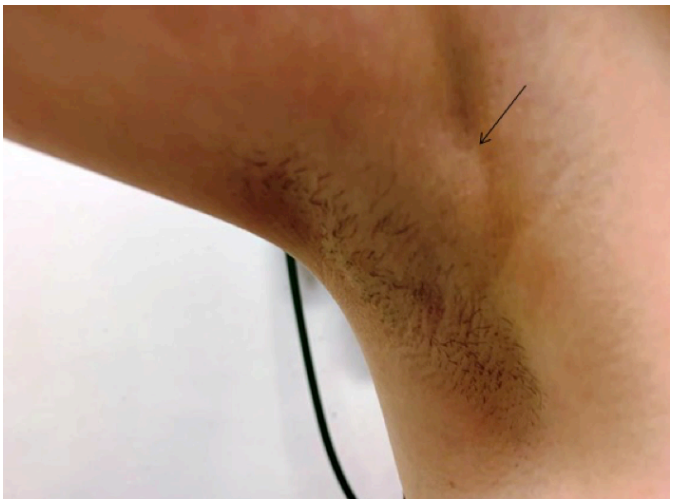

Figure 1 - Slight swelling in right axilla

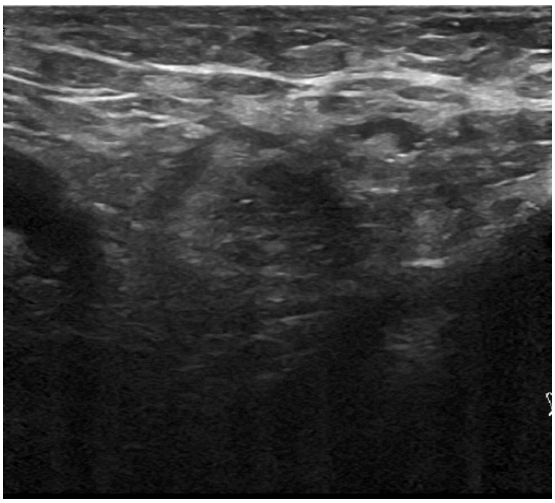

Figure 2 - Sonography revealing mammary tissue in axilla

DISCUSSION/CONCLUSIONS

EBT, or accessory breast tissue, is an uncommon entity affecting 2–6% of females and 1–3% of males,[1,4, 5,7-10] more frequently diagnosed in Asian people (prevalence of 5% in the Japanese vs. 0.6% in the Caucasian population).[3,9,10] It presents bilaterally in two-thirds of cases and in the axillae in 70% (other possible locations are the vulva and groin).[1,3-5,7,11,13] The condition usually occurs sporadically, but a hereditary predisposition has been reported.[3,5,13,14] Because EBT is under the same hormonal influence as normal breast tissue, it usually appears during periods of hormonal stimulation, as menstruation, pregnancy, and lactation.[1-3,5,8,14,15] In the present case, the condition developed in a girl younger than usually reported.

EBT results from an error during embryonic development. During the 6th week, the mammary ridges originate pairs of mammary glands, all of which involute around the third month, except one.[1,2,5,8,14,15] When more than one pair remains, the condition is named polymastia (presence of accessory glandular tissue) or polythelia (if supernumerary nipples are present).[1,4,5,13-15] In 1915, Kajava devised a classification system of polymastia that is still used nowadays, in which Class I concerns complete breast, with glandular tissue, nipple, and areola; Class II only glandular tissue and nipple, with no areola; Class III only glandular tissue and areola, with no nipple; Class IV only

glandular tissue; Class V only nipple and areola, with no glandular tissue; Class VI only the nipple (also designated as polythelia); Class VII only the areola; and Class VIII only a patch of hair.[12,14] The present case falls into class IV.

Due to concomitant development of the mammary structure and genitourinary system, the association of EBT and urological anomalies such as supernumerary kidneys, failure of renal development, renal adenocarcinoma, hydronephrosis, and ureteric stenosis has been reported.[3-5,8] For this reason, abdominal sonography should be performed as soon as the diagnosis is confirmed. In this case, this exam revealed a duplication of the excretory system in both kidneys.

The clinical presentation is variable. The most common symptoms are swelling of the affected region with associated pain, discomfort, and restriction of movements, which are exacerbated during menstruation and pregnancy.[2-4,8,12,13,15] Some women also complain of cosmetic problems, which may lead to psychological disturbances, especially in adolescence.[8,9,14] Physical examination should include the contralateral breast since the condition is bilateral in most cases.[1,3,7]

Sonographic examination is key for diagnosis, allowing the identification of a hypoechoic septate tissue similar to orthotopic mammary tissue. In addition, proper mass characterization is also relevant and should include shape, borders, internal components, vascularity, and relationship with adjacent tissues.[5,10] Magnetic resonance imaging can be required in some cases and typically shows an ill-defined subcutaneous mass.[2,3,6,8,14]

Some authors consider surgical removal as the treatment of choice, either for esthetic reasons or prophylactically to prevent the development of potential complications, like fibroadenoma or carcinoma.[1,3-5,8,10,13] However, potential surgical complications, such as contour irregularity, seroma, or recurrence, should also be weighted in the treatment decision.[4,12] In the present case, due to pain and cosmetic concerns, the option was to remove the ectopic tissue on the right axilla. In addition, the patient was kept on regular medical surveillance and advised to perform self-examination of the left axilla.

With this case, the authors intend to emphasize the importance of considering EBT in the differential diagnosis of axillary swelling in adolescents. Despite being a rare condition, the pathological and psychological problems associated with the condition require investigation and monitoring.

TAKE-HOME MESSAGES

The diagnosis of EBT (ectopic breast tissue) should be considered in adolescents and young women presenting with axillary swelling, particularly in those with menstrual cycle changes.

Abdominal ultrasound should be performed at diagnosis due to the acknowledged association between EBT and urologic anomalies.

Similarly to normally located breast tissue, EBT can undergo pathological changes, such as inflammation, fibrosis, fibroadenoma, and carcinoma, requiring continuous surveillance.

Some authors argue in favor of surgical removal for cosmetic and prophylactic reasons.

AUTHORSHIP

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Sónia Pinto Pereira - Validation; Writing - review & editing

Ana Sofia Marinho - Validation; Writing - review & editing

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REFERENCES

1. Ritter L, Sorge I, Till H, Hirsch W. Accessory Breast Tissue (Mamma Aberrata) as a Rare Differential Diagnosis of Soft Tissue Swelling in the Axilla. Fortschr Röntgenstr 2013; 185: 74-5.
2. Laor T, Collins MH, Emery KH, Donnely LF, Bove KE, Ballard ET. MRI appearance of accessory breast tissue: a diagnostic consideration for an axillary mass in a peripubertal or pubertal girl. Am J Roentgenol 2004; 183 (6):1779-81.
3. Teixeira IP, Azzopardi C, Chowdhury R, Zsolt O, Castro M, Teh J. Ectopic breast tissue presenting as an enlarging abdominal mass. Radiology Case Reports 2020; 15: 733–40.
4. Singal R, Mehta SK, Bala J, Zaman M, Mittal A, Gupta G, *et al*. A Study of Evaluation and Management of Rare Congenital Breast Diseases. Journal of Clinical and Diagnostic Research 2016; 10(10): PC18-24.
5. Surd A, Mironescu A, Gocan H. Fibroadenoma in axillary supernumerary breast in a 17 years old girl: case report. Journal of Pediatric and Adolescent Gynecology 2016.
6. Navarro O. Soft Tissue Masses in Children. Radiologic Clinics of North Americ 2011; 49(6): 1235–59.
7. Burdick AE, Thomas KA, Welsh E, Powell J, Elgart GW. Axillary polymastia. Journal of the American Academy of Dermatology 2003; 49(6): 1154-6.
8. Kogut M, Bider M, Enk A, Hassel JC. Axillary Accessory Breast Tissue – Case Report and Review of Literature. Journal der Deutschen Dermatologischen Gesellschaft 2014.
9. Seifert F, Rudelius M, Ring J, Gutermuth J, Andres C. Bilateral axillary ectopic breast tissue. The Lancet 2012; 380: 835.
10. Gentile P, Izzo V, Cervelli V. Fibroadenoma in the Bilateral Accessory Axillary Breast. Aesth Plast Surg 2010; 34:657–9.
11. Guray M, Sahin AA. Benign breast diseases: classification, diagnosis and management. Oncologist 2006; 11(5):425-49.
12. Patel P, Ibrahim A, Zhang J, Nguyen JT, Lin SJ, Lee BT. Accessory

Breast Tissue. Eplasty 2012; 12: ic5.
13. Alghamdi H, Abdelhadi M. Accessory Breasts: When to Excise? The Breast Journal 2005; 11(2): 155–7.
14. Amaranathan A, Balaguruswamy K, Bhat RV, Bora MK. AN Ectopic Breast Tissue Presenting with Fibroadenoma in Axilla. Case Reports in Surgery 2013.
15. Waldman RA, Finch J, Grant-Kels JM, Whitaker-Worth D. Skin diseases of the breast and nipple - Benign and malignant tumors. J Am Acad Dermatol 2019; 80: 1467-81.

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Received for publication: 19.08.2020
Accepted in revised form: 30.04.2021

NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2022, vol 31, n.º 1

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):68-72. doi:10.25753/BirthGrowthMJ.v31.i1.23848

CASE REPORTS

Maculopapular cutaneous Mastocytosis

Mastocitose cutânea maculopapular

Crisbety Pinho[1], Inês Barreto[1], Sandra Rebimbas[2], Sónia Coelho[3]

ABSTRACT

Mastocytosis is a rare disorder caused by proliferation and accumulation of mast cells in various tissues, with characteristic symptoms associated with the release of their mediators. Its cutaneous form, usually benign, is the most frequent among children.

The authors report the case of a two-month-old male infant who presented to the Emergency Department with small, tan-to-brown macules and papules distributed mainly on the trunk, which progressively became nodular and bullous, with one month of evolution. Darier´s sign was positive.

The absence of systemic signs and analytic (including serum tryptase level) and echographic changes was consistent with the diagnosis of maculopapular cutaneous mastocytosis, or *urticaria pigmentosa*, subsequently confirmed by skin biopsy.

Treatment with anti-histaminic therapy and topical immunosuppressant and avoidance of triggering factors led to a positive outcome.

Keywords: Darier; mastocytosis; Pediatrics

RESUMO

A mastocitose é uma doença rara causada por proliferação e acumulação de mastócitos em vários tecidos, com sintomas característicos associados à libertação dos seus mediadores. A forma cutânea, habitualmente benigna, é a mais comum entre as crianças.

