ISSN: 2184-3333
e-ISSN: 2184-4453

Indexada/*Indexed in*: SciELO, Latindex, Free Medical Journals, Indexrmp, Scopus, DOAJ, COPE , RCAAP

PORTUGUESE JOURNAL OF PEDIATRICS

Vol. 55 No 1 January / March 2024

https://pjp.spp.pt

SPP
SOCIEDADE PORTUGUESA DE PEDIATRIA

PERMANYER
www.permanyer.com

ISSN: 2184-3333
e-ISSN: 2184-4453

PORTUGUESE JOURNAL OF PEDIATRICS

PORTUGUESE JOURNAL OF PEDIATRICS

former Acta Pediátrica Portuguesa

The official journal of the Portuguese Society of Pediatrics
https://pjp.spp.pt • pjp@spp.pt

EDITORIAL BOARD

SCIENTIFIC BOARD

ADVISORY AND TECHNICAL ASSISTANCE

Editorial Assistant
Sónia Gaspar

PUBLISHER

Sociedade Portuguesa de Pediatria • Portuguese Society of Pediatrics

REGISTRY

Legal Deposit: 455459/19 • ISSN: 2184-3333 online • Quaterly editions

Original papers should be deposited in their electronic version through the following URL:

http://publisher.portuguesejournalofpediatrics.permanyer.com

PERMANYER
www.permanyer.com

Permanyer
Mallorca, 310 – Barcelona Cataluña, España
permanyer@permanyer.com

www.permanyer.com

ISSN: 2184-3333
Ref.: 10034APTG241

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

EDITORIAL

Revisiting vitamin D supplementation in pediatric age in Portugal

Luís Pereira-da-Silva

Editor-in-Chief

NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa and Hospital Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central. Lisbon, Portugal

ORCID: 0000-0002-6480-1048

Vitamin D insufficiency has been a cause for concern among health professionals who care for Portuguese children and adolescents, and interesting studies have been published in the last decade[1-6].

In this issue, an excellent state-of-the-art on vitamin D supplementation in Portuguese children and adolescents is provided by renowned national experts[7]. It is a didactic and practical review on this topic, useful for pediatricians and family doctors who provide pediatric primary care.

Some aspects revisited in this article are worth highlighting.

To implement a prophylactic supplementation strategy with a certain nutrient, prior knowledge on the prevalence of its status in the target population is necessary. Unfortunately, representative data on hypovitaminosis D in the Portuguese pediatric population is lacking[7]. As the authors state, based on prevalence data from the northern region of Portugal[2,3] and a systematic review of vitamin D status in southern European countries that included children and adolescents[8], it can be speculated that in Portugal the prevalence of vitamin D insufficiency in pediatric age is high. It is worth mentioning an higher than expected prevalence of hypovitaminosis D reported in populations that benefit from high sun exposure[9].

The serum 25(OH)D level is the recommended biomarker to define vitamin D insufficiency or deficiency. Although there is no full consensus, for clinical purposes it is pragmatic to consider that levels below 20 ng/mL (50 nmol/L) indicate individuals at risk[7]. Screening for 25(OH)D serum levels and vitamin D supplementation should not be universal and is only recommended in specific, well-defined situations[7].

Serum 25(OH)D cutoffs used to define hypovitaminosis D have been based on the effects of vitamin D on bone health. This strategy narrows the target to the tip of the iceberg, disregarding the wide spectrum of extra-skeletal effects of vitamin D deficiency at the level of other organs and systems that are dependent on the action of this pre-hormone, such as the immune and cardiovascular systems[9]. Other important disorders associated with hypovitaminosis D in childhood and adolescence have been described, including metabolic syndrome and mood disturbances[9]. In the future, it would be desirable to determine serum 25(OH)D cutoff points specific for extra-skeletal disorders related to vitamin D deficiency in pediatric age.

In infants born at term, it is consensual that daily supplementation with 400 IU of vitamin D_3 should be universal in the first year of life[7]. Beyond this age, supplementation should be considered in risk groups, particularly children and adolescents who consume diets low in vitamin D, obese children, and those deprived of minimally recommended sun exposure[7]. For preterm infants born with a weight of less than 1800 g, the European Society for Pediatric Gastroenterology Hepatology and Nutrition very recently reduced the

Correspondence:
Luís Pereira-da-Silva
E-mail: l.pereira.silva@nms.unl.pt

Received: 10-12-2023
Accepted: 22-12-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):1-2
DOI: 10.24875/PJP.23000058

recommended daily intake of vitamin D_3 from 800-1000 IU/kg/d[10] to 400-700 IU/kg/d[11]. This reduction was justified by the lack of safety data with the use of higher doses and by the most recent data on the effect of vitamin D_3 supplementation on bone mineral density in this population. In the revised guidelines for enteral nutrition in preterm infants by the Portuguese Neonatal Society[12], the recommended intake of vitamin D was updated accordingly.

Along with vitamin D supplementation, it is important not to neglect educational measures, including diet and sun exposure recommendations provided in this review, which if followed can avoid pharmacological measures[7].

The Portuguese Journal of Pediatrics welcomes original studies and reviews on the supplementation of other vitamins and micronutrients in Portuguese children and adolescents.

References

1. Rêgo C, Nazareth M, Lopes C, Graça P, Pinto E. Suplementação vitamínica e mineral em Portugal durante o primeiro ano de vida. Resultados do EPACI Portugal 2012. *Acta Pediatr Port.* 2016:47(3):211-20.
2. Ferreira S, Tomada I, Carreiro E, Poínhos R, Rêgo C. Défice de vitamina D: comorbilidade da obesidade pediátrica ou consequência do estilo de vida? *Acta Pediatr Port.* 2016:47(1):38-45.
3. Cabral M, Araújo J, Teixeira J, Barros H, Martins S, Guimarães JT, et al. Vitamin D levels and cardiometabolic risk factors in Portuguese adolescents. *Int J Cardiol.* 2016;220:501-7.
4. Cabral M, Araújo J, Lopes C, Barros H, Guimarães JT, Severo M, et al. Relationship between dietary vitamin D and serum 25-hydroxyvitamin D levels in Portuguese adolescents. *Public Health Nutr.* 2018;21(2):325-32.
5. Monteiro E, Baptista N, Faria A, Loureiro H. Deficiência de vitamina D em crianças com doença celíaca. *Acta Port Nutr.* 2019;19:56-9.
6. Faria HC, Carneiro S, Santos C, Cristóvão C, Neto AS. A realidade acerca da vitamina D numa população adolescente. *Gazeta Médica.* 2020;7(3):247-53.
7. Rêgo C, Cordeiro Ferreira G, Fonseca MJL, Moura Relvas M, Ferreira R, Pinto da Costa S. A reviewed approach to vitamin D supplementation in pediatric age in Portugal. *Port J Pediatr.* 2024;55(1):40-47.
8. Manios Y, Moschonis G, Lambrinou CP, Tsoutsoulopoulou K, Binou P, Karachaliou A, el al. A systematic review of vitamin D status in southern European countries. *Eur J Nutr.* 2018;57(6):2001-36.
9. Antonucci R, Locci C, Clemente MG, Chicconi E, Antonucci L. Vitamin D deficiency in childhood: old lessons and current challenges. *J Pediatr Endocrinol Metab.* 2018;31(3):247-60.
10. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al.; ESPGHAN Committee on Nutrition. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50(1):85-91.
11. Embleton ND, Jennifer Moltu S, Lapillonne A, van den Akker CHP, Carnielli V, Fusch C, et al. Enteral nutrition in preterm infants (2022): A position paper from the ESPGHAN Committee on Nutrition and Invited Experts. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-68.
12. Pereira-da-Silva L, Pissarra S, Gomes G, Barroso R, Fernandes C, Virella D, et al.; on behalf of the Portuguese Neonatal Society. Guidelines for enteral nutrition in infants born preterm: 2023 update by the Portuguese Neonatal Society. Part I. Nutrient requirements and enteral feeding approach during the hospital stay. *Port J Pediatr.* 2023;54(4):253-63.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

ACKNOWLEDGMENT TO REVIEWERS

The editorial board of the Portuguese Journal of Pediatrics would like to thank all the reviewers who collaborated in the editorial process of the manuscripts submitted in 2023, being fully aware that the work of scientific review by peers is the highest expression of scientific citizenship.

Therefore, on behalf of all the readers, authors, and editors of the Portuguese Journal of Pediatrics, thank you!

Adelaide Taborda
Albina Ramires
Alexandra Gavino
Alexandra Luz
Ana Cristina Gomes
Ana Luísa Mendes
Ana Raquel Silva
Ana Reis Melo
Ana Rita Soares
Andreia Forno
Arminda Jorge
Carla Costa
Carla Pereira
Carolina Faria
Céu Espinheira
Cláudia Fernandes
Cristina Amaro
Cristina Mendes
Daniela Pinto
Eduarda Ferreira
Elisa Galo
Elisa Proença
Flávia Correa
Gonçalo Cassiano
Guilhermina Reis
Helena Mansilha
Helena Loreto
Hugo Cavaco
Inês Balacó
Isabel Sampaio
Joana Rodrigues
João Brissos
João Subtil
José Nascimento Cunha
Leonor Ramos
Lígia Peralta
Madalena Tavares
Mafalda Paiva
Margarida Crujo
Maria Adriana Rangel
Maria Amélia Cavaco
Maria Flores
Maria Francelina Lopes
Maria João Rodrigo
Maria Miguel Almiro
Profª Doutora Maria Teresa Neto
Mariana Borges
Mariana Rodrigues
Marta Correia
Marta Janeiro
Mónica Cró Braz
Patrícia Vaz Silva
Paula Fonseca
Paula Maio
Paula Rego de Sousa
Paulo Sousa
Pedro Louro
Pedro Mantas
Pedro Flores
Piedade Lemos
Raquel Gonçalves
Renato Silva
Rita Machado
Rosário Ferreira
Rute Baeta Batista
Rute Neves
Sandra Sousa
Sara Duarte Brito
Sara Pedroso
Sílvia Bacalhau
Sofia Bota
Sofia Helena Ferreira
Sofia Martins
Susana Castanhinha
Telma Francisco
Tiago Proença Santos
Víctor Viana

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

Respiratory syncytial virus under 2 years of age: hospitalization trends and risk factors for severe disease – preliminary data from the Portuguese sentinel network