Os autores descrevem o caso de um lactente do sexo masculino com dois meses de idade admitido no Serviço de Urgência por lesões maculares e papulares, pequenas, de coloração castanha-avermelhada, distribuídas principalmente pelo tronco, que progressivamente se tornaram nodulares e bolhosas, com um mês de evolução. O sinal de Darier foi positivo.

A ausência de sintomas sistémicos e alterações analíticas (incluindo nos níveis de triptase sérica) e ecográficas foi consistente com o diagnóstico de mastocitose cutânea maculopapular, ou *urticaria pigmentosa*, subsequentemente confirmado através de biópsia da lesão.

O tratamento com anti-histamínicos e imunossupressor tópico e a evicção de fatores desencadeantes conduziram a uma evolução positiva.

Palavras-chave: Darier; mastocitose; Pediatria

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INTRODUCTION

Mastocytosis refers to a heterogeneous group of diseases characterized by atypical mast cell proliferation and accumulation in one or more organs, together with the release of inflammatory mediators with local and systemic effects.[1,2]

Although the condition's etiopathogenesis is uncertain, in some cases it is associated with mutations in c-KIT (mast/stem cell growth factor receptor), leading to increased receptor function and consequent proliferation and accumulation of mast cells.[1-3] The most commonly described c-KIT mutation is D816V in exon 17, accounting for the substitution of valine for aspartate in codon 816. This mutation is present in 80% of mastocytosis cases in adults and only 35% in children, with the latter having other c-KIT mutations in 40% and no mutation in 25% of cases.[4,5] Although c-KIT mutations seem to play a central role in mastocytosis, the fact that some (adult and pediatric) patients present no mutations suggests that other, yet undetermined, factors play a role in clinical presentation.

In childhood-onset mastocytosis (which accounts for approximately two-thirds of cases), the disease usually begins in the first year of life (60-80% of cases), most commonly in the first six months, and the vast majority (80%) refer to cutaneous forms.[1,4-6] A systematic review of 1,747 cases reported a preponderance of male gender (male-to-female ratio of 1.4).[4]

Although a considerable proportion of cases are benign and tend to regress by adolescence, up to 30-50% present with extensive cutaneous forms.[1,7] A recently published review reported regression of cutaneous lesions in 67% of cases and stabilization in 27%, with 2–9% of cases having a fatal outcome after a median follow-up of 6 years.[4]

In adult-onset mastocytosis, other tissues, such as the bone marrow, liver, spleen, lymph nodes, and gastrointestinal tract, can be involved (systemic form), and lesions are monomorphic and smaller in size.[1,5] Although rare, systemic forms can also occur in children.[4]

CASE REPORT

A two-month-old male infant with no relevant medical history was admitted to the Emergency Department with dermatosis with one month of evolution. The condition presented as small-to-medium-sized, tan-to-reddish brown macules (the largest being around 1.5 cm in diameter) and papules, initially distributed over the lower limbs and rapidly spreading to the upper limbs, trunk, face, sparing mucous membranes, scalp, palms, and soles. In the upper and lower limbs, some lesions evolved to nodules and small plaques with around 3 cm of maximum diameter, some with blister formation (**Figures 1-3**).

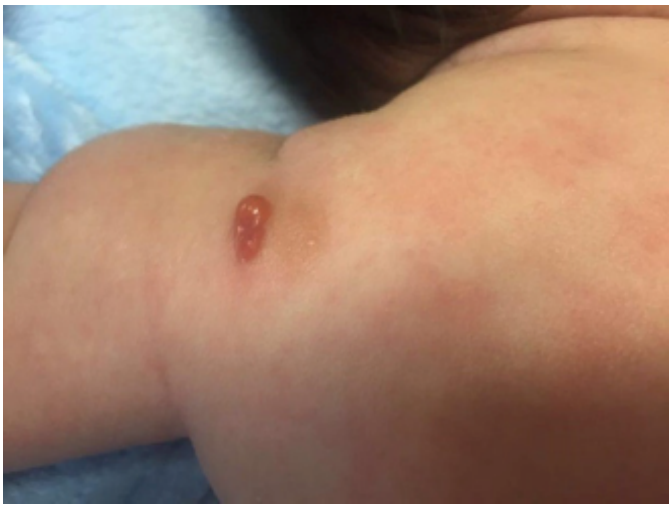
Systemic symptoms, such as dyspnea, vomiting, diarrhea, and acute anaphylactic reactions were excluded. Upon slight lesion scratching or rubbing, a wheal and flare reaction developed, known as positive Darier's sign. Exposure to physical stimuli, such as pressure (clothes), heat, and sweating, was reported as triggering factors. Lymphadenopathy, hepatosplenomegaly, or fracture signs were not identified.

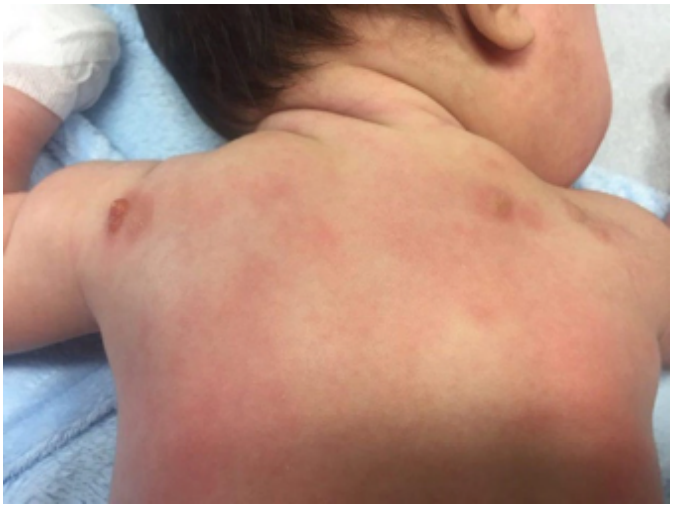
The initial laboratory study included complete blood count with differential, coagulation profile, C-reactive protein, serum electrolytes, and renal and liver function tests, which revealed no abnormal values. Abdominal and renal ultrasound were normal.

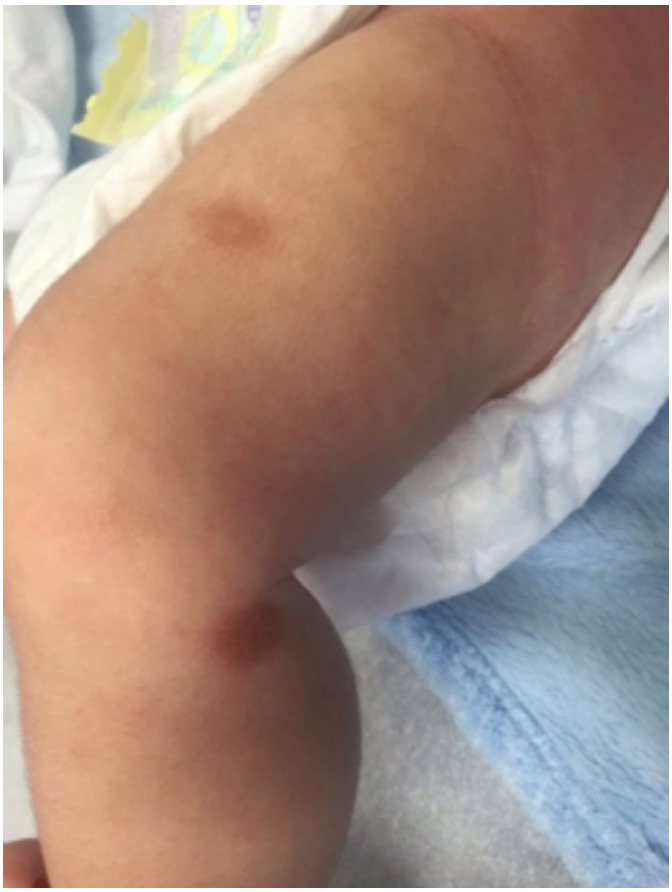
The infant was promptly referred to the Dermatology Department with clinical suspicion of cutaneous mastocytosis.

Despite the characteristic lesions and presence of positive Darier´s sign, a differential diagnosis should be performed in cases of children with macular, nodular, and/or bullous lesions. In the present case, this included bullous impetigo, bullous arthropod bite, linear IgA bullous dermatosis, incontinentia pigmenti, and bullous pemphigoid.[7]

Skin biopsy was performed in the Dermatology consultation, with histopathological staining with toluidine blue showing a dense inflammatory infiltrate of mast cells in the papillary and reticular dermis. Serum tryptase level was 6 ng/mL (reference value <11 ng/mL). The absence of systemic signs or symptoms, normal serum







Figures 1-3 - Hyperpigmented macules and nodular and bullous lesions

total tryptase level, and skin biopsy findings (dense infiltrate of mast cells in the dermis forming agglomerations) allowed to establish the diagnosis of maculopapular cutaneous mastocytosis.

The infant was treated with an oral antihistamine agent and topical immunosuppressant (tacrolimus 0.03%) twice daily. Avoidance of triggering factors, such as skin friction of lesions and exposure to hot temperatures, was recommended, including in bath. No recommendations were made regarding other triggering factors not implicated in this case (e.g., foods and medications).

Significant improvement was observed following the implementation of pharmacologic and non-pharmacologic measures, with lesions clearing up and decreasing in number. The patient is currently 25 months (23 months of follow-up) and remains on topical immunosuppressants but has discontinued antihistamines. He presents only tan macules and patches, with no new cutaneous symptoms (blistering lesions, flushes, or itch) since the age of seven months.