Ana R. Torres[1a], Aryse Melo[2b], Carlos Aniceto[1c], Raquel Guiomar[2d], Vânia Gaio[1e], Teresa Bandeira[3f], Inês Azevedo[4,5g], and Ana P. Rodrigues[6h] on behalf of the VigRSV network***

[1]Department of Epidemiology, National Health Institute Doutor Ricardo Jorge, Lisbon; [2]Department of Infectious Diseases, National Health Institute Doutor Ricardo Jorge, Lisbon; [3]Unidade de Pneumologia Pediátrica, Centro Hospitalar Universitário Lisboa Norte, Lisbon; [4]Sociedade Portuguesa de Pediatria, Lisbon; [5]Serviço de Pediatria, Centro Hospitalar Universitário São João, Porto; [6]Department of Epidemiology, National Health Institute Doutor Ricardo Jorge, Lisbon. Portugal

ORCID: [a]0000-0003-0486-647X; [b]0000-0002-6655-8715; [c]0000-0002-7779-7228; [d]0000-0002-4563-6315; [e]0000-0001-7626-4991; [f]0000-0002-6214-3117; [g]0000-0002-0090-8612; [h]0000-0003-2264-4723

***VigRSV network: Filipa Bazenga, Joana Nunes, Lídia Carvalho, Carolina Constant, Rosário Barreto, Susana Castanhinha, Rita Corte-Real, Beatriz Sousa, Margarida Freitas, Luis Miguel Silva, Florbela Cunha, Leonor Cardoso, Bruno Esteves, Regina Abreu, Ana Foles, Joana Brandão Silva, Paulo Lopes, Rita Marques, Raquel Marques, Mariana Reis, Ana Loureiro, Teresa Nunes, Eurico Jorge Gaspar, Eliana Costa, Miguel Félix, Lucília Araújo, Jorge Rodrigues, José Alves, Lina Winckler, Maria Manuel Zarcos, Carla Cruz, José Lupi, Sidónia Nunes, José Alves, Luísa Preto, Teresa Magalhães, Alberto Caldas Afonso, Manuel Magalhães, Alexandra Estrada, and Almerinda Pereira*

Abstract

Introduction and Objectives: Respiratory Syncytial Virus (RSV) infection is an important cause of hospitalization in children under five years. A national RSV sentinel network was set up in Portugal in April 2021. We describe the trends in RSV hospitalizations until September 2022 and identify risk factors for severe disease. **Methods:** Acute respiratory infections in hospitalized children under two years were reported and tested for RSV. RSV disease severity was defined by the need for ventilation or admission to an intensive care unit. Risk ratios were used to assess the association between gender, age group, gestational age, birthweight, chronic conditions, RSV subtype and severity of disease. **Results:** We detected two RSV off-season epidemics in June 2021 to February 2022 and May to September 2022. 63.3% of RSV-related hospitalizations occurred in children under six months old and 8.0% had chronic conditions. 11.0% had severe disease. Children under six months and with chronic conditions had, respectively, an 18-fold risk and a 2-fold risk of developing severe illness. **Discussion:** The off-season RSV epidemics were probably triggered by the relaxation of COVID-19 physical distancing measures and immunity debt. In the first epidemic, the proportion of children with severe disease was higher than reported by previous studies, however, this result is probably overestimated due to the high proportion of cases notified by central hospitals. Age < 6 months and chronic conditions predispose to severe disease. As several factors may change the pattern of RSV activity, causing more severe outbreaks at different times, countries should implement year-round RSV surveillance systems.

Keywords: Child. Human. Palivizumab. Respiratory syncytial virus. Respiratory syncytial virus infections/epidemiology. Respiratory syncytial virus infections/prevention and control.

Vírus sincicial respiratório em crianças com menos de 2 anos: tendências nas hospitalizações e fatores de risco para doença grave – dados preliminares da rede de vigilância sentinela Portuguesa

Resumo

Introdução e Objetivos: O vírus sincicial respiratório (VSR) é uma importante causa de hospitalização em crianças com menos de cinco anos de idade. Em abril de 2021, foi implementado um sistema de vigilância sentinela de VSR em Portugal.

***Correspondence:**
Ana R. Torres
E-mail: a.rita.torres@insa.min-saude.pt

Received: 21-10-2022
Accepted: 10-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):4-12
DOI: 10.24875/PJP.M23000129

Neste trabalho, descrevem-se tendências nas hospitalizações de VSR até setembro de 2022 e identificam-se fatores de risco para doença grave. **Métodos:** Foram reportados, e testados para VSR, casos de Infeção respiratória aguda em crianças hospitalizadas com menos de 2 anos de idade. Definiu-se doença grave pela necessidade de ventilação ou de internamento em Unidade de Cuidados Intensivos. Utilizaram-se riscos relativos para avaliar a associação entre sexo, grupo etário, idade gestacional, peso à nascença, comorbilidades, subtipo de VSR e gravidade da doença. **Resultados:** Detetaram-se duas epidemias de RSV fora de época, em junho 2021-fevereiro 2022 e maio-setembro de 2022. 63,3% das hospitalizações por VSR ocorreram em crianças com menos de 6 meses e 8,0% tinha comorbilidades. 11,0% desenvolveu doença grave. Crianças com menos de seis meses e com comorbilidades tiveram, respetivamente, um risco 18 e 2 vezes superior de desenvolver doença grave. **Discussão:** As epidemias de VSR fora de época foram provavelmente desencadeadas pelo relaxamento das medidas de distanciamento social, no âmbito de combate à pandemia de COVID-19, e pela falta de imunidade por ausência de exposição à doença. Na primeira epidemia, a proporção de crianças com doença grave foi superior ao reportado em outros estudos, contudo, este resultado está provavelmente sobrestimado pela proporção elevada de casos notificados por hospitais centrais. Idade inferior a seis meses e comorbilidades predispõem a doença grave. Uma vez que diversos fatores podem afetar a sazonalidade de VSR, causando epidemias mais severas e em diferentes alturas do ano, recomenda-se a implementação de sistemas de vigilância contínua de VSR.

Palavras-chave: Criança. Humano. Infecções por vírus respiratório sincicial/epidemiologia. Infecções por vírus respiratório sincicial/prevenção e controlo. Palivizumab. Vírus sincicial respiratório.

Keypoints

What is known

– Respiratory Syncytial Virus (RSV) infection is an important cause of hospitalization in children under five years. Seasonal data on RSV detections have been available in Portugal since 2013-2014, however, data on RSV disease burden is sparse.

What is added

– Two RSV off-season epidemics were identified in Portugal. The off-season RSV epidemics were probably triggered by the relaxation of COVID-19 physical distancing measures and immunity debt. In the first epidemic, the proportion of children with severe disease was higher than reported by previous national studies.

Introduction

Respiratory Syncytial Virus (RSV) infection is an important cause of lower respiratory tract infections and hospitalizations worldwide. Infants are the most affected age group, representing 45% of all hospital admissions and deaths from RSV[1]. It is estimated that, in 2015, RSV was responsible for 33.1 million acute lower respiratory tract infections in children younger than five years, resulting in 3.2 million hospitalizations and overall mortality of 118,200[1].

Therefore, reliable data on the burden of RSV infections and the identification of risk factors for severe disease are of utmost importance to aid healthcare professionals and policymakers in informed decision-making and to raise awareness among parents of vulnerable children. Additionally, after an RSV vaccine becomes available in Europe in the coming years, a stable surveillance system will allow to assess vaccine effectiveness and impact on disease burden[2-5]. In 2016, the World Health Organization (WHO) established an RSV surveillance pilot study (2016-2018) based on the Global Influenza Surveillance and Response System (GISRS) in 14 countries[6]. The aim was to standardize RSV surveillance and provide evidence to support Public Health and to inform about the RSV vaccination policy. Based on the key outcomes of the pilot project, several recommendations were proposed, including prioritizing RSV surveillance in children under two years of age and focusing on severe RSV disease that requires hospitalization[6].

Even though seasonal data on RSV detection has been available in Portugal since 2013-2014, data on RSV disease burden is sparse[7-9]. Therefore, following WHO recommendations, a national RSV sentinel network was set up in Portugal to monitor RSV infections in hospitalized children under two years of age. In this work, we describe trends in RSV hospitalizations from the beginning of the surveillance network to most recent data (April 2021 to September 2022). As a secondary objective, we aim to identify risk factors for RSV severe outcomes.

Methods

Setting

The RSV surveillance (VigRSV) network was set up in April 2021 with four hospitals. Until May 2022, it has

gradually expanded to 20 public and private hospitals, from the five mainland regional health administrations (North, Center, Lisbon and Tagus Valley, Alentejo and Algarve) and Madeira Island. The VigRSV network is coordinated by the Portuguese Reference Laboratory for Influenza and other Respiratory Viruses. Detailed information on the participating hospitals is provided in the supplementary material (Table S1).

Case definition

Hospitals reported and tested all acute respiratory infections (ARI) admitted for at least 24 hours. An extended ARI case definition was used for children under two years of age: acute onset of respiratory symptoms (cough, sore throat, shortness of breath or coryza), plus a clinician's judgment that the patient's signs and symptoms are to attributable to a respiratory infection[10]. For children under six months, apnoea and sepsis were also inclusion criteria. Every site reported ARI case-based data using a standardized electronic form. Data collection included the date of symptoms onset, age and gender, clinical history treatment and complications during hospitalization. For this study, we focused on hospitalized ARI cases positive for RSV (RSV-related hospitalizations). All RSV-positive samples were sent to the Portuguese National Reference Laboratory for Influenza and Other Respiratory Virus and genetically characterized. More information on the generic RSV surveillance workflow within the established sentinel surveillance system is presented in supplementary material (Fig. S1).

Study population

The study population comprised children aged 0-2 years living in the geographically defined catchment area of the non-sentinel hospitals (catchment population). The catchment area of the surveillance hospitals is the area that attracts the individuals who usually seek healthcare at the sites when they get sick[11]. To estimate the catchment areas and respective population, we reviewed hospital discharge registries, and for each site, we prepared a hot-spot map based on the place of residency of children aged 0-2 years who were hospitalized due to severe acute respiratory infections (SARI). This map corresponded to a least 85% of SARI cases for each sentinel site in the years between 2018 and 2020. Furthermore, for each selected municipality within the hot spot map, we computed the proportion of SARI in children aged 0-2 years admitted by participating hospitals among all SARI admissions in children aged 0-2 years registered in the muni-cipality. Finally, to estimate the individual contribution of each selected municipality to the catchment population, we applied previously estimated proportions to the most recent resident population estimates for municipalities[12]. This resulted in a total catchment population of 84,547 individuals corresponding to 51.5% of the resident population aged 0-2 years in Portugal. The supplementary material provides detailed information on each sentinel hospital's catchment population (Fig. S2 and Table S1).

Study period

All data was updated on September 16th 2022, and data from the beginning of the RSV surveillance network to the most recent data period between week 14 of 2021 (2021-W14) and week 36 of 2022 (2022-W36) (April 5th 2021 to September 11th 2022) was used as an observation period.

RSV molecular detection and subtyping

Molecular detection of RSV was performed in each participating hospital. Positive RSV samples were sent to the Portuguese National Reference Laboratory for Influenza and other respiratory viruses to be sub-typed as RSV A or RSV B, using a commercial real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) kit[13]. The subtype was also confirmed in all RSV-positive samples with cycle threshold (Ct) values < 25, by partial sequencing of the G gene, using a protocol adapted from that described by Trento et al.[14].

Outcome measures

The primary outcomes of interest were the incidence of RSV-related hospitalizations in children aged 0-2 years and the number of hospitalized children aged 0-2 years with severe RSV infection, assessed by the need for ventilation or admission to an intensive care unit (ICU).

Exposure variables

Risk factors for RSV severe disease included gender (male/female), age group (< 6 months/6-23 months), gestational age category (pre-term/term), birthweight category (low weight/normal weight), presence of chronic conditions (at least one of the following: congenital heart disease, chronic obstructive pulmonary disease, trisomy 21 or immunodeficiency; yes/no) and RSV virus subtype (A/B). Pre-term was defined as a

patient born at gestational age < 37 weeks. Low birthweight was defined as < 2500 g.

Statistical analysis

Weekly incidence of RSV-related hospitalizations, by date of symptoms onset, were used to plot epidemic curves. Demographic and epidemiological characteristics were described using proportions. Crude risk ratios (RR) and 95% confidence intervals (CI) were used to assess the association between gender, age group, gestational age category, birthweight category, chronic diseases, and severity of RSV disease. Comparison of frequency data was performed by the chi-square test or by Fisher's exact test in case of expected frequencies less than five. A p-value < 0.05 was considered evidence of statistical significance. All analyses were performed using R 4.1.2 statistical software[15].

Ethical statement

This study received ethical approval from the Ethical Committee of the Portuguese National Health Institute Doutor Ricardo Jorge. Legal representatives of study participants provided written informed consent. All questionnaires and samples were pseudonymized and the identification key is in possession of the attending physician who performed the data collection.

Results

Trends in RSV-related hospitalizations

Between 2021-W14 and 2022-W36, among a population under surveillance of 84,547 individuals aged 0-2 years, 300 RSV-related hospitalizations were reported. We identified a first surge of RSV-related hospitalizations in June 2021. Following a period with inexistent RSV infections, we observed an increasing trend in RSV-related hospitalizations incidence rate since 2021-W23, peaking in 2021-W31 with a weekly incidence rate of 87.7 per 100,000 population. The RSV-related hospitalizations incidence rate subsided after 2021-W31, however, an increase was registered again in 2021-W37 (incidence rate of 57.5 per 100,000 population) resulting in an elevated incidence rate until 2022-W05. After a period with low RSV detections, a second surge of RSV infections was observed in May 2022, peaking in 2022-W26 with an RSV-related hospitalizations incidence rate of 58.7 per 100,000 population (Fig. 1).

The number of weekly reporting sites increased until 2022-W19, in line with an increasing number of participants in the RSV surveillance network. However, we registered a decrease in the number of reporting sites since the beginning of summer (Fig. 1).

Characteristics of RSV-related hospitalizations

We observed that 63.3% of RSV-related hospitalizations occurred in children under six months old, 16.8% in pre-term children, and 8.0% in children with at least one chronic condition. Severe RSV disease, defined by admission to an ICU unit or ventilation, was observed in 11.0% of children (11.0% were admitted to ICU and 9.7% needed ventilation). More RSV A (64.4%) than RSV B (35.6%) infections were detected (Table 1).

We also analyzed the characteristics of RSV-related hospitalizations in two separate periods: 2021-W23 to 2022-W05 (first epidemic) and 2022-W19 to 2022-W36 (second epidemic) (Fig. 1). We observed that the proportion of children under six months old, children with chronic diseases, and children with complications during the hospitalization (admitted to ICU or needing ventilation) was higher in the period 2021-W23 to 2022-W05 than in the period 2022-W19 to 2022-W36 (Table 1). Although, we have a small number of RSV sub-typed samples in the period 2022-W19 to 2022-W36, we detected more RSV B than RSV A infections, in opposition to those observed in the 2022-W19 to 2022-W36 period (Table 1).

Severity of RSV disease

Children under six months and those suffering from chronic conditions had, respectively, an 18-fold risk (RR: 18.53; 95% CI: 2.57-133.71) and a 2-fold risk (RR: 2.56; 95% CI: 1.17-5.58) of having severe illness compared to children aged 6-23 months and those without chronic conditions (16.8% in children under six months vs. 0.9% in children aged 6-23 months; 25.0% in children with chronic diseases vs. 9.8% in children without chronic conditions) (Table 2).

Discussion

We report two RSV off-season epidemics in June 2021-February 2022 and May-September 2022. We observed an increasing trend in RSV-related hospitalizations since June 2021, coinciding with the easing of non-pharmaceutical interventions (NPI) implemented in Portugal to fight the COVID-19 pandemic, namely, the end of mandatory teleworking and the ban on mass

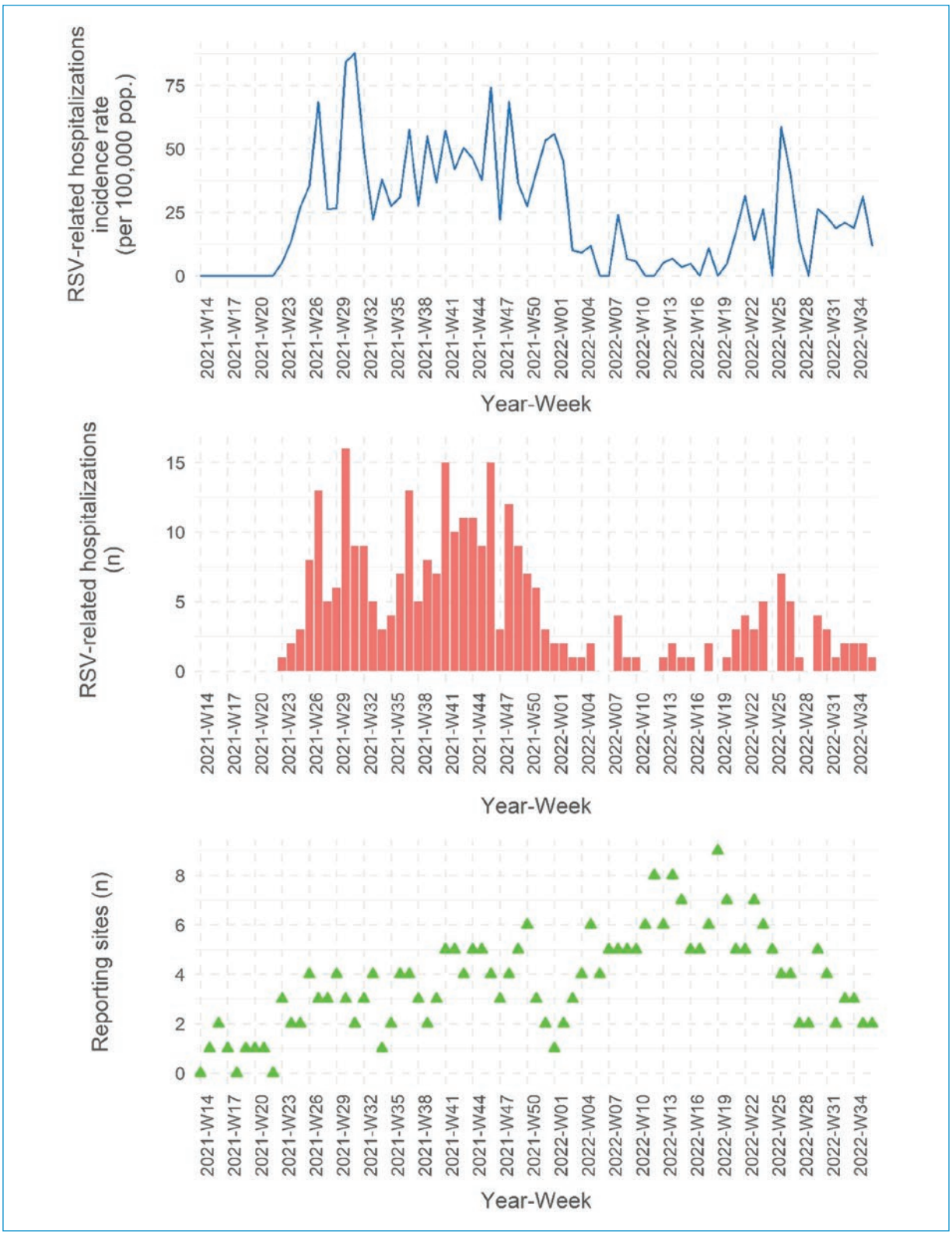

Figure 1. Weekly incidence rate of RSV-related hospitalizations (per 100,000 population) in children aged 0-2 years, number of RSV-related hospitalizations in children aged 0-2 years, and number of reporting sites, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022).
RSV: respiratory syncytial virus.

Table 1. Characteristics of RSV-related hospitalizations in children aged 0-2 years, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022)

	Analysis period 2021-W14 to 2022-W36	First epidemic 2021-W23 to 2022-W05	Second epidemic 2022-W19 to 2022-W36
	n (%)	n (%)	n (%)
Overall	300	243	44
Gender			
Male	155 (51.7)	128 (52.7)	21 (47.7)
Female	145 (48.3)	115 (47.3)	23 (52.3)
Age group			
< 6 months	190 (63.3)	164 (67.5)	18 (40.9)
6-23 months	110 (36.7)	79 (32.5)	26 (59.1)
Gestational age category			
Pre-term	50 (16.8)	38 (15.8)	8 (18.2)
Term	248 (83.2)	203 (84.2)	36 (81.8)
Birthweight category			
Low weight	43 (14.6)	33 (13.9)	7 (15.9)
Normal weight	252 (85.4)	205 (86.1)	37 (84.1)
Chronic conditions			
Yes	24 (8.0)	21 (8.6)	3 (6.8)
No	276 (92.0)	222 (91.4)	41 (93.2)
RSV subtype			
A	85 (64.4)	79 (67.5)	4 (40.0)
B	47 (35.6)	38 (32.5)	6 (60.0)
Severe RSV disease			
Yes	33 (11.0)	30 (12.3)	3 (6.8)
No	267 (89.0)	213 (87.7)	41 (93.2)

RSV: respiratory syncytial virus.