DISCUSSION

Based on the 2016 World Health Organization (WHO) revised classification, mastocytosis can be divided into cutaneous, systemic, or localized.[8] In the cutaneous form, firstly described in 1869 by *Nettleship* and *Tay*, the only affected organ is the skin, and three main presentations can be found: maculopapular cutaneous mastocytosis (or *urticaria pigmentosa*; 40-70%), solitary mastocytoma (20-50%), and diffuse cutaneous mastocytosis (3-8%).[4,8,9]

Cutaneous mastocytosis is usually suspected by the presence of typical skin lesions, particularly in children. Darier´s sign is the basic and most important diagnostic test and should be investigated in all patients.[5,6] It is more pronounced in children due to the higher concentration of mastocytes in the affected skin.[10]

Serum tryptase level is a marker of mast cell activity that, when increased (>20 ng/mL), suggests systemic involvement.[1,11] It directly correlates with the number of mast cells, including in bone marrow biopsy, and disease severity.[1,11,12] Serum tryptase levels tend to decrease with time in concert with improving symptoms. Carter *et al*. argue that there is value in determining their levels at 6-to-12-month intervals.[12]

Skin biopsy with histological examination with special stains, such as toluidine blue, giemsa, or monoclonal antibodies to mast cell tryptase or CD117 (KIT), typical shows mast cell infiltrates in a multifocal pattern, confirming the diagnosis.[10,13] Eosinophils are commonly found in the dermis, with hyperpigmentation of the basal layer also frequently observed.[10]

Bone marrow biopsy is usually not recommended in pediatric-onset cutaneous mastocytosis, except in the presence of systemic symptoms, analytical changes (including increased serum tryptase levels), or absence of improvement with prompt treatment.[2,6,10] Among patients with high tryptase levels (>20 ng/mL) and severe mediator symptoms, organomegaly appears to be a strong indicator of those who may require bone marrow biopsy.[12] WHO proposes a stepwise approach for the diagnosis of the condition, in which patients must have one major criterion (typical skin lesions) and one of two minor criteria (histological – multifocal dense infiltrates of mast cells [≥15 mast cells per cluster] or scattered mast cells [≥20 per high microscopic power field]) – or molecular – point mutation at codon 816 of c-KIT in the affected skin tissue) to be diagnosed with cutaneous mastocytosis.[5,10,14]

Management of cutaneous mastocytosis includes counseling parents about the disease pathophysiology and the importance of avoiding possible mast cell degranulation triggers.[15] Treatment of cutaneous lesions is mainly symptomatic and has only recently been proposed, with no specific treatments available until now.[15]

Topical medications include glucocorticoids, which may reduce the number of lesions if applied once daily over 8-12 weeks.[10] Topical calcineurin inhibitors applied twice daily may reduce mast cell degranulation by inhibiting T-cell activation and cytokine release, offering a safe alternative to glucocorticoids.[10]

Chronic administration of oral antihistamines (the mainstay of

treatment) is often useful in reducing cutaneous and gastrointestinal symptoms, with oral cromolyn sodium specifically used for the latter.[10] Other systemic therapies, such as oral corticosteroids or narrow-band ultraviolet B, can also be used in children in selected cases.[10]

In conclusion, the present report described the case of a two-month-old boy with macular and nodular lesions (some with bullous formation) and positive Darier´s sign, suggestive of cutaneous mastocytosis, which was later confirmed by skin biopsy. The absence of systemic symptoms and normal laboratory tests (including serum tryptase levels) excluded the systemic form of the condition. The use of a topical immunosuppressant, a member of the calcineurin inhibitor class, led to significant lesion improvement a few months later, with no serious adverse effects. Some reports of this treatment can be found in the literature, with the largest case series of 18 patients supporting its use.[15] Treatment duration until complete resolution was two to nine months in previously reported cases, and eight months in the above-mentioned largest case series.[15] In the present case, a favorable outcome was achieved after 23 months of follow-up. Although the child presented no new lesions after the first five months of treatment, topical treatment was kept due to the association of longer treatment with an increased likelihood of lesion resolution.[15]

Some predictors of prognosis have been put forward but not fully confirmed, including diagnosis before the age of two years, clinical improvement with treatment, and absence of systemic signs (as in the present case).[4,7]

AUTHORSHIP

Crisbety Pinho - Infant´s follow-up ; Bibliographic research; Writing - original draft; Writing - review & editing

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REFERENCES

1. Castells M, Metcalfe D, Escribano L. Guidelines for the Diagnosis and Treatment of Cutaneous Mastocytosis in Children. Am J Clin Dermatol 2011; 12(4): 259–70.
2. Tamay Z, Özçeker D. Current approach to cutaneous mastocytosis in childhood. Turk Pediatri Ars 2016; 51(3): 123–7.
3. Pardanani A. CME Information: Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. Am J Hematol 2016; 91(11): 1146–59.
4. Méni C, Bruneau J, Georgin-Lavialle S, Le Saché de Peufeilhoux L, Damaj G, Hadj-Rabia S, *et al.* Paediatric mastocytosis: a systematic review of 1747 cases. Br J Dermatol 2015; 172(3): 642–51.
5. Hartmann K, Escribano L, Grattan C, Brockow K, Carter M. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol 2016; 137(1): 35–45.
6. Klaiber N, Kumar S, Irani A-M. Mastocytosis in Children. Curr Allergy Asthma Rep 2017; 17(80).
7. Tarjuelo DV, Majlis PZ, Ortiz LB, Hermosa JMH. Mastocitosis cutánea. Acta Pediatr Esp 2007; 65(6): 282–5.
8. Valent P, Aki C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017; 129(11): 1420–7.
9. Matito A, Azaña JM, Torrelo A, Alvarez-Twose I. Cutaneous Mastocytosis in Adults and Children: New Classification and Prognostic Factors. Immunol Allergy Clin North Am 2018; 38(3): 351–63.
10. Tharp MD. Mastocytosis. In: Kang S, Amagai M, Bruckner A L, Enk A H, Margolis D J, McMichael A J, Orringer J S, editors. Fitzpatrick´s Dermatology in General Medicine. Ninth edition. McGraw-Hill Education; 2019. p. 710-22.
11. Alvarez-Twose I, Vañó-Galván S, Sánchez-Muñoz L, Morgado JM, Matito A, Torrelo A, *et al.* Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. Allergy 2012; 67(6): 813–21.
12. Carter MC, Clayton ST, Komarow HD, Brittain EH, Scott LM, Cantave D, *et al.* Assessment of clinical findings, tryptase levels, and bone marrow histopathology in the management of pediatric mastocytosis. J Allergy Clin Immunol 2015; 136(6): 1673–9.
13. Alemán GM, El Habr C, Norris DI, Dámaso TM, Borrego L, Sangueza OP. Cutaneous Mastocytosis With Atypical Mast Cells in a 7-Year-Old Girl. Am J Dermatopathol 2017; 39(4): 310–2.
14. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, *et al.* Standards and standardization in mastocytosis: Consensus Statements on Diagnostics, Treatment Recommendations and Response Criteria. Eur J Clin Invest 2007; 37(6): 435–53.
15. Mashiah J, Harel A, Bodemer C, Hadj-Rabia S, Goldberg I, Sprecher E, *et al.* Topical pimecrolimus for paediatric cutaneous mastocytosis. Clin Exp Dermatol 2017; 43(5): 559–65.
16. Vaz AS, Rodrigues J, Moura L, Mascarenhas R. Early diagnosis of cutaneous mastocytosis in an infant: the importance of a clinical sign. BMJ Case Rep 2019; 12(1).

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Received for publication: 03.03.2021
Accepted in revised form: 31.05.2021

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):73-76. doi:10.25753/BirthGrowthMJ.v31.i1.19381

IMAGING CASES

Pulmonary clinical case

Caso clínico pneumológico

Catarina de Abreu Amaro[1], Pedro Protásio[2], Carlos Rodrigues[1], Sofia Ferreira[1]

A previously healthy 15-year-old male was admitted to the Emergency Department with steady and progressively worsening abdominal pain in the right lower quadrant (RLQ), accompanied by anorexia with 12 hours of evolution.

On admission, he was afebrile, and the physical examination revealed good general condition, soft abdomen with localized tenderness in RLQ without significant rigidity, and positive Blumberg and Rovsing signs. The remaining physical exam was normal. As the clinical picture suggested acute appendicitis, preoperative assessment was performed, excluding difficult airway and cardiopulmonary abnormalities.

Urgent laparoscopic appendectomy was performed under general anesthesia, without complications during endotracheal intubation or mechanical ventilation. The patient remained hemodynamically stable, with normal urine output and minimal blood loss, and 150 mL of 0.9% saline solution were administered during the unremarkable 55-minute surgical procedure.

Immediately after extubation, during which no vomit or aspiration were observed, the patient developed hypoxemia (SpO_2 82%), intense productive cough (requiring aspiration of clear frothy secretions), tachypnea, and subcostal retractions, requiring additional O_2 (FiO_2 40% using Venturi mask). Blood pressure was 135/60 mmHg, and heart rate was 70 bpm. He was sleepy yet easily awakened, with proper peripheral perfusion and normal central and peripheral pulse, no edema, and normal cardiac auscultation. Thorax expansion was symmetrical and pulmonary auscultation showed symmetrical decreased breath sounds with dispersed fine crackles. Arterial gasometry showed pH 7.36, pCO2 45 mmHg, pO_2 48 mmHg, HCO_3^- 26.8 mmol/L, and BE -0.5 mmol/L and chest radiograph revealed bilateral diffuse opacities with ill-defined edges (**Figure 1**). Cardiac evaluation was normal, showing no arrhythmias in the electrocardiogram, left ventricle overload pattern or ST-T changes, and four balanced-size chambers, normal left systo-diastolic ventricular function, normal left atrial filling pressure, normal aortic flow, and no pulmonary hypertension in transthoracic echocardiography.

Forty milligrams of intravenous furosemide were administered with the previously described oxygen supplementation, with quick clinical recovery and improvement in gasometric parameters and chest radiograph findings (**Figure 2**).

Treatment with intravenous furosemide in decreasing dosages and oxygen supplementation in decreasing flow rates were maintained for approximately 50 hours. Due to favorable evolution, the patient was discharged four days after surgery, asymptomatic and with normal chest radiography results.

What is your diagnosis?