Table 2. Risk factors for severe RSV-related hospitalizations, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022)

	n (%)	RR (95% CI)	p-value
Gender			
Masculine	19 (12.3)	0.79 (0.41-1.51)	0.472
Feminine	14 (9.7)		
Age group			
< 6 months	32 (16.8)	18.53 (2.57-133.71)	< 0.001
6-23 months	1 (0.9)		
Gestational age category			
Pre-term	9 (18.0)	1.86 (0.92-3.76)	0.134
Term	24 (9.7)		
Birthweight category			
Low weight	7 (16.3)	1.58 (0.73-3.41)	0.270
Normal weight	26 (10.3)		
Chronic conditions			
Yes	6 (25.0)	2.56 (1.17-5.58)	0.044
No	27 (9.8)		
RSV subtype			
A	14 (16.5)	0.65 (0.25-1.68)	0.444
B	5 (10.6)		

RSV: respiratory syncytial virus.

gatherings[16]. As transmission pathways of RSV include aerosols, inhalation of virus-laden liquid droplets, close contact with infected individuals, and contact with contaminated surfaces, activities such as mass gatherings had a plausible direct impact on increasing infectious social contacts[17]. On the other hand, the end of mandatory teleworking with more parents resorting to childcare providers and increasing mobility has the potential to accelerate RSV transmission in the community. After easing COVID-19 NPIs, similar out-of-season epidemics were also experienced in several countries worldwide[18-24]. The incidence rate of RSV-related hospitalizations subsided as the summer progressed, in temporal association with increased in mobility in parks, retail, and recreation[25]. Therefore, we postulate that summer holidays and the consequent absence of school activities were responsible for the disruption in RSV transmission and decreased RSV-related hospitalizations. However, the incidence of RSV-related hospitalizations increased again following the re-opening of the schools, this time with a continuous surge of cases throughout the autumn/winter, until February 2022. We registered a new period of anomalous RSV activity, from May 2022 onwards, although, with lower intensity than the June 2021-February 2022 epidemic. This RSV epidemic followed the end of the mask mandate in Portugal on April 22nd 2022[16]. Considering RSV transmission pathways, we hypothesize, that lifting the mask mandate facilitated RSV transmission in Portugal. However, the impact of mask mandates may go beyond the direct impact on RSV incidence. It may be an indirect consequence of changes in the population´s daily activities, supported by an increase in mobility trends for transit stations and a decrease in residential places in Portugal after lifting the mask mandate, or an indirect consequence of altered risk perception, which was found to be associated with restrictions imposed to mitigate the pandemic in a Portuguese study[26,27]. Given that the COVID-19 pandemic had an impact on the circulation of RSV and the risk of infection or pressures in the healthcare systems may occur at different times, year-round RSV surveillance systems are recommended in order to monitor RSV activity throughout the year.

The proportion of RSV-related hospitalizations with severe disease in June 2021-February 2022, was higher than that reported by previous national studies[8,9]. We postulate that this result may be overestimated due to the high number of cases reported by central hospitals. Nonetheless, we could not undertake a sensitivity analysis excluding cases reported by central hospitals due to the small number of hospitals reporting in the beginning of the surveillance network. However, we also hypothesize that the absence of RSV circulation during the first COVID-19 pandemic year may be associated with diminished immunity in young children and, consequently, an increased risk of developing severe disease[28]. This hypothesis is in line with a study conducted in the setting of a delayed surge of RSV in the USA which showed a more severe disease course[29]. Additionally, surveillance data from New Zealand, for children aged 0-4 years, show that, in 2021, the RSV-related ICU incidence rate was 2-8 times higher than the average peaks between 2015 and 2019[22].

We found that children under six months old and children with chronic conditions had an increased risk of severe illness. These results are consistent with a systematic literature review on the risk factors for severe RSV in young children[30]. Additionally, the lower proportion of children under 6 months and with chronic conditions hospitalized due to RSV in May-September 2022, compared to the June 2021-February 2022 period, may be associated with the lower proportion of severe RSV cases observed. However, we still have to consider that: (1) immunity debt in May-September 2022 was expected to be lower than in June 2021-February 2022 and, hence, we expected to observe a decreased proportion of severe cases; (2) although, no association was found between RSV subtype and severity of disease, previous studies showed RSV subtype A to be associated with a more severe disease compared with subtype B[31]. Consequently, the lower proportion of RSV severe cases in the second epidemic wave may also be related to dominance of the RSV subtype B, even if statistical significance was not reached because of the small sample size. In the long term, we aim to compute adjusted risk-ratios with a larger sample size and test these hypotheses.

We detected more RSV A than RSV B infections in June 2021-February 2022. However, we have a small number of sub-typed samples in May-September 2022 and more RSV B samples were detected. Evidence in the related literature shows that following an RSV infection, individuals gain transient immunity with an average duration of 2 years[32]. As this immunity is partial in its efficacy, and greater for the homologous challenge (60%) than heterologous (16%), the A/B dominance patterns observed in June 2021-February 2022 and May-September 2022 are expected[32].

This study has several limitations. Firstly, the number of reporting sites varied during our analysis period, specifically, with a higher proportion of central hospitals reporting during the first RSV epidemic wave and a decreasing participation rate during the second RSV

epidemic wave, coincident with the beginning of summer. We expect that participation rates will increase at the beginning of the influenza and other respiratory virus surveillance seasons, in week 40 of 2022, even though, an attempt should be made to engage hospitals in year-round surveillance. Also, the Azores islands were not yet included in the surveillance network and thus, an attempt should be made to engage the local hospitals of the region in order to cover all the Portuguese territory. Nevertheless, our surveillance network has the advantage of including a large study population, corresponding to 51.5% of Portuguese children aged 0-2 years, and thereby, it provides useful information on RSV epidemiology. Finally, as this surveillance network was implemented in 2021, we lack baseline data regarding RSV-related hospitalizations from previous seasons and, therefore, we cannot make a comprehensive assessment of the epidemics, or set thresholds to assess the impact of disease in the population.

Acknowledgments

The authors warmly thank Dr. David Lito for critical reviewing this work.

Supplementary data

Supplementary data are available at DOI: 10.24875/PJP.M23000129. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Vol. 390, The Lancet. 2017. p. 946-58.
2. Mollers M, Barnadas C, Broberg EK, Penttinen P, Teirlinck AC, Fischer TK, et al. Current practices for respiratory syncytial virus surveillance across the EU/EEA Member States, 2017. Eurosurveillance [Internet]. 2019;24(40). Available from: http://dx.doi.org/10.2807/1560-7917.ES.2019.24.40.1900157
3. Teirlinck AC, Broberg EK, Berg AS, Campbell H, Reeves RM, Carnahan AS, et al. Recommendations for respiratory syncytial virus surveillance at the national level. Eur Respir J. 2021;58(3).
4. McKimm-Breschkin JL, Hay AJ, Cao B, Cox RJ, Dunning J, Moen AC, et al. COVID-19, Influenza and RSV: Surveillance-informed prevention and treatment – Meeting report from an isirv-WHO virtual conference. Antiviral Res. 2022;197(December 2021).
5. Mejias A, Rodriguez-Fernandez R, Peeples ME, Ramilo O. Respiratory Syncytial Virus Vaccines: Are We Making Progress? Pediatr Infect Dis J. 2021;38(10):1-9.
6. World Health Organization (WHO). WHO strategy for global respiratory syncitial virus surveillance project based on the influenza platform. Geneva; 2019.
7. INSA. Boletim de Vigilância Epidemiológica da Gripe e Outros Vírus Respiratórios [Internet]. [cited 2022 Aug 29]. Available from: https://www.insa.min-saude.pt/category/informacao-e-cultura-cientifica/publicacoes/atividade-gripal
8. Mendes-da-Silva A, Gonçalves-Pinho M, Freitas A, Azevedo I. Trends in hospitalization for acute bronchiolitis in Portugal: 2000-2015. Pulmonology. 2019;25(3):154-61.
9. Bandeira T, Azevedo I, Rodrigues F, Januário G, Tomé T, Díez DJ, et al. Understanding the burden of RSV hospitalizations among young children: an administrative database analysis from 2015 2018 Spain and Portugal. In: Annual Meeting of the European Society for Paediatric Infectious Diseases. 2019.
10. World Health Organization (WHO). RSV surveillance case definitions [Internet]. [cited 2022 Jun 20.] Available from: https://www.who.int/teams/global-influenza-programme/global-respiratory-syncytial-virus-surveillance/case-definitions
11. World Health Organization (WHO). A manual for estimating disease burden associated with seasonal influenza. 2015.
12. Statistics Portugal. Estimates of resident population [Internet]. [cited 2022 May 27]. Available from: https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0011166&xlang=pt
13. Gimferrer L, Andrés C, Rando A, Piñana M, Codina MG, Martin M del C, et al. Evaluation of Seegene Allplex Respiratory Panel 1 kit for the detection of influenza virus and human respiratory syncytial virus. J Clin Virol [Internet]. 2018;105(April):31-4. Available from: https://doi.org/10.1016/j.jcv.2018.05.006
14. Trento A, Casas I, Calderón A, Garcia-Garcia ML, Calvo C, Perez-Breña P, et al. Ten Years of Global Evolution of the Human Respiratory Syncytial Virus BA Genotype with a 60-Nucleotide Duplication in the G Protein Gene. J Virol. 2010;84(15):7500-12.
15. R Core Team. R: A language and environment for statistical computing. Vienna, Austria [Internet]: R Foundation for Statistical Computing; 2017.
16. República Portuguesa XXII Governo. Legislação COVID-19 [COVID-19 Legislation] [Internet]. [cited 2022 Feb 23]. Available from: https://dre.pt/dre/geral/legislacao-covid-19
17. Kutter JS, Spronken MI, Fraaij PL, Fouchier RA, Herfst S. Transmission routes of respiratory viruses among humans. Curr Opin Virol [Internet]. 2018;28:142-51. Available from: http://dx.doi.org/10.1016/j.coviro.2018.01.001
18. Weinberger Opek M, Yeshayahu Y, Glatman-Freedman A, Kaufman Z, Sorek N, Brosh-Nissimov T. Delayed respiratory syncytial virus epidemic in children after relaxation of COVID-19 physical distancing measures, Ashdod, Israel, 2021. Euro Surveill [Internet]. 2021;26(29):2017-21. Available from: http://dx.doi.org/10.2807/1560-7917.ES.2021.26.29.2100706
19. Vaux S, Viriot D, Forgeot C, Pontais I, Savitch Y, Barondeau-Leuret A, et al. Bronchiolitis epidemics in France during the SARS-CoV-2 pandemic: The 2020–2021 and 2021–2022 seasons. Infect Dis Now. 2022;52(6):374-8.
20. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N, Ujiie M. Resurgence of respiratory syncytial virus infections during covid-19 pandemic, tokyo, japan. Emerg Infect Dis. 2021;27(11):2969-70.
21. Foley DA, Yeoh DK, Minney-Smith CA, Martin AC, Mace AO, Sikazwe CT, et al. The Interseasonal Resurgence of Respiratory Syncytial Virus in Australian Children following the Reduction of Coronavirus Disease 2019-Related Public Health Measures. Clin Infect Dis. 2021;73(9):E2829-30.