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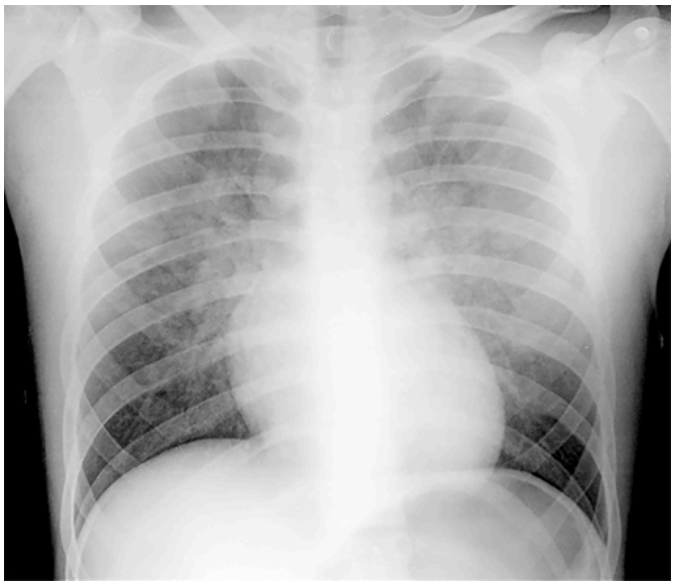

Figure 1 - Antero-posterior chest radiograph few minutes after the onset of respiratory distress, showing bilateral diffuse opacities with ill-defined edges

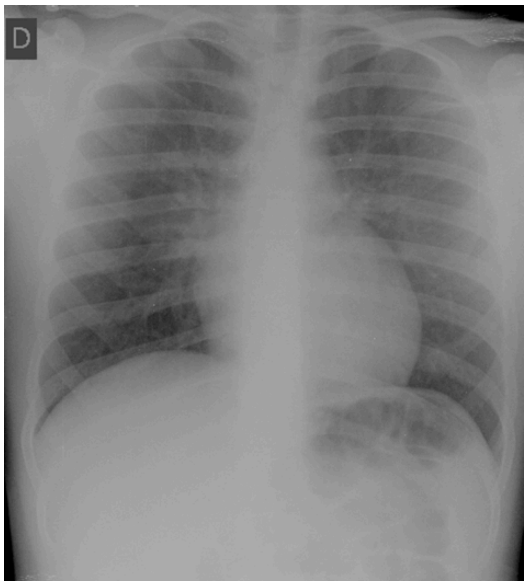

Figure 2 - Antero-posterior chest radiograph hours after starting intravenous furosemide and supplementary oxygen administration, showing reduction of bilateral diffuse opacities

DIAGNOSIS

Post-extubation acute pulmonary edema

DISCUSSION

Post-extubation acute pulmonary edema (PEAPE) is an uncommon complication of tracheal extubation, occurring in 0.1% of patients undergoing general anesthesia.[1-4] It has rarely been reported in pediatric age, but the actual global incidence is thought to be underestimated, as many cases of postoperative respiratory distress may be misdiagnosed or unrecognized.[1,2]

PEAPE has a multifactorial etiology. The main triggering factor is secondary to upper airway obstruction caused by laryngospasm resulting from an exaggerated and prolonged laryngeal closure reflex, triggered by the mechanical stimuli of pharynx or larynx manipulation (like in the extubation procedure).[1,3-5-8,9] The deep inspiratory effort against a closed glottis generates high negative intra-thoracic pressure transmitted to the lungs, leading to fluid transudation from pulmonary vessels to the interstitium and alveoli.[1,3-5-8] At the same time, afterload and preload of the left ventricle increase worsening fluid transudation, finally resulting in the typical signs and symptoms of acute pulmonary edema.[1,3,4,6] Moreover, pulmonary vasoconstriction caused by hypoxia and marked release of catecholamines associated with hypoxemia and hypercapnia (caused by upper airway obstruction) also contribute to this type of acute pulmonary edema.[1,8]

Well-developed thoracic and abdominal muscles are mentioned as risk factors for this complication, explaining its higher incidence in healthy young individuals, capable of generating very high intrathoracic pressure.[1-3,5,6] Other factors may also contribute, including obesity, short neck, sleep apnea, nasopharyngeal pathology, and smoke, neither observed in the present case.[1,3,5,6]

In agreement with the present case, PEAPE mostly occurs immediately after tracheal extubation, with immediate onset of respiratory distress.[1-3,6] However, delayed presentation (up to 24 hours post airway obstruction relief) has also been reported.[1,2,4,6,7,10] The presence of tachypnea, tachycardia, dyspnea, intense cough, sometimes pink frothy bronchial secretions, progressive oxygen desaturation, and basal/widespread rales or fine crackles and ronchi on chest auscultation suggests PEAPE diagnosis in the appropriate setting, as in this case.[2,4,5,7]

This diagnosis requires a high index of suspicion, as the presentation mimics aspiration pneumonia, pulmonary thromboembolism, anaphylaxis, myocardial dysfunction, and other causes of pulmonary edema, including cardiogenic, opioid-induced, neurogenic, and iatrogenic fluid overload.[1-5,7,10]

As observed in this case, chest radiograph shows rapid bilateral changes compatible with pulmonary edema, including diffuse interstitial and alveolar infiltrates and should be performed to confirm the diagnosis and exclude other causes of postoperative acute respiratory distress, particularly aspiration pneumonia.[1,2,4,5,7]

In the present case, the patient's past medical history, course in the operating room, with low fluid infusion volume, and clinical and radiological findings, together with cardiac assessment excluding

cardiogenic etiology, were consistent with post-extubation acute pulmonary edema.

If promptly diagnosed and managed, most PEAPE cases resolve within 3-48 hours, as observed in this case.[2,3,4,8,10] Treatment includes maintaining the airway and providing supplemental oxygen, with the addition of positive end-expiratory pressure or continuous positive airway pressure (guided by physical examination, pulse oximetry, and arterial blood gas determination), which significantly reduces increased breathing work and ventricular afterload and helps in alveoli recruitment [1-4 8,10] In severe cases, invasive mechanical ventilation may be necessary.[2-4] Although diuretics are often used, their role in PEAPE treatment is unclear, and their use is thus controversial.[4,7,10] Despite that, the present patient was successfully treated with furosemide, like in other similar previous reports, probably due to "direct" vascular effects occurring apart from its primary diuretic action, contributing to pulmonary edema resolution regardless of fluid balance.[2,4,7,11] Elevated catecholamine levels are thought to accelerate the rate of alveolar fluid clearance in PEAPE.[8] However, since vascular pressure may be high, diuresis is unlikely to be harmful (provided that vascular status and renal function are normal), and enhances pulmonary edema resolution, as in this case.[8]

PEAPE is an uncommon but relevant anesthesia-related emergency, which may worsen the prognosis of low-risk surgical procedures.[3] This case highlights the importance of keeping a high degree of suspicion in children and adolescents presenting with signs of respiratory distress and hypoxia after general anesthesia, as prompt diagnosis and treatment are crucial for a favorable outcome.

ABSTRACT

Post-extubation acute pulmonary edema (PEAPE) is an uncommon complication of tracheal extubation, occurring in 0.1% of patients undergoing general anesthesia. It has rarely been described in pediatric age, but its incidence is thought to be underestimated, as many cases of post-operative respiratory distress may be misdiagnosed or unrecognized.

A formerly healthy 15-year-old male diagnosed with acute appendicitis was submitted to a laparoscopic appendectomy under general anesthesia. Immediately after extubation, he developed signs and symptoms of respiratory distress, and chest radiograph was compatible with acute pulmonary edema. Due to suspicion of PEAPE, supplementary oxygen and intravenous furosemide were administered, with favorable outcome.

PEAPE is a major anesthesia-related emergency, which may worsen the prognosis of low-risk surgical procedures.

A high degree of suspicion should be maintained in children and adolescents presenting with signs of respiratory distress and hypoxia after general anesthesia, as prompt diagnosis and treatment are crucial for a favorable outcome.

Keywords: acute pulmonary edema; acute respiratory distress; adolescent; extubation; pulmonary edema

RESUMO

O edema pulmonar agudo pós-extubação (EPAPE) é uma complicação rara da extubação traqueal, que ocorre em 0,1% dos doentes submetidos a anestesia geral. Raramente é reportado em idade pediátrica, embora a sua incidência esteja previsivelmente subestimada devido a erros diagnósticos/não reconhecimento de muitos casos de dificuldade respiratória em contexto pós-operatório.

Um rapaz de 15 anos previamente saudável, diagnosticado com apendicite aguda, foi submetido a apendicectomia laparoscópica sob anestesia geral. Imediatamente após a extubação, desenvolveu sinais e sintomas de dificuldade respiratória, e a radiografia do tórax foi compatível com edema agudo do pulmão. Perante suspeição de EPAPE, foi administrado oxigénio suplementar e furosemida endovenosa, com evolução favorável.

O EPAPE é uma importante emergência médica relacionada com a anestesia, que pode agravar o prognóstico de procedimentos cirúrgicos de baixo risco.

É importante relembrar este diagnóstico em crianças e adolescentes que apresentem sinais de dificuldade respiratória e hipóxia após anestesia geral, dado que um rápido diagnóstico e tratamento são essenciais para uma evolução favorável.

Palavras-chave: adolescente; dificuldade respiratória aguda; edema pulmonar agudo**;** edema pulmonar; extubação

AUTORSHIP

Catarina de Abreu Amaro - Involved in the clinical management of the patient; Revision of the literature; Drafting of the article

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Sofia Ferreira - Involved in the clinical management of the patient; Revision of the literature; Reviewing of the article; Final revision and approval of the article

REFERENCES

1. Castro ML, Chaves P, Canas M, Moedas ML. Edema agudo do pulmão post-extubação traqueal – Caso clínico. *Rev Port Pneumol*. 2009; 15(3):537-41.
2. Zurda T, Muzha D, Dautaj B, Kurti B, Marku F, *et al.* Acute postoperative negative pressure pulmonary edema as

complication of acute airway obstruction: case report. *J Anesth Clin Res*. 2016; 7:603.

3. Perez RO, Bresciani C, Jacob CE, Perez CG, Coser RB, *et al.* Negative pressure post-extubation pulmonary edema complicating appendectomy in a young patient: case report. *Curr Surg*. 2004; 61(5):463-5.
4. Udeshi A, Cantie SM, Pierre E. Postobstructive pulmonary edema. *J Crit Care*. 2010; 25:508e1-508.e5.
5. Ricardo J, Anarya MJ, Barbosa M, André N, Magno P, *et al.* Forma rara de edema pulmonar agudo: a propósito de um caso clínico. *Rev Port Cardiol*. 2011; 30(10):799-801.
6. Mulkey Z, Yarbrough S, Guerra D, Roongsritong C, Nugent K, Phy MP. Postextubation pulmonary edema: a case series and review. *Respir Med.* 2008; 102(11):1659-62.
7. Bhaskar B, Fraser JF. Negative pressure pulmonar edema revisited: pathophysiology and review of management. *Saudi J Anaesth.* 2012; 5(3):308-13.
8. Bhattacharya M, Kallet RH, Ware LB, Matthay MA. Negative-pressure pulmonary edema. *Chest.* 2016; 150(4):927-33.
9. Orliaguet GA, Gall O, Savoldelli GL, Couloigner V. Case scenario: Perianesthetic management of laryngospasm in children. *Anesthesiology*. 2012; 116:458-71.
10. Bajwa SJS, Kulshrestha A. Diagnosis, prevention and management of postoperative pulmonary edema. *Ann Med Health Sci Res*. 2012; 2(2):180-5.
11. Pikkers P, Dormans TPJ, Russel FGM, Hughes AD, *et al.* Direct vascular effects of furosemide in humans. *Circulation.*1997;96:1847-52.

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Received for publication: 09.02.2020
Accepted in revised form: 24.02.2021

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):77-79. doi:10.25753/BirthGrowthMJ.v31.i1.19015

IMAGING CASES

Dermatology clinical case

Caso clínico dermatológico

Telma Luís [1], Tatiana Clemêncio[2], Lea Santos[1], Manuela Loureiro[3]

A previously healthy 17-year-old male adolescent was admitted to the Pediatric Emergency Department due to a non-itchy progressive skin eruption with four days of evolution. He mentioned history of trauma on the elbows and right ankle one week earlier and reported odynophagia and low fever (axillary temperature of 37.6ºC) in the previous week, which solved with symptomatic treatment. Other symptoms or medications were denied. No family history of autoimmune diseases was reported.

On admission, crusty abrasion lesions were present on the patient's elbows and right ankle. A well-defined erythematous plaque with adherent white scales was observed around skin lesions of the ankle (**Figure 1**). Several erythematous papular drop-like lesions, most of which with overlying scales, were observed on the trunk and limbs (**Figures 2 and 3**).

What is your diagnosis?

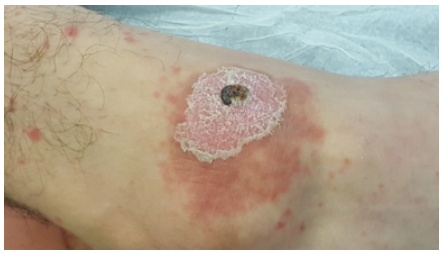
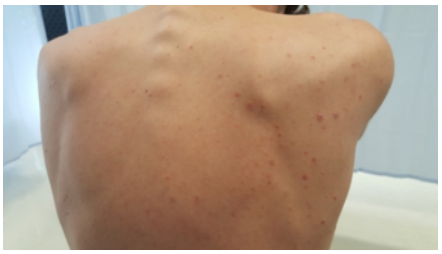
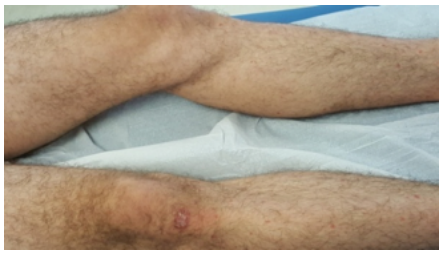


Figure 1 - Well-defined erythematous plaque with adherent white scales around the ankle crust





Figures 2 and 3 - Erythematous papular drop-like lesions, most with overlying scales, on the trunk and lower limbs

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DIAGNOSIS

Guttate psoriasis secondary to trauma (Koebner phenomenon) and upper airway infection.

The adolescent was discharged with calcipotriol/betamethasone topic treatment once a day and a skin emollient and fully recovered within a few weeks. After one year of follow-up, he remains asymptomatic and without relapse.

DISCUSSION

Guttate psoriasis is the second most common psoriasis variant in pediatric age, usually affecting patients older than five years.[1-4] It typically presents with acute onset of numerous small, erythematous, scaly papules ("drop-like lesions") and plaques with centripetal progression and symmetrical distribution. The trunk and proximal extremities are typically involved, although lesions may also occur in other locations, such as the scalp, hands, feet, and nails. The palms and soles are rarely affected.[4] Pruritus may be present. Skin eruption may present as a new-onset disorder in patients with no previous history of psoriasis or as a new psoriasis presentation in patients with preexisting chronic plaque-type disease.[5]

The interplay between genetic and environmental factors seems to account for disease development. Positive family history may be present. Streptococcal upper airway infection is a major trigger of the condition, occurring in 56-85% of cases.[4] Perianal streptococcal infection may also precede guttate psoriasis in children.[6-7] The latency period between streptococcal infection and the appearance of skin lesions is typically two to three weeks. Multiple other infectious agents have been linked to guttate psoriasis, although less frequently than *streptococcus*. Drug therapy may sometimes precipitate a guttate-type flare. The most commonly implicated medications include lithium, beta-blockers, antimalarial drugs, nonsteroidal anti-inflammatory drugs, and biologic agents.[4] Trauma is also an important trigger due to the Koebner phenomenon. In this entity, skin lesions appear at the injury site, with wound healing triggering hyperproliferative changes in the surrounding healthy skin that can lead to guttate psoriasis. Lesions usually appear 10-14 days after trauma. The Koebner phenomenon occurs in 50% of children with psoriasis.[4,8]

In the present case, both previous upper airway infection and trauma were present, which precluded the identification of the exact trigger and allowed to admit the existence of two environmental triggers.

In most cases, clinical history and physical examination are sufficient to diagnose the condition. Laboratory studies should only be required to rule out other diagnoses or identify the etiological agent. In challenging cases, a skin biopsy can be performed to support the diagnosis.

The differential diagnosis includes lichen planus, chronic lichenoides pityriasis, pityriasis rubra pilaris, pitiriasis rosea, and secondary syphilis.[4]

Guttate psoriasis may spontaneously remit, intermittently recur, or persist and progress to chronic plaque psoriasis.[7,9-11] The course of the disease is unpredictable. Disease remission is the most common course in patients lacking a preceding history of psoriasis and typically occurs over the course of several weeks to a few months.[1,7,9-11]

First-line treatments include phototherapy and topical agents (corticosteroids and vitamin D analogs, such as calcipotriol, tacalcitol, or calcitriol).[12,13] Topical agents may be used in monotherapy or combination and are usually able to control mild-to-moderate forms of the disease. Combined topical agents achieve more prolonged remission without rebound effect compared to corticosteroid monotherapy. Topical monotherapy or combined therapy should be used once to twice daily for around two weeks, although longer periods can be required. Low-potency corticosteroids are typically used on atrophy-prone sites, such as the face and intertriginous areas. Topical calcineurin inhibitors may alternatively be used in these thinner skin areas.[14] Medium-to-high-potency corticosteroids are indicated for lesions on the trunk and extremities. Vitamin D analogs should be applied on the skin at night and cleared in the morning to avoid triggering sun hypersensitivity. Cutaneous irritation is the most common adverse effect of these agents, which should thus be avoided in the face and flexures.[4] Phototherapy or even heliotherapy should be considered in cases of widespread lesions (when application of topical agents is unfeasible) or lesions refractory to topical therapy.[4] Moderate-to-severe cases may require combining phototherapy and topical agents.[4] Systemic immunomodulatory and immunosuppressive therapies used in chronic plaque psoriasis may also be attempted in patients with severe or persistent disease that fails to respond to first-line therapies.[12,15] An emollient cream should always be used despite the selected therapy option.[4] Patients with an active source of streptococcal infection should also be treated with antibiotic therapy.

This report highlights the importance of considering the clinical diagnosis of guttate psoriasis (a frequent psoriasis variant in pediatric ages) in cases of widespread skin eruption after trauma and/or infection, avoiding unnecessary exams.

ABSTRACT

The case of a teenager with guttate psoriasis secondary to trauma and upper airway infection is reported. Guttate psoriasis is the second most common psoriasis variant in pediatric age. Infection and trauma (leading to Koebner phenomenon) seem to be major triggers of the condition. The diagnosis is clinical. Most cases with no previous history of psoriasis spontaneously remit. Topical corticosteroids and vitamin D analogs, as well as phototherapy, are the first-line treatments.

Keywords: guttate psoriasis; infection; Koebner phenomenon; trauma

RESUMO

É descrito um caso de psoríase guttata secundária a traumatismo e infeção respiratória superior num adolescente. A psoríase guttata é a segunda variante mais frequente de psoríase em idade pediátrica. Infeção e traumatismo (com consequente fenómeno de Koebner) parecem ser fatores desencadeantes importantes desta condição. O diagnóstico é clínico. A maioria dos casos sem história prévia de psoríase sofre remissão espontânea. Corticoides e análogos da vitamina D tópicos, bem como fototerapia constituem o tratamento de primeira linha.

Palavras-chave: fenómeno de Koebner; infeção; psoríase guttata; traumatismo

AUTORSHIP

Telma Luís - Resources; Writing (drafting the initial manuscript and reviewing of the manuscript)

Tatiana Clemêncio - Writing (drafting the initial manuscript and reviewing of the manuscript)

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REFERENCES

1. Ko HC, Jaw SW, Song M, Kim MB, Kwon KS. Clinical course of guttate psoriasis: long-term follow-up study. J Dermatol 2010; 37:894.
2. Ferrándiz C, Pujol RM, García-Patos V, Bordas X, Smandía JA. Psoriasis of early and late onset: a clinical and epidemiologic study from Spain. J Am Acad Dermatol 2002; 46:867.
3. Kwon HH, Kwon IH, Youn JI. Clinical study of psoriasis occurring over the age of 60 years: is elderly-onset psoriasis a distinct subtype? Int J Dermatol 2012; 51:3.
4. Romiti R, Arnone M, Maragno L, Takahashi MDF. Psoríase na infância e na adolescência. Na Bras Dermatol. 2009; 84:9-22.
5. Mallon E, Bunce M, Savoie H, Rowe A, Newson R, Gotch F, *et al*. HLA-C and guttate psoriasis. Br J Dermatol 2000; 143:1177.
6. Norrlind R. Psoriasis following infections with hemolytic streptococci. Acta Derm Venereol 1950; 30:64.
7. Prinz JC. Psoriasis vulgaris -a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. Clin Exp Dermatol 2001; 26:326.
8. Rigopoulos D, Gregoriou S, Katrinaki A, Korfitis C, Larios G, Stamou C, et al. Characteristics of psoriasis in Greece: an epidemiological study of a population in a sunny Mediterranean climate. Eur J Dermatol 2010; 20:189.
9. Mercy K, Kwasny M, Cordoro KM, Menter A, Tom W. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. Pediatr Dermatol 2013; 30:424.
10. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? Arch Dermatol 1996; 132:717.
11. Williams RC, McKenzie AW, Roger JH, Joysey VC. HL-A antigens in patients with guttate psoriasis. Br J Dermatol 1976; 95:163.
12. Chalmers RJ, O'Sullivan T, Owen CM, Griffiths CE. A systematic review of treatments for guttate psoriasis. Br J Dermatol 2001; 145:891.
13. Mason AR, Mason J, Cork M, Dooley G, Edwards G. Topical treatments for chronic plaque psoriasis. Cochrane Database Syst Rev 2009; CD005028.
14. Malecic N, Young H. Tacrolimus for the management of psoriasis: clinical utility and place in therapy. Psoriasis (Auckl) 2016; 6:153-63.
15. Chalmers RJ, O'Sullivan T, Owen CM, Griffiths CE. Interventions for guttate psoriasis. Cochrane Database Syst Rev 2000; CD001213.