22. Hatter L, Eathorne A, Hills T, Bruce P, Beasley R. Respiratory syncytial virus: paying the immunity debt with interest. Lancet Child Adolesc Heal [Internet]. 2021;5(12):e44-5. Available from: http://dx.doi.org/10.1016/S2352-4642(21)00333-3
23. Tenenbaum T, Doenhardt M, Diffloth N, Berner R, Armann JP. High burden of RSV hospitalizations in Germany 2021-2022. Infection [Internet]. 2022;(0123456789):1-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/35904753%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC9334552
24. Loconsole D, Centrone F, Rizzo C, Caselli D, Orlandi A, Cardinale F, et al. Out-of-Season Epidemic of Respiratory Syncytial Virus during the COVID-19 Pandemic: The High Burden of Child Hospitalization in an Academic Hospital in Southern Italy in 2021. Children. 2022; 9(6):848.
25. Google. COVID-19 Community mobility reports [Internet]. [cited 2022 Aug 3]. Available from: https://www.google.com/covid19/mobility
26. Stevens NT, Sen A, Kiwon F, Morita PP, Steiner SH, Zhang Q. Estimating the Effects of Non-Pharmaceutical Interventions and Population Mobility on Daily COVID-19 Cases: Evidence from Ontario. Can Public Policy. 2022;48(1):144-61.
27. Escola Nacional de Saúde Pública. Opinião Social: Perceção de risco acompanha situação epidemiológica e é sensível ao contexto [Social Opinion: Risk perception follows epidemiological situation and is sensitive to context] [Internet]. [cited 2022 Aug 3]. Available from: https://barometro-covid-19.ensp.unl.pt/opiniao-social-percecao-de-risco-acompanha-situacao-epidemiologica-e-e-sensivel-ao-contexto
28. Lancet T, Medicine R. COVID-19 pandemic disturbs respiratory virus dynamics. Lancet Respir. 2022;2600(22):2600.
29. Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. Pediatrics. 2021;148(3).
30. Shi T, Vennard S, Mahdy S, Nair H. Risk Factors for Poor Outcome or Death in Young Children With Respiratory Syncytial Virus-Associated Acute Lower Respiratory Tract Infection: A Systematic Review and Meta-Analysis. J Infect Dis. 2022;226(1):S10-6.
31. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus - A comprehensive review. Clin Rev Allergy Immunol. 2013;45(3):331-79.
32. White LJ, Waris M, Cane PA, Nokes DJ, Medley GF. The transmission dynamics of groups A and B human respiratory syncytial virus (hRSV) in England & Wales and Finland: Seasonality and cross-protection. Epidemiol Infect. 2005;133(2):279-89.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

DYRK1A-related intellectual disability syndrome: a cohort of Portuguese patients

Raquel Gouveia-Silva[a], João Rodrigues-Alves[b], Juliette Dupont[c], Oana Moldovan[d], Patrícia Dias, Márcia Rodrigues[e], Ana Medeira, and Ana B. Sousa*

Serviço de Genética Médica, Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar e Universitário Lisboa Norte, Lisbon, Portugal

ORCID: [a]0000-0002-5470-5490; [b]0000-0002-8659-1862; [c]0000-0001-8257-5067; [d]0000-0003-0274-4313; [e]0000-0001-6174-2524

Abstract

Introduction: *DYRK1A* heterozygous pathogenic variants have been shown to cause a syndromic form of intellectual disability (ID) with impaired speech development, features of autism spectrum disorder (ASD), microcephaly, and a recognizable facial gestalt that evolves with age. Patients can also present with gait disturbance or hypertonia, epilepsy, brain imaging, ocular, and foot anomalies. **Methods:** This is a cross-sectional study. Clinical data on patients with *DYRK1A* pathogenic variants identified at the Clinical Genetics Department of Santa Maria Hospital, in Lisbon, were retrospectively collected from medical records using a detailed clinical questionnaire. **Results**: We describe eight unrelated patients, six females and two males, aged 4 to 24. Fetal growth restriction (FGR) was present in 5/8, and microcephaly in 7/8. ID, ranging from mild to severe, and language impairment or absent speech were documented in all patients. ASD and/or stereotypic behavior were reported in 6/8. Five patients presented visual anomalies, most commonly optic disc pallor (in 4). Three main facial features were consistently reported: deep-set eyes, thin upper lip, and micro/retrognathia. Foot and hand anomalies were frequent. **Discussion/Conclusions:** Our cohort illustrates the variable degree of severity of a syndromic form of ID, which includes mild cases. Microcephaly and a typical neurobehavioral phenotype are in accordance with the literature, as well as some common dysmorphisms. Interestingly, optic disc pallor seems to be a frequent finding, highlighting the need for ophthalmological surveillance. Our study adds evidence to the existence of a consistent clinical phenotype of *DYRK1A*-related ID, hopefully contributing to increased awareness and improving the recognition of this entity.

Keywords: *DYRK1A*. Intellectual disability. Portuguese cohort.

Perturbação do desenvolvimento intelectual associada ao gene DYRK1A: uma coorte de doentes portugueses

Resumo

Introdução: Variantes patogénicas em heterozigotia no gene *DYRK1A* causam uma forma sindromática de perturbação do desenvolvimento intelectual (PDI) com comprometimento do desenvolvimento da linguagem, características de perturbação do espectro do autismo (PEA), microcefalia e um gestalt facial reconhecível que evolui com a idade. Os doentes também podem apresentar distúrbios da marcha ou hipertonia, epilepsia, alterações cerebrais estruturais, anomalias oculares e nos pés.

***Correspondence:**
Raquel Gouveia-Silva
E-mail: ana.g.f.silva@chln.min-saude.pt

Received: 03-01-2023
Accepted: 20-06-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):13-19
DOI: 10.24875/PJP.M23000130

Métodos: Trata-se de um estudo transversal. Os dados clínicos de doentes com variantes patogénicas no gene *DYRK1A* identificados no Departamento de Genética Clínica do Hospital de Santa Maria, em Lisboa, foram recolhidos retrospetivamente a partir de registos médicos através de um questionário clínico detalhado. **Resultados:** Descrevemos oito doentes não aparentados, seis do sexo feminino e dois do sexo masculino, com idades entre 4 e 24 anos. A restrição do crescimento fetal (RCF) esteve presente em 5/8 e a microcefalia em 7/8. PDI, ligeira a grave, com compromisso da linguagem ou a sua ausência, foi documentada em todos os casos. PEA e/ou comportamento estereotipado foram relatados em 6/8. Cinco pacientes apresentaram anomalias visuais, mais frequentemente palidez do disco óptico (em 4). Três características faciais principais foram consistentemente relatadas: olhos afundados, lábio superior fino e micro/retrognatia. Anomalias nos pés e nas mãos foram frequentes. **Discussão/Conclusões:** A nossa coorte ilustra o grau variável de gravidade de uma forma sindromática de PDI, que inclui casos ligeiros. A microcefalia e um fenótipo neurocomportamental típico estão de acordo com a literatura, assim como alguns dismorfismos comuns. Curiosamente, a palidez do disco óptico parece ser um achado frequente, destacando a necessidade de vigilância oftalmológica. O nosso estudo acrescenta evidências da existência de um fenótipo clínico consistente de PDI relacionada ao gene *DYRK1A*, contribuindo para aumentar e melhorar o reconhecimento desta entidade.

Palavras-chave: *DYRK1A*. Perturbação intelectual. Coorte portuguesa.

Keypoints

What is known
- *DYRK1A*-related intellectual disability syndrome is a rare condition with variable degrees of developmental delay reported.
- Loss-of-function DYRK1A pathogenic variants include disruptive balanced rearrangements, copy number variants, and single nucleotide variants (SNVs).
- No genotype-phenotype correlations could be consistently drawn.

What is added
- We report a new cohort of patients with *DYRK1A*-related intellectual disability syndrome.
- With advances on next-generation sequencing techniques, we expected an earlier diagnosis, raising awareness about common dysmorphic features, delineating a typical gestalt.
- Considering the prevalence of eye problems, namely optic disc pallor, a careful ophthalmological evaluation must be performed.

Introduction

DYRK1A (dual-specificity tyrosine phosphorylation regulated kinase 1A) is a protein kinase encoded on human chromosome 21[1-3]. The gene is dosage-sensitive with an impact on neurodevelopment[4]. *DYRK1A* is over expressed in Down syndrome (DS) and plays a relevant role in neuronal proliferation, differentiation, plasticity, and aging, making it a primary target for the development of DS therapeutics[2,5]. Dysregulation of *DYRK1A* levels also occurs in neurodegenerative diseases, such as Alzheimer and Parkinson[6].

Since 2008, the *DYRK1A* gene has gained attention in the clinical setting, starting with the description of two patients with microcephaly, fetal growth restriction, and febrile seizures. Both had a *de novo* balanced translocation that truncated the *DYRK1A* gene, suggesting *DYRK1A* haplo-insufficiency is associated with brain developmental changes[7].