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Received for publication: 06.12.2019
Accepted in revised form: 04.03.2021

NASCER E CRESCER
BIRTH AND GROWTH MEDICAL JOURNAL
year 2022, vol 31, n.º 1

Nascer e Crescer - Birth and Growth Medical Journal
2022;31(1):80-82. doi:10.25753/BirthGrowthMJ.v31.i1.21324

IMAGING CASES

Persistent fever and hemoptoic sputum – clinical case

Febre persistente e expectoração hemoptóica – caso clínico

Sara Mosca[1], Adriana Magalhães[2], Isabel Couto Guerra[1], Inês Azevedo[3,4,5]

A 15-year-old female teenager with Chiari type I malformation (a pathogenic microdeletion of the chromosome 16 – 16p13.11 microdeletion syndrome – associated with global development delay) presented to the Emergency Department (ED) with a history of fever with 24 hours of evolution. She had choked with an olive pit the day before, saying that it was spontaneously expelled through coughing. Despite the absence of respiratory signs or symptoms and possible non-radiopaque nature of the foreign body, expiratory chest radiograph and abdominal x-ray were performed, showing no changes, and the girl was discharged with the probable diagnosis of viral infection. Eleven days later, she returned to the ED with persistent fever, dysphagia, and productive cough with hemoptoic sputum. On admission, she presented nasal obstruction and crackles and decreased lung sounds on the right hemithorax. No hypoxia, respiratory distress, or expiratory stridor were identified. Laboratory assessment revealed leucocytosis (14,670/µL) with neutrophilia (11,190/µL) and increased C-reactive protein (250 mg/L), and chest x-ray showed a small-volume pneumomediastinum and a less prominent right cardiac silhouette, suggesting condensation on the right lower lobe (**Figure 1A**).

What is your diagnosis?

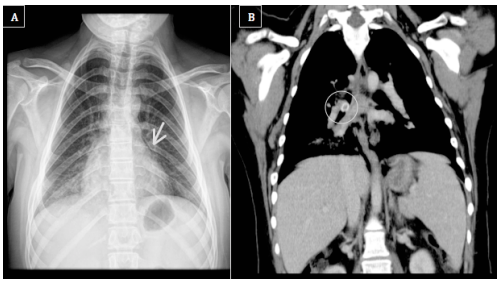

Figure 1 – Radiological and Computed tomography findings
A- Chest x-ray revealing a small pneumomediastinum and a less prominent right cardiac silhouette ; B –Chest computed tomography (CT) scan showing intermedius bronchus obstruction.

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DIAGNOSIS

Foreign body aspiration

DISCUSSION

In the present case, chest computed tomography (CT) scan revealed an obstruction of the bronchus intermedius by a foreign body (**Figure 1B**). Rigid bronchoscopy was later performed with extraction of an olive pit. The patient had favorable clinical outcome after a full 10-day treatment course with amoxicillin and clavulanic acid and prednisolone.

The clinical findings, complementary exam results, and favorable outcome in this case confirmed the diagnosis of foreign body aspiration (FBA) with pneumonia.

FBA is a relevant concern in pediatric age, particularly in children under the age of five years and in vulnerable children, like those with global development delay or neuromuscular disorders.[1-5] The girl in the present case had Chiari type I malformation and 16p13.11 microdeletion syndrome, with global development delay, thus having a high risk of FBA.[6] Besides potentially life-threatening, FBA can remain undetected due to absent or atypical history and misleading clinical and/or imagiological findings. It is not uncommon to find patients treated for suspicion of other disorders, such as infectious diseases, asthma, or psychiatric conditions.[2] A high index of clinical suspicion, combined with accurate history, with or without abnormal radiological features, is mandatory to recognize this entity and prevent delayed diagnosis and complications.[1,2]

Clinical symptoms are associated with the patient's age, size, location, and type (organic, inorganic) of foreign body, and time elapsed from the moment of aspiration until presentation. The most common complaint is sudden onset of cough, which can present with wheezing and/or signs of respiratory distress. For patients who delay seeking medical support, fever, flank pain, crackles, and diminished breathing sounds may be observed, similarly to the present case.[1-4] Recurrent pneumonia, that occur in the same anatomic location, can also be a form of presentation. Foreign body extraction is crucial for successful treatment.

In the first hours, local hyperinflation at the affected side represents an indirect radiological finding potentially suggestive of FBA. Later signs include pleural effusion and/or consolidation. However, all of these are nonspecific.[1,4] Importantly, the absence of pulmonary signs on chest x-ray should not rule out FBA, since at least 90% of foreign bodies are non-opaque. Consequently, it is crucial to determine whether the patient should undergo additional imaging exams, as CT scan or bronchoscopy, based only on the possibility of aspiration. CT scan might help in cases with atypical presentation or radiologic findings, as the differential diagnosis includes tracheobronchial obstruction caused by external compression (e.g., tumors, cardiac enlargement) or intraluminal obstruction (e.g., granulomatous tissue, cystic fibrosis, asthma).[2,4] Due to radiation exposure and possible need for general anesthesia, there is conflicting evidence in the literature regarding the benefit of performing CT scan before bronchoscopy. Nevertheless, CT is a non-invasive, feasible, and reliable imaging technique that can prevent unnecessary endoscopic procedures under general anesthesia.[5] It can be performed with intra-rectal/nasal midazolam administration and a tolerable amount of radiation nowadays.[5] Still, rigid bronchoscopy remains the gold standard, as it enables not only a definite diagnosis but also extraction of the foreign body(ies) and oxygen administration.[4]

In conclusion, every parent should be aware of early symptoms of FBA, as most events occur with no witnesses. Also health professionals should maintain a high index of suspicion, especially in cases with atypical history and nonspecific imaging findings. Additional imaging exams and rigid bronchoscopy should be used to confirm FBA diagnosis and treat the condition, crucial for a favorable clinical outcome.

ABSTRACT

Foreign body aspiration (FBA) is a common and serious problem in children. Considering that signs and symptoms can be non-specific and subtle, it is of utmost importance to recognize vulnerable patient groups, combine an accurate history with complete physical examination, and follow a structured diagnostic approach towards correct diagnosis. In the present case, a high index of suspicion was essential to prevent a delay in FBA diagnosis, discuss the appropriate management strategy and improve patient outcomes.

Keywords: adolescent; aspiration; bronchoscopy; pneumonia

RESUMO

A aspiração de corpo estranho é um problema comum e sério em idade pediátrica. Considerando que os sinais e sintomas da aspiração podem ser subtis e pouco específicos, é de extrema importância reconhecer os grupos vulneráveis, associar uma história clínica precisa a um exame físico completo e seguir uma abordagem diagnóstica estruturada e abrangente, de forma a obter o diagnóstico correto. O presente caso clínico ilustra a importância de manter um elevado índice de suspeição para evitar atrasos no diagnóstico, permitindo discutir a abordagem terapêutica e otimizar a evolução clínica.

Palavras-chave: adolescente; aspiração; broncoscopia; pneumonia

AUTHORSHIP

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Isabel Couto Guerra - Conceptualization, Methodology; Writing – review & editing; Supervision

Inês Azevedo - Methodology; Writing – review & editing; Supervision

REFERENCES

1. Bakal U, Keles E, Sarac M, Karlidag T, Kaygusuz I, Kazez A. A study of foreign body aspiration in children. J Craniofac Surg. 2016;27(4):e358–63.
2. Sersar SI, Rizk WH, Bilal M, El Diasty MM, Eltantawy TA, Abdelhakam BB, *et al*. Inhaled foreign bodies: Presentation, management and value of history and plain chest radiography in delayed presentation. Otolaryngol - Head Neck Surg. 2006;134(1):92–9.
3. Tenjović D, Petrović S, Dautović GV, Lovrenski J, Rodić BB. Clinical and radiological characteristics of unrecognised foreign body aspiration into respiratory tract in children. Med Pregl. 2013;66(5–6):214–9.
4. Salih A., Alfaki M. A-ED. Airway foreign bodies: A critical review for a common pediatric emergency. World J Emerg Med. 2016;7(1):5–12.
5. Pitiot V, Grall M, Ploin D, Truy E, Ayari Khalfallah S. The use of CT-scan in foreign body aspiration in children: A 6 years' experience. Int J Pediatr Otorhinolaryngol. 2017;102:169–73.
6. Smith, Amanda & Jnah, Amy & Newberry, Desi. (2018). Chromosome 16p13.11 Microdeletion Syndrome in a Newborn: A Case Study. Neonatal Network. 37. 303-309. 10.1891/0730-0832.37.5.303.

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Received for publication: 31.10.2020
Accepted in revised form: 04.05.2021

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AIMS AND SCOPE

Nascer e Crescer – Birth and Growth Medical Journal is a peer-reviewed scientific journal edited by the Department of Education, Training and Research of Centro Hospitalar Universitário do Porto (DEFI/CHUPorto). Published quarterly since 1992, it is indexed in SciELO and referenced in several scientific databases.

Its main goal is to disseminate and develop scientific knowledge, promoting research in Maternal-Fetal, Neonatal, and Pediatric Health.

Nascer e Crescer – Birth and Growth Medical Journal publishes material in the form of editorials, original articles, review articles, clinical cases, imaging cases, letters to the editor, and current perspectives.

The journal follows an open access policy and makes its articles fully available at https://revistas.rcaap.pt/nascercrescer, under the Creative Commons: Attribution-Noncommercial 4.0 International license (CC BY-NC 4.0).

The journal charges no fees to authors or readers.

The management of scientific content is the sole responsibility of the editorial staff.

AUTHORSHIP AND RESPONSIBILITY CRITERIA

Nascer e Crescer – Birth and Growth Medical Journal subscribes to the guidelines for submitting manuscripts to biomedical journals issued by the International Committee of Medical Journal Editors (ICMJE) and the Committee on Publication Ethics (COPE).

Designated authors or coauthors should meet all four criteria for authorship in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" of ICMJE:

1. substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data;
2. drafting the article or revising it critically for important intellectual content;
3. final approval of the version to be published;
4. agreement in taking responsibility for the accuracy and integrity of the work.

The cover letter should specify the contribution of each author to the manuscript.

Everyone who has contributed to the manuscript but does not fully meet authorship criteria should be referred to in the "Acknowledgements" section.

Ethics in publishing

Authors must ensure that the study originating the manuscript has complied with the ethical principles for human dignity and applicable legislation and rules, in accordance with the Declaration of Helsinki.

When applicable, authors should mention that informed consent was obtained from study participants and that the study protocol was approved by the Ethics Committee of participating institutions.

A conflict of interest and funding statement is mandatory.

PUBLICATION GUIDELINES

SUBMISSION

Manuscripts should be submitted via the online submission website at https://revistas.rcaap.pt/nascercrescer.

Manuscripts should be submitted in a current Microsoft Word version, together with a cover letter and authorship and conflict of interest statements.

Manuscripts should be written in English language and have the following structure: 1 – Title in English and Portuguese; 2 – Authors; 3 – Abstract and keywords in English and Portuguese; 4 – Main text; 5 – References; 6 – Figures; 7 – Tables; 8 – Legends; 9 – Acknowledgements and clarifications.

Pages should be consecutively numbered in the same order as the previous structure.

First page

a. Clear and concise title, in English and Portuguese, without the identification of the institution where the study took place;
b. author names (first and last or clinical name) followed by their affiliations (Unit, Department, Institution), email, and ORCID ID;
c. identification of the Corresponding Author, with postal address, email, and telephone number.

Second page

a. Abstract in Portuguese and English, avoiding the use of abbreviations.
b. Abstracts should be organized and formatted according to the considered type of article.
c. Immediately after the abstract, keywords in English and Portuguese should be provided in alphabetical order, which will be used for indexing purposes. Keywords should be in accordance with the recommended nomenclature in Medical Subject Headings (MeSH).

TEXT

Editorials

Editorials are to be submitted upon invitation by the Editor or Editorial Board and generally concern comments on currently relevant topics. Editorials should not exceed 1200 words and have a maximum of two figures or tables and 15 references. Abstract is not required.

Original Articles

Full articles should be divided into Introduction, Material and Methods, Results, Discussion, and Conclusions. Articles should be no longer than 5000 words and have a maximum of eight tables or figures and 40 references. The abstract should follow the same structure as the main text and be no longer than 250 words. A maximum of seven keywords should be used.

Review Articles

Review articles should be divided into Introduction, Objectives, Main Text, and Conclusions and not exceed 5000 words, five tables or figures, and 80 references. The abstract should not exceed 250 words and be structured according to the main text. A maximum of seven keywords should be used.

Clinical Cases

This type of article reports one or several clinical cases which, due to their rarity, therapeutic innovation, or other feature, are relevant to the scientific community. Clinical cases should be exemplary, properly studied and discussed, and include a brief introduction, the description of the case(s), and a concise discussion including a brief conclusion. The text must not exceed 2500 words and 15 references. The abstract should have a maximum of 150 words and have the same structure as the main text. A maximum of seven keywords is allowed.

Imaging Cases

This type of article is appropriate for clinical cases in which image proves crucial for the diagnosis. Images can be related to the clinical observation or complementary exams of the patient. The text should be no longer than 2000 words and start with a description of the case followed by the question: What is your Diagnosis? This should be followed by the diagnosis, patient's management, and a brief discussion. A maximum of 10 references can be used. The abstract and keywords (a maximum of five) should be at the end of the text.

Letters to the Editor

Letters to the Editor consist of comments regarding articles previously published in NASCER E CRESCER or short notes regarding a specific subject or clinical case. They should not exceed 500 words and five references and may include one figure or table. In the case of comments to articles previously published in the journal, these should refer to articles published over the last semester and the authors of the article will be invited to reply. Both the letter and the authors' reply will be published in the same journal issue.

Current Perspectives

Perspectives are commissioned by the Editorial Board and address current topics of interest within the scope of the journal. They should not exceed 1200 words and ten references and may include one figure or table. Authors who wish to submit this type of article should send a summary to the Editor-in-Chief, indicating the authors and affiliations and the title, for assessment of the relevance of the work.

General Guidelines

- Abbreviations used should be adequately specified. When required, they should be defined when first mentioned in the text. If more than six abbreviations are used, an explanatory table with all abbreviations should be included. Abbreviations should not be used in the title.
- Measurements should be expressed in international units (SI units, The SI for the Health Professions, WHO, 1977), using the respective abbreviations adopted in Portugal.
- Numbers one to ten should be written out in words unless used as units of measurement or have decimals. Numbers greater than nine should be written in Arabic numerals unless they are at the beginning of a sentence.
- Results should not be duplicated in the text and in tables/figures; only the main results should be mentioned in the text.

REFERENCES

- References should be numerically cited in the order they appear in the text using Arabic numerals in superscript (ex.:4).
- Consecutive references are given as a range with an en rule, indicating only the first and the last (ex.:4-7). When non-consecutive, all references should be indicated, separated by a comma (ex.:4,7,9).
- All references should conform to the Uniform Requirements for Manuscript Submitted to Biomedical Journals (www.nlm.nih.gov/bsd/uniform_requirements.html), and journal names should follow the Index Medicus Authors may refer to the NLM's Citing Medicine webpage for formatting recommendations regarding different reference types.

Examples:

a. Medical journal: list the six first authors followed by et al. (in italic) in the case of six or more authors, followed by article title, journal name, publication year, volume, number, and pages. : 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): 622-65. https://doi: 10.1097/00006454-198611000-00004.
b. Book chapter: author(s), chapter title, name(s) of the Editor(s), book title, edition number, city and name of the publisher, publication year, first and last page number of the chapter. Ex.: Phillips SJ, Whisnant Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.
c. Book: author(s), book title, edition number, city and name of the publisher, publication year, and page numbers. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on 2nd. London: Taylor & Francis; 2013. p. 120.
d. Electronic reference: journal article in electronic format. Ex.: Jeha G, Kirkland Etiology of hypocalcemia in infants and children. January, 2010. (Assessed May 8, 2013). Available at: http://www.uptodate.com.

FIGURES AND TABLES

- Figures and tables should be submitted on an individual page, in high-quality digital format, with an accompanying explanatory title and legend whenever necessary.
- Tables and figures should be consecutively numbered with Arabic numerals in the order they appear in the text.
- All abbreviations and symbols should have an accompanying legend.
- If the figure or table is an integral or modified copy from another publication, the original source and authorization for use should be mentioned when appropriate.
- Clinical pictures and complementary exams of patients should be anonymized to prevent their identification and accompanied by the respective consent for publication, signed by the patient or a legal representative.
- The total number of figures and tables should not exceed what is stipulated for each article type.

ACKNOWLEDGMENTS AND DECLARATIONS

Acknowledgments and the declarations of conflict of interest and funding source should be mentioned on the last page of the article.

ARTICLE STRUCTURE – AUTHOR GUIDELINES

Publication type	Abstract		Keywords	Text		Figures and Tables	References
	Maximum word count	Structure		Maximum word count (excluding References and illustrations)	Structure	Maximum number	Maximum number
Editorial	-	-	-	1200	-	1/2	15
Original Articles	250	• Introduction/Aim • Material and Methods • Results • Discussion/Conclusions	3 to 7	5000	• Introduction/Aim • Material and Methods • Results • Discussion • Conclusions	8	40
Review Articles	250	• Introduction • Aims • Main text • Conclusions	3 to 7	5000	• Introduction/Aim • Methods • Main Text • Discussion/Conclusions	8	80
Clinical Cases	150	• Introduction • Clinical Case(s) • Discussion/Conclusions	3 to 7	2500	• Introduction (brief) • Clinical Case(s) • Discussion/Conclusions	5	15
Imaging Cases	150	• Introduction • Clinical Case(s) • Discussion/Conclusions	3 to 7	2000	• Case discription • Diagnosis • Discussion/Conclusions	2/3	10
Letters to Editor	-	-	-	500	-	-	5
Current Perspectives	-	-	-	1200	-	1	10

REVISION PROCESS

Every manuscript undergoes a double-blind peer-review process, after which the Editor may:

a. accept it without changes;
b. accept it after changes suggested by reviewers;
c. reject it.

If the paper is accepted with changes, these should be made by the authors within thirty days and highlighted in the manuscript with shading and notes where necessary. The new version with changes will be again revised by the reviewers for final approval.

PROOFS

After acceptance of an article, proofs will be sent to the authors in electronic format for revision, with indication of the revision deadline according to the editorial requirements of NASCER E CRESCER. Failure to comply with the proposed deadline exonerates NASCER E CRESCER from accepting the revised version, and the version sent is assumed to be final.

INFORMATION AND CLAIMS

For inquiries or claims regarding the editorial process or final decision regarding your article, please contact NASCER E CRESCER secretariat via email: nascerecrescer@chporto.min-saude.pt or phone: +351 915 676 516.

INSTRUÇÕES AOS AUTORES

OBJETIVOS E ÂMBITO

A Nascer e Crescer – Birth and Growth Medical Journal é uma revista científica, peer-reviewed, editada pelo Departamento de Ensino, Formação e Investigação do Centro Hospitalar Universitário do Porto (DEFI/CHUPorto). Com publicação trimestral regular desde 1992, encontra-se indexada na SciELO e referenciada em diversas bases científicas.

O seu objetivo principal é difundir e desenvolver o conhecimento científico, promovendo a investigação nas áreas da Saúde Materno Fetal, Neonatal e Pediátrica.

É composta por editorial, artigos originais, artigos de revisão, casos clínicos, casos de imagem, cartas ao editor e perspetivas atuais.

A revista segue uma política de acesso aberto e disponibiliza os seus artigos em formato integral através do site https://revistas.rcaap.pt/nascercrescer, sob a licença Creative Commons: Atribuição-Não Comercial 4.0 Internacional (CC BY-NC 4.0).

A Nascer e Crescer – Birth and Growth Medical Journal não cobra taxas aos seus autores e leitores.

A gestão dos conteúdos científicos é da inteira responsabilidade do corpo redatorial.

CRITÉRIOS DE AUTORIA E RESPONSABILIDADE

A Revista Nascer e Crescer – Birth and Growth Medical Journal subscreve as normas para apresentação de manuscritos a revistas biomédicas elaboradas pelo International Committee of Medical Journal Editors (ICMJE), e pelo Committee On Publications Ethics (COPE).

A inclusão de autores num artigo científico deve ter por base o indicado no "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" do ICMJE. A autoria ou coautoria exige cumulativamente:

1. Contribuição na conceção ou desenho do estudo; participação na aquisição, análise e interpretação dos dados;
2. Participação na redação do manuscrito e na revisão crítica do conteúdo;
3. Aprovação da versão final para publicação;
4. Concordância da responsabilidade na exatidão e integridade de todo o trabalho.

Na carta de apresentação deve ser especificado o contributo de cada autor para o trabalho.

Todos aqueles que tenham participado em alguma tarefa na investigação, mas que não cumpram na íntegra os critérios de autoria devem ser listados na secção "Agradecimentos".

Questões éticas

Os autores devem garantir que o estudo, que originou o artigo submetido, respeitou os princípios éticos e deontológicos, bem como a legislação e as normas aplicáveis, conforme recomendado na Declaração de Helsínquia.