In 2011, a *de novo* micro-deletion involving the last three exons of *DYRK1A* was described in a female with microcephaly and intellectual disability[8]. Considering these chromosomal rearrangements, as well as large deletions encompassing additional genes (that may contribute to extra-*DYRK1A*-related features)[9,10,11], van Bon et al. proposed that the heterozygous disruption of this gene causes a distinctive neuro-developmental syndrome, including mild to severe ID, microcephaly, and impaired speech[3].

One year later, Courcet et al. described a patient with an Angelman-like phenotype carrying a frameshift variant affecting the N-terminal part of the gene[12,13]. As more patients with single nucleotide variants in *DYRK1A* were documented, this gene was definitely placed on the list of genes responsible for syndromic ID. Furthermore, it has also been linked to autism spectrum disorder (ASD), with studies showing that *DYRK1A* syndrome accounts for 0.1-0.5% of individuals with ID and/or autism[3,12,14].

Core symptoms of *DYRK1A*-related ID syndrome (*OMIM#614104*) (also known as *DYRK1A*-haploinsufficiency syndrome or autosomal dominant mental retardation 7, MRD7) are ID with impaired speech development of variable degree, features of ASD with anxious and/or stereotypic behavior problems, microcephaly, and a recognizable facial gestalt that evolves with age[3,15]. Patients can also present with gait disturbance or hypertonia, epilepsy, brain-MRI anomalies, feeding issues, eye problems, and foot anomalies[15-17].

Loss-of-function *DYRK1A* pathogenic variants include disruptive balanced rearrangements, copy number variants, and single nucleotide variants (SNVs)[16]. About 500 families are part of the *DYRK1A* Syndrome International Association (DSIA). According to our acknowledge, there are around 112 patients reported in the literature[1,3,7,12-25] of whom with chromosomal abnormalities, including large deletions, translocations, inversions, inversion/deletions, and other complex rearrangements, and 87 patients harboring a SNV. Most reported SNVs were frameshift variants, followed by nonsense, missense, and splice site variants[16].

With this report, we aim to contribute to further delineating the phenotype of this still under-recognized but increasingly diagnosed condition.

Methods

This is a retrospective and cross-sectional study. Clinical data on patients with *DYRK1A* variants identified at the Genetics Department of Santa Maria Hospital, in Lisbon, were collected from medical records during 2022. We searched in our internal database (Microsoft® Office Access 2019) for patients with this diagnosis followed from January 2010 until December 2022 in our genetic service of a tertiary level hospital. Patient characterization was performed through a detailed questionnaire, completed by the clinician and organized into a standardized form designed in Microsoft® Office Excel 2010. This form was based on international registries and available literature, including information on the demographics, patient and family history, clinical and laboratory findings, genetic studies, and evolution. The molecular diagnosis was possible through whole exome sequencing (WES, CentoXome® from the Centogene laboratory in Germany) in all cases.

Results

A diagnosis of *DYRK1A*-related ID syndrome was made for eight unrelated patients, six females and two males, aged 4 to 24 years old, all representing simplex cases with a pathogenic or likely pathogenic variant in the *DYRK1A* gene. The summary of their main clinical features is shown in table 1.

FGR was present in 5/8. Further growth evaluation showed short stature in 4/8 and microcephaly in 7/8. ID, ranging from mild to severe, and language impairment (6/8) or absent speech (2/8) were documented in all patients. ASD and/or stereotypic behavior were present in 6/8. Only two patients had epilepsy, brain anomalies on MRI were present in 3/7, and 4/8 had gait disturbance (often ataxic) and hypertonic extremities, with no need to use support devices. Five patients had visual anomalies (strabismus, astigmatism, hypermetropia, optic nerve anomalies), with optic disc pallor present in four of them.

Characteristic facial features consistently reported were deep-set eyes (7/8), thin upper lip (8/8), and micro/retrognathia (5/8). Foot anomalies were described in 5/8 patients. Additional common features included thick eyebrows, prominent nose, large or dysplastic ears, and large mouth (Fig. 1).

The diagnosis was made on whole exome sequencing (WES) in all cases, but suspected clinically in four. *DYRK1A* variants were classified as pathogenic or likely pathogenic using ACMG criteria. All variants were located between exons four and ten, and 7/8 were loss of function, including three frameshift, two splicing, and two nonsense variants. There was only one missense variant not affecting the kinase domain. Parental segregation studies confirmed all cases were *de novo* (Table 1).

Patient 6 had an additional pathogenic variant in *PKD2* gene, explaining the presence of renal cysts.

Discussion

The purpose of this study was to characterize the *DYRK1A*-related ID syndrome patients diagnosed in our Medical Genetics Department. No Portuguese cohort has been published so far, and this syndrome is still unknown to many medical professionals dealing with ID/ASD patients. We have attempted to further delineate the phenotype of these patients by comparing them with those already described in the literature harboring a causative variant in *DYRK1A* gene. The clinical findings were consistent with the literature (Table 1).

Clinically, it is worth emphasizing the variable degree of severity of ID[3,6,15], which includes two mild cases in this cohort. Language impairment is seen in a significant proportion of patients[15,17], with completely absent speech in two of ours. ASD, stereotypes, anxious behavior, hyperactivity, and sleep disturbances have also been frequently observed[3,15], and were reported in all but two individuals in this cohort. Conversely, only two patients had epilepsy, which is lower than in the literature[12,17]. Seizures of the atonic, absence, and generalized myoclonic types have all been previously described[1,3,12,13]. FGR was present in 5/8 patients and can be a non-specific clue for the diagnosis of *DYRK1A*-related ID syndrome in the prenatal setting[3,13,20], but more reports are needed to reinforce this finding. Head circumference at birth is known to be between –1 and –4 SD, and abnormally slow head growth causes the

Table 1. Clinical characteristics of our cohort of Portuguese patients with *DYRK1A*-related intellectual disability syndrome and literature comparison

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Total n = 8 (%)	Patients in literature (%) 1,3, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,22, 23, 24
Age (years)	14	19	12	24	4	18	5	7	-	-
Genotype	c. 361C>T, p. (Gln121*)	c. 1405C>T, p. (Gln469*)	c. 665-9_ 665-5del	c. 562A>G, p.(Lys188Glu)	c. 336_348del, p.(Ala113Glufs*33)	c. 358del, p. (Gln120Asnfs*30)	c. 951+4_ 951+7del	c. 894del, p. (Lys299Asnfs*7)	-	-
Type of variant	Nonsense*	Nonsense	Splicing*	Missense	Frameshift	Frameshift	Splicing*	Frameshift	-	-
Classification	Likely pathogenic	Likely pathogenic	Pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Pathogenic	Likely pathogenic	-	-
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	-	-
Sex	F	F	F	M	F	M	F	F	-	-
FGR	-	+	+	-	+	+	+	-	5/8 (63%)	33-64%
Microcephaly	-	+	+	+	+	+	+	+	7/8 (88%)	68-98%
Short stature	-	+	+	+	-	-	+	-	4/8 (50%)	10-41%
DD/ID	Mild-Moderate	Moderate	Mild	Severe	Moderate	Severe	Moderate	Moderate	8/8 (100%)	95-100%
Speech impairment	Impaired	Impaired	Impaired	Absent speech	Impaired	Impaired	Absent speech	Impaired	8/8 (100%)	96-100%
ASD/ Stereotypic behaviour	-	+	+	+	+	-	+	+	6/8 (75%)	29-50%
Feeding issues	-	-	-	+	-	-	+	+	3/8 (38%)	48-82%
Gait disturbance and/or hypertonia	-	-	-	+	+	-	+	+	4/8 (50%)	NA
Epilepsy	-	-	-	+	-	+	-	-	2/8 (25%)	20%-67%

(Continues)

Table 1. Clinical characteristics of our cohort of Portuguese patients with *DYRK1A*-related intellectual disability syndrome and literature comparison *(continued)*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Total n = 8 (%)	Patients in literature (%) 1,3, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,22, 23, 24
Brain MRI anomalies	Megacisterna magna, hipoplasia of optic nerve and chiasma, corpus callosum agenesis	-	-	Cerebellar atrophy	-	-	NA	Bilateral ventricular enlargement	3/7 (43%)	31%-59%
Eye anomalies	Strabismus, astigmatism, hypermetropia, optic disc pallor, optic nerve bilateral atrophy	-	Strabismus, optic disc pallor	Strabismus, optic disc pallor	Temporal optic disc pallor	Strabismus	-	-	5/8 (63%)	46%-58%
Hand/feet anomalies	+	+	-	+	+	+	-	-	5/8 (63%)	37-50%
Deep set eyes	+	+	+	+	+	+	-	+	7/8 (88%)	10-29%
Large ears	+	+	+	+	-	-	-	-	4/8 (50%)	50-58%
Dysplastic ears	-	-	+	-	-	+	-	+	3/8 (38%)	NA
Long/flat filtrum	-	+	-	-	+	-	-	+	3/8 (38%)	NA
Thin upper lip	+	+	+	+	+	+	+	+	8/8 (100%)	NA
Micro/ retrognathia	+	-	-	+	+	+	-	+	5/8 (63%)	37%-54%
Additional features	Long eyelashes, bulbous nose tip, prominent supraciliary arch	Bitemporal narrowing, thick eyebrows, hypotelorism, malar hypoplasia, large mouth	Metopic prominence	Thick eyebrows, long nose, malar hypoplasia, large mouth		Renal cysts due to *PKD2* heterozygous pathogenic variant				

*Previously reported variants. ASD: autism spectrum disorder; DD: developmental delay; F: female; FGR: fetal growth restriction; ID: intellectual disability; M: male; NA: not available.