Nos casos aplicáveis é obrigatório que os autores mencionem a existência de consentimento informado dos participantes, assim como a aprovação do protocolo do estudo pela Comissão de Ética das instituições envolvidas.

É obrigatório o envio da declaração de conflito de interesses ou financiamento.

NORMAS DE PUBLICAÇÃO

SUBMISSÃO

Os manuscritos devem ser submetidos através da plataforma online da revista: https://revistas.rcaap.pt/nascercrescer.

O documento deve seguir numa versão atual do Microsoft Word, acompanhado da carta de apresentação e declaração de autoria e conflito de interesses.

O trabalho deve ser apresentado em língua inglesa com a seguinte ordem: 1 – Título em inglês e português; 2 – Autores; 3 – Resumo e palavras-chave em inglês e português; 4 – Corpo do artigo; 5 – Referências Bibliográficas; 6 – Figuras; 7 – Quadros; 8 – Legendas; 9 – Agradecimentos e esclarecimentos.

As páginas devem ser numeradas de acordo com a sequência referida anteriormente.

Na primeira página

a. Título explícito e conciso, em inglês e português, nunca identificando a instituição onde decorreu o estudo;
b. Os nomes dos autores (primeiro e último ou nome clínico) seguidos das respetivas afiliações (Serviço, Departamento, Instituição), contactos de email e ORCID ID;
c. Identificação do autor responsável para troca de correspondência, indicando o seu endereço postal, email e telefone.

Na segunda página

a. Resumo em inglês e português, evitando a utilização de abreviaturas;
b. Os resumos devem seguir a estrutura específica de acordo com a tipologia do artigo apresentado;
c. Subsequentes ao resumo devem constar as palavras-chave, em inglês e português, por ordem alfabética, que servirão de base à indexação do artigo. Os termos devem estar em concordância com o Medical Subject Headings (MeSH).

TEXTO

Editoriais

Submetidos a convite do Editor ou Conselho Editorial, constituem comentários sobre tópicos atuais. Não podem exceder as 1200 palavras, um máximo de duas figuras ou tabelas e 15 referências bibliográficas. Não possuem resumo.

Artigos Originais

O texto deve ser estruturado em Introdução, Material e Métodos, Resultados, Discussão e Conclusões. Não deverá exceder as 5000 palavras, oito tabelas ou quadros e 40 referências bibliográficas. O resumo segue a estrutura do texto não excedendo as 250 palavras. As palavras-chave serão no máximo sete.

Artigos de Revisão

Seguindo a estrutura: Introdução, Objetivos, Desenvolvimento e Conclusões, não devem exceder as 5000 palavras, cinco tabelas ou figuras e 80 referências bibliográficas. O resumo, com um máximo de 250 palavras, segue a estrutura do texto. As palavras-chave serão no máximo sete.

Casos clínicos

Este tipo de artigo relata um ou vários casos clínicos, que devido

à sua raridade, inovação terapêutica, ou outro fator relevante, se considere de interesse para a comunidade científica. Devem ser exemplares, devidamente estudados e discutidos e conter uma breve introdução, descrição do(s) caso(s) e discussão sucinta que incluirá uma conclusão sumária, num texto elaborado até 2500 palavras. Poderá incluir até 15 referências bibliográficas. O Resumo, com o máximo de 150 palavras, segue a estrutura do texto. As palavras-chave serão no máximo sete.

Casos de imagem

Dedicada a casos clínicos em que a imagem se revele fundamental para o diagnóstico. As imagens podem ser relativas à observação clínica do doente ou a meios complementares de diagnóstico. O texto com o máximo de 2000 palavras, deve iniciar com uma descrição do caso e finalizar com a pergunta: Qual o seu Diagnóstico? Segue-se a apresentação do diagnóstico, orientação do doente e breve discussão. Poderá incluir até 10 referências bibliográficas. O resumo e palavras-chave (no máximo cinco) devem surgir no final do texto do artigo.

Cartas ao Editor

As cartas ao editor constituem um comentário a um artigo publicado na NASCER E CRESCER, ou uma nota sobre um tema ou caso clínico. Não deverá exceder as 500 palavras, cinco referências bibliográficas e poderá incluir uma imagem ou tabela. No caso de comentários a artigos da Revista, estes devem remeter para artigos publicados no último semestre, sendo dada aos autores a possibilidade de resposta do artigo. A carta e a resposta dos autores serão publicadas no mesmo número da Revista.

Perspetivas Atuais

Constituída por artigos redigidos por convite, endereçado pelo corpo redatorial, podem abordar temas atuais relacionados com a temática da Revista. Não deverão exceder as 1200 palavras, dez referências bibliográficas, podendo conter uma imagem ou tabela. Caso um autor pretenda submeter um artigo a esta rubrica deverá previamente enviar um resumo, com indicação dos autores, afiliações e título do artigo ao editor-chefe, para que este avalie a sua pertinência.

Normas gerais

- As abreviaturas utilizadas devem ser objeto de especificação. Quando necessária a sua utilização, devem ser explicitadas na primeira vez que são mencionadas no texto. Se utilizadas mais do que seis, recomenda-se a inclusão de um quadro onde todas serão explicadas. Não se aceitam abreviaturas nos títulos dos trabalhos.
- Os parâmetros ou valores medidos devem ser expressos em unidades internacionais (SI units, The SI for the Health Professions, WHO, 1977), utilizando as respetivas abreviaturas adotadas em Portugal.
- Os números de um a nove devem ser escritos por extenso, exceto quando utilizados como unidades de medida ou estão acompanhados de decimais. Números superiores a nove são escritos em algarismos árabes, exceto se no início da frase.
- Relativamente aos resultados, a informação não deverá ser referida em duplicado no texto e nos quadros / tabelas, bastando salientar no texto os resultados principais.

REFERÊNCIAS BIBLIOGRÁFICAS

- As referências devem ser classificadas e numeradas por ordem de entrada no texto, com algarismos árabes, formatados sobrescritos (ex.: 4).
- Referências sequenciais devem ser feitas indicando apenas a primeira e a última, unidas por hífen (ex.:4-7). Quando não sequenciais devem ser separadas por vírgulas (ex.:4,7,9)
- Os autores devem verificar se todas as referências estão em conformidade com os requisitos do Uniform Requirements for Manuscript submitted to biomedical journals (www.nlm.nih.gov/bsd/uniform_requirements.html) e se utilizam os nomes abreviados das publicações adotadas pelo Índex Medicus. Os autores podem consultar a página NLM's Citing Medicine relativamente às recomendações de formato para os vários tipos de referência.

Seguem-se alguns exemplos:

a. Revista médica: listar os primeiros seis autores, seguidos de et al (em itálico) se ultrapassar seis, título do artigo, nome da revista, ano, volume, número e páginas. Ex.: 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.
b. Capítulo em livro: autor(es), título do capítulo, nome(s) do(s) Editor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação, primeira e última páginas do capítulo. 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.
c. Livro: autor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação e número de páginas. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on guide. 2nd edition. London: Taylor & Francis; 2013. p. 120.
d. Referência eletrónica: artigo de revista em formato eletrónico. Ex.: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. Janeiro, 2010. (Acedido em 8 de maio de 2013). Disponível em: http://www.uptodate.com.

FIGURAS E QUADROS

- Apresentadas em página individual, em formato digital de boa qualidade, acompanhado de título e legenda explicativa quando necessário.
- Cada quadro e figura deverão ser numerados sequencialmente, em numeração árabe, por ordem de referência no texto.
- Todas as abreviaturas ou símbolos necessitam de legenda.
- Se a figura ou quadro é cópia integral ou modificada de uma publicação, deve ser mencionada a sua origem e autorização para a utilização quando apropriado.
- Fotografias ou exames complementares de doentes deverão impedir a sua identificação, sendo acompanhadas de autorização para a publicação, dada pelo doente ou seu responsável legal.
- O total de figuras e quadros não deve ultrapassar o número indicado para cada tipologia de artigo.

AGRADECIMENTOS E ESCLARECIMENTOS

Os agradecimentos, a indicação da existência, ou não, de situações de conflito de interesse de algum dos autores, bem como, informação sobre as fontes de financiamento do estudo devem figurar na última página.

ESTRUTURA DOS ARTIGOS - NORMAS DE PUBLICAÇÃO

Tipo de Artigo	Resumo		Palavras-chave (Português e Inglês)	Texto		Figuras e Quadros	Bibliografia
	Número máximo de palavras	Estrutura		Número máximo de palavras (excluindo Referências e Ilustrações)	Estrutura	Número	Número máximo de referências
Editorial	-	-	-	1200	-	1/2	15
Artigos Originais	250	• Introdução/Objetivo • Material e Métodos • Resultados • Discussão/Conclusões	3 a 7	5000	• Introdução/Objetivo • Material e Métodos • Resultados • Discussão • Conclusões	8	40
Artigos de revisão	250	• Introdução • Objetivos • Desenvolvimento • Conclusões	3 a 7	5000	• Introdução/Objetivo • Métodos • Desenvolvimento • Discussão/Conclusões	8	80
Casos Clínicos	150	• Introdução • Caso(s) clínicos(s) • Discussão/Conclusões	3 a 7	2500	• Introdução (breve) • Caso(s) clínicos(s) • Discussão/Conclusões	5	15
Casos Imagem	150	• Introdução • Caso(s) clínicos(s) • Discussão/Conclusões	3 a 7	2000	• Descrição do caso • Diagnóstico • Discussão/Conclusões	2/3	10
Carta ao editor	-	-	-	500	-	-	5
Perspetivas Atuais	-	-	-	1200	-	1	10

PROCESSO DE REVISÃO

Os artigos estão sujeitos a um processo de revisão por pares duplamente cega sendo da responsabilidade do Editor a decisão de:

a. aceitar sem alterações;
b. aceitar com alterações propostas pelos revisores;
c. recusar

No caso de o artigo ser aceite com alterações, estas devem ser realizadas pelos autores no prazo de trinta dias, identificando as mesmas a sombreado e adicionando notas sempre que necessário. A versão corrigida será revista novamente pelos revisores, para aprovação final.

PROVAS DE ARTIGOS ACEITES

Após a aceitação de publicação, as provas tipográficas do manuscrito serão enviadas aos autores em formato eletrónico para revisão, contendo a indicação do prazo de envio em função das necessidades de publicação da Revista. Na ausência de resposta dos autores nos prazos estipulados, assume-se como definitiva a versão enviada.

INFORMAÇÕES E RECLAMAÇÕES

Para qualquer consulta ou reclamação, relacionada com o processo editorial do seu artigo ou com a decisão final, contacte o nosso secretariado através do email: nascerecrescer@chporto.min-saude.pt ou pelo telefone 915 676 516.