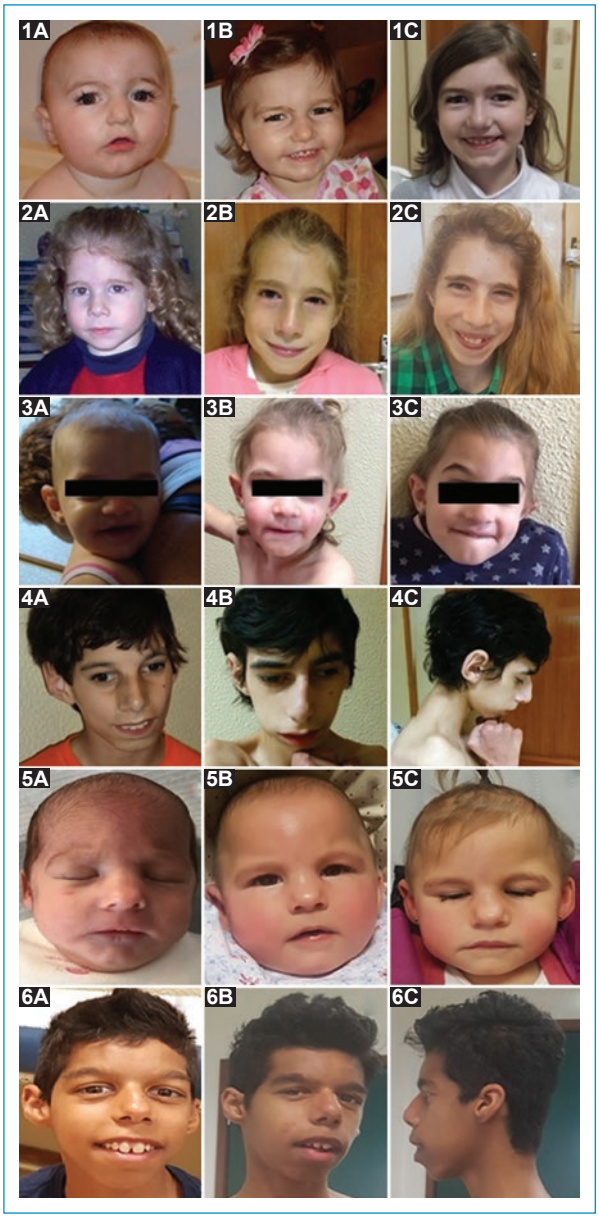

Figure 1. Images depicting similar and key dysmorphic features of presented cases, namely deep set eyes, thin upper lip and micro/retrognathia. **1A:** patient 1 at 11 months. **1B:** 5 years. **1C:** 10 years. **2A:** patient 2 at 3 years. **2B:** 11 years. **2C:** 13 years. **3A:** patient 3 at 1 year. **3B:** 3 years. **3C:** 6 years. **4A:** patient 4 at 13 years. **4B and C:** at 19 years. **5A:** patient 5 at 1 month. **5B:** 6 months. **5C:** 2 years. **6A:** patient 6 at 13 years. **6B and C:** 18 years.

deviation to further increase over time to –2 to –5 SD in the majority of individuals[3,15,17]. Accordingly, microcephaly was present in all but one patient in this report.

Gait disturbances, broad-based or stiffed, has been reported in a smaller fraction of individuals[17], with about half of the cases presenting this characteristic, very similar to what happens in our cohort.

Brain anomalies were described in 3/7 patients who had an MRI, including ventricular enlargement, sub-ependymal cysts, hypoxic-ischemic-like anomalies, corpus callosum agenesis, and cerebellar atrophy. Brain MRI anomalies are not well established in the literature, involving from grey matter to cerebral spinal fluid and ventricle anomalies[25,26].

Ocular anomalies were reported in five patients in our cohort, in line with Méjécase et al., who describe ocular features in 60.3% of patients with *DYRK1A* SNVs, predominantly refractive errors[16]. Optic nerve anomalies, including optic disc pallor, have been reported in 22.9% of patients[16], and were present in half of our cases.

Several publications refer to a typical gestalt or common dysmorphisms[1,3,13,15,18,20]. All patients in this report had a thin upper lip, and deep-set eyes were described in all but one (Fig. 1). Other frequent features include micro/retrognathia and large ears. In adulthood, the nasal bridge may become high and the alae nasi underdeveloped, giving the nose a more prominent appearance[3], as shown in patient 6 (Figs. 1-6 A, B, C).

Hand and feet anomalies were also frequent in our cohort and in previously reported patients[15,17], namely long splayed fingers, clinodactyly, mild cutaneous syndactyly of toes, hallux valgus, and short fifth toe.

The majority of variants elicited in our cohort were truncating, namely frameshift (Table 1), which is in accordance with previous reports[16]. Only three missense variants were previously reported in the literature[3,26]. No genotype-phenotype correlations could be consistently drawn. All cases were *de novo*.

From the above, it is clear that all *DYRK1A*-related syndrome ID patients need guidance for educational and behavioral problems, and should be regularly monitored for growth parameters and nutritional status, as well as have lifelong specialist follow up for issues affecting particular organs and systems[6,16,23]. Early motor intervention is also relevant regarding gait disorders and hypertonia, in order to avoid the use of a mobility device in the future[17]. Of note, taking into account the prevalence of eye problems, multidisciplinary care must include a careful ophthalmological evaluation.

All in all, national and international registries[27], and other forms of data sharing, are paramount in acquiring new insights into the pathophysiology and genetic mechanisms underlying this condition, which will ultimately contribute to improve patient management. In line with this endeavor, we hope this clinical review contributes to raise awareness of *DYRK1A*-related ID syndrome, namely among Portuguese doctors, so as to prompt the diagnosis of more patients.

Acknowledgments

The Genetics Service at Hospital de Santa Maria collaborates with the European Reference Network on Congenital Malformations and Rare Intellectual Disability (ERN-ITHACA) at the date of publication.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Bronicki LM, Redin C, Drunat S, Piton A, Lyons M, Passemard S, et al. Ten new cases further delineate the syndromic intellectual disability phenotype caused by mutations in DYRK1A. Eur J Hum Genet. 2015 Nov;23(11):1482-7.
2. Duchon A, Herault Y. DYRK1A, a Dosage-Sensitive Gene Involved in Neurodevelopmental Disorders, Is a Target for Drug Development in Down Syndrome. Front Behav Neurosci. 2016:Jun 3;10:104.
3. van Bon BW, Coe BP, Bernier R, Green C, Gerdts J, Witherspoon K, et al. Disruptive de novo mutations of DYRK1A lead to a syndromic form of autism and ID. Mol Psychiatry. 2016 Jan;21(1):126-32.
4. Liu F, Liang Z, Wegiel J, Hwang YW, Iqbal K, Grundke-Iqbal I, et al. Overexpression of Dyrk1A contributes to neurofibrillary degeneration in Down syndrome. FASEB J. 2008 Sep;22(9):3224-33.
5. Meissner LE, Macnamara EF, D'Souza P, Yang J, Vezina G; Undiagnosed Diseases Network, Ferreira CR, Zein WM, Tifft CJ, Adams DR. DYRK1A pathogenic variants in two patients with syndromic intellectual disability and a review of the literature. Mol Genet Genomic Med. 2020;8(12):e1544.
6. Arbones ML, Thomazeau A, Nakano-Kobayashi A, Hagiwara M, Delabar JM. DYRK1A and cognition: A lifelong relationship. Pharmacol Ther. 2019;194:199-221.
7. Møller RS, Kübart S, Hoeltzenbein M, Heye B, Vogel I, Hansen CP, et al. Truncation of the Down syndrome candidate gene DYRK1A in two unrelated patients with microcephaly. Am J Hum Genet. 2008 May;82(5):1165-70.
8. van Bon BW, Hoischen A, Hehir-Kwa J, de Brouwer AP, Ruivenkamp C, Gijsbers AC, et al. Intragenic deletion in DYRK1A leads to mental retardation and primary microcephaly. Clin Genet. 2011;79(3):296-9.
9. Fujita H, Torii C, Kosaki R, Yamaguchi S, Kudoh J, Hayashi K, et al. Microdeletion of the Down syndrome critical region at 21q22. Am J Med Genet A. 2010;152A:950-3.
10. Lyle R, Béna F, Gagos S, Gehrig C, Lopez G, Schinzel A, et al. Genotype-phenotype correlations in Down syndrome identified by array CGH in 30 cases of partial trisomy and partial monosomy chromosome 21. Eur J Hum Genet. 2009 Apr;17(4):454-66.
11. Matsumoto N, Ohashi H, Tsukahara M, Kim KC, Soeda E, Niikawa N. Possible narrowed assignment of the loci of monosomy 21-associated microcephaly and intrauterine growth retardation to a 1.2-Mb segment at 21q22.2. Am J Hum Genet. 1997 Apr;60(4):997-9.
12. Courcet JB, Faivre L, Malzac P, Masurel-Paulet A, Lopez E, Callier P, et al. The DYRK1A gene is a cause of syndromic intellectual disability with severe microcephaly and epilepsy. Journal of Medical Genetics. 2012 Dec;49(12):731-736.
13. Ji J, Lee H, Argiropoulos B, Dorrani N, Mann J, Martinez-Agosto JA, et al. DYRK1A haploinsufficiency causes a new recognizable syndrome with microcephaly, intellectual disability, speech impairment, and distinct facies. Eur J Hum Genet. 2015 Nov;23(11):1473-81.
14. O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, et al. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science. 2012 Dec 21;338(6114):1619-22
15. Earl RK, Turner TN, Mefford HC, Hudac CM, Gerdts J, Eichler EE, et al. Clinical phenotype of ASD-associated *DYRK1A* haploinsufficiency. Mol Autism. 2017 Oct 5;8:54.
16. Méjécase C, Way CM, Owen N, Moosajee M. Ocular Phenotype Associated with *DYRK1A* Variants. Genes (Basel). 2021 Feb 5;12(2):234.
17. van Bon BWM, Coe BP, de Vries BBA, Eichler EE. DYRK1A Syndrome. 2015 Dec 17 [Updated 2021 Mar 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.
18. Redin C, Gérard B, Lauer J, Herenger Y, Muller J, Quartier A, et al. Efficient strategy for the molecular diagnosis of intellectual disability using targeted high-throughput sequencing. J Med Genet. 2014 Nov;51(11):724-36. doi: 10.1136/jmedgenet-2014-102554.
19. Ruaud L, Mignot C, Guët A, Ohl C, Nava C, Héron D, et al. DYRK1A mutations in two unrelated patients. Eur J Med Genet. 2015 Mar;58(3):168-74.
20. Luco SM, Pohl D, Sell E, Wagner JD, Dymeny DA, Daoud D. Case report of novel DYRK1A mutations in 2 individuals with syndromic intellectual disability and a review of the literature. BMC Med Genet. 2016;17:15.
21. Evers JM, Laskowski RA, Bertolli M, Clayton-Smith J, Deshpande C, Eason J, et al. Structural analysis of pathogenic mutations in the DYRK1A gene in patients with developmental disorders. Hum Mol Genet. 2017 Feb 1;26(3):519-526.
22. Murray CR, Abel SN, McClure MB, Foster J 2nd, Walke MI, Jayakar P, et al. Novel Causative Variants in *DYRK1A, KARS*, and *KAT6A* Associated with Intellectual Disability and Additional Phenotypic Features. J Pediatr Genet. 2017 Jun;6(2):77-83.
23. Blackburn ATM, Bekheirnia N, Uma VC, Corkins ME, Xu Y, Rosenfeld JA, et al. DYRK1A-related intellectual disability: a syndrome associated with congenital anomalies of the kidney and urinary tract. Genet Med. 2019 Dec;21(12):2755-2764.
24. Qiao F, Shao B, Wang C, Wang Y, Zhou R, Liu G, et al. A *De Novo* Mutation in *DYRK1A* Causes Syndromic Intellectual Disability: A Chinese Case Report. Front Genet. 2019 Nov 19;10:1194.
25. Okazaki T, Yamada H, Matsuura K, Kasagi N, Miyake N, Matsumoto N, et al. Clinical course of epilepsy and white matter abnormality linked to a novel DYRK1A variant. Hum Genome Var. 2021 Jul 12;8(1):26.
26. Frewer V, Gilchrist CP, Collins SE, Williams K, Seal ML, Leventer RJ, et al. A systematic review of brain MRI findings in monogenic disorders strongly associated with autism spectrum disorder. J Child Psychol Psychiatry. 2021 Nov;62(11):1339-1352.
27. Turnbull C, Scott RH, Thomas E, Jones L, Murugaesu N, Pretty FB, et al. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. BMJ. 2018 Apr 24;361:k1687.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

Voluntary drug intoxication in adolescents: impact of COVID-19 pandemic

Beatriz Sá[a], Mariana Lopes[b], and José Robalo*

Serviço de Pediatria, Centro Hospitalar de Leiria, Leiria, Portugal

ORCID: [a]0000-0002-9528-5795; [b]0000-0001-8395-1896

Abstract

Introduction and Objectives: The COVID-19 pandemic caused social isolation and disruption of routines, with an increase in psychiatric symptoms in adolescents, namely suicide attempts. Voluntary drug intoxication is the most common form of attempted suicide in young people. Our objective was to evaluate the impact of COVID-19 pandemic in cases of voluntary drug intoxication in adolescents. **Methods:** A retrospective study conducted on adolescents admitted to the Pediatric Emergency Department for voluntary drug intoxication between January 2020 and June 2021. We defined a pre-COVID period: January/2019-February/2020, and COVID period: March/2020-June/2021. **Results:** There were 64 admissions for voluntary drug intoxication in a total of 50 adolescents, 76.0% of whom were female. The mean age was 15.6 ± 1.6 years. There were 19 intoxications in the pre-COVID period (1.4 cases/month) and 45 in the COVID period (2.8 cases/month). Most commonly used drugs were paracetamol (23.4%), alprazolam (21.9%) and sertraline (20.3%), with 39.1% of intoxications using more than 1 drug. In 59.4% it was the first voluntary drug intoxication. A trigger was identified in 75.0% of cases. There was previous follow-up in Child Psychiatry in 67.2% of cases. In the COVID period there was an increase of other coexisting self-harming behaviors ($p = 0.017$) and fewer urgent transfers to Child Psychiatry ($p = 0.002$). Male sex was associated with older age ($p < 0.001$) and familiar instability ($p = 0.004$). **Discussion:** There was a two-fold increase of voluntary drug intoxication during the pandemic, consistent with the literature on its impact on young people's mental health, which reinforces the importance of preventive action in adolescents at risk.

Keywords: Adolescent. COVID-19. Drug overdose.

Intoxicações medicamentosas voluntárias em adolescentes: impacto da pandemia COVID-19

Resumo

Introdução e Objetivos: A pandemia COVID-19 causou isolamento e disrupção da rotina, com consequente aumento da sintomatologia psiquiátrica em adolescentes, nomeadamente tentativas de suicídio. A intoxicação medicamentosa voluntária é a forma de tentativa de suicídio mais frequente nos jovens. O objetivo deste estudo foi avaliar o impacto da pandemia nos casos de intoxicação medicamentosa voluntária em adolescentes. **Métodos:** Estudo retrospetivo realizado em adolescentes admitidos na urgência pediátrica por intoxicação medicamentosa voluntária entre 1 de Janeiro de 2019 e 30 de junho de 2021. Definiu-se como período pré-COVID: Janeiro/2019-Fevereiro/2020, e período COVID: Março/2020-Junho/2021. **Resultados:** Houve 64 admissões por intoxicação medicamentosa voluntária, num total de 50 adolescentes, 76,0% do sexo feminino. A idade média

***Correspondence:**
Beatriz Sá
E-mail: beatriz.svs@gmail.com

Received: 18-01-2023
Accepted: 24-05-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):20-26
DOI: 10.24875/PJP.M23000131

foi 15,6 ± 1,6 anos. Houve 19 intoxicações no período pré-COVID (1,4 casos/mês) e 45 no período COVID (2,8 casos/mês). Os fármacos mais usados foram paracetamol (23,4%), alprazolam (21,9%) e sertralina (20,3%), sendo 39,1% das intoxicações com mais do que 1 fármaco. Em 59,4% dos casos foi a primeira intoxicação medicamentosa voluntária. Identificou-se desencadeante em 75,0% dos casos. Tinham seguimento pedopsiquiátrico prévio 67,2%, associados a menor menção a desencadeante (p = 0,030). No período COVID houve aumento da coexistência de outros comportamentos auto-lesivos (p = 0,017) e diminuição das transferências urgentes para Pedopsiquiatria (p = 0,002). O sexo masculino associou-se a maior idade (p < 0,001) e instabilidade familiar (p = 0,004). **Discussão:** Observou-se uma duplicação das intoxicações medicamentosas voluntárias durante a pandemia, concordante com a literatura acerca do impacto na saúde mental dos jovens, o que reforça a importância de atuar preventivamente em adolescentes de risco.

Palavras-chave: Adolescente. COVID-19. Intoxicação medicamentosa.

Keypoints

What is known
- Voluntary drug intoxication is the most common form of attempted suicide in young people.
- COVID-19 pandemic has had a negative impact in mental health in all age groups.

What is added
- We found a two-fold increase in cases of voluntary drug intoxications in Portuguese adolescents during the first months of the COVID-19 pandemic.
- There was no change in demographic and social profile between the pre-COVID and COVID groups.

Introduction

Several studies have demonstrated an increase in psychopathology in children and adolescents in the last decade[1], with approximately 20% of children and adolescents having an emotional, mental or behavior disorder diagnosed[2]. Consequently, suicide is the second most common cause of death between ages of 15 and 19 years old in Europe[3] and the United States of America[4]. Therefore, attempted suicide is the most common psychiatric emergency in young people, frequently observed in the Pediatric Emergency Department (PED), with voluntary drug intoxication (VDI) being the most commonly used method in this age[5].

Social and political measures imposed during the first months of the COVID-19 pandemic, with social distancing and daily routine disruption, led to increased isolation of many teenagers, aggravating symptoms of anxiety, depression and suicide ideation[6-10], mainly in those already at risk or with previous psychiatric illness[2,7,11,12]. Most studies to date show an increase in affluence to PED for suicide attempts and VDI since the beginning of the pandemic[6,12]. Contrastingly, Fidanci et al. described a decrease in the number of admissions to PED when comparing the period between April and October 2019 and the similar period in 2020. According to these authors, this decrease was justified by the protective effect of parental supervision and retraction from negative social environments in school and peer groups[13]. However, the contrary can also be true, with school and social interaction being protective factors in cases of instability, or even violence, within the family[10,11,14].

Therefore, our main objective in this study was to evaluate the impact of the COVID-19 pandemic in cases of VDI in adolescents admitted to PED in our hospital. As a secondary objective, we also aimed to characterize the socio-demographic profile of these adolescents.

Methods

A retrospective descriptive study was conducted in the 14 months preceding the beginning of the COVID-19 pandemic in Portugal and in the first 16 months of the pandemic, between 1 January, 2019 and 30 June, 2021. The study population was defined as all adolescents (ages 10-17 years old) admitted to PED of a level I hospital during that period. The only inclusion criterion was admission for voluntary drug intoxication.

We defined the pre-COVID period (PCP) as the period between 1 January, 2019 and 28 February, 2020 (14 months), and the COVID period (CP) between 1 March, 2020 and 30 June, 2021 (16 months).

We analyzed demographic variables, the drugs that were used (number and type), clinical symptoms, personal medical history and identifiable triggers.

Statistical treatment of data was done using SPSS® version 26, with simple descriptive analysis and Chi-square test or Fisher's exact test to assess the association between two categorical variables,

Mann-Whitney test or Student t-test to assess the association between categorical and numeric variables, and the Pearson correlation coefficient to assess the correlation between two numeric variables. The significance level in this study was $p < 0.05$.

This study was approved by the Ethics Committee of our hospital.

Results

Characterization of the population sample

In our study's period, 75,918 children and adolescents were admitted to the PED in a level I hospital (PCP: n = 49.175; CP: n = 26,743). Among these, there were 64 admissions for VDI, in a total of 50 adolescents, of whom 38 (76.0%) were females. Mean age was 15.6 ± 1.6 years. Nine adolescents were admitted for VDI more than once during the study's period: six females (15.8% of total female adolescents) and three males (25.0% of total male adolescents) (p = 0.668). An unstable family situation was described in 32 (64.0%) cases, with 30 (60.0%) having separated parents and 4 adolescents (5.6%) were institutionalized. Male gender was associated with increased age (15,0 ± 1,6 in females vs. 16,8 ± 0,8 in males, p < 0,001) and family instability (51.2% in females vs. 89.5% in males, p = 0.004). Socio-demographic characterization of these adolescents is described in table 1.

Almost all VDI (92.1%) happened at home. It was the adolescent's first VDI in 38 cases (59.4%), with the number of previous VDI varying between one and five (median [interquartile area] = 1 [1,2]). There was a record of previous psychiatric diagnosis in 78.9% of cases, predominantly depression (42.2%), with 67.2% having Child Psychiatry follow-up appointments at the time of VDI. Other concurrent self-harming behaviors (SHB) were present in 54.7% of cases, mainly self-mutilation (46.9%). There was a positive association between the existence of other SHB and number of previous VDI (p = 0.001).

A trigger was possible to identify in 42 VDI (75.0%, n.º total = 56), most frequently a breakup/conflict with partner (35.7%) and conflict with a family member (33.3%) (Table 2). The presence of other SHB, previous psychiatric diagnosis and previous Child Psychiatry appointments were associated with fewer references to a trigger (p = 0.023, p = 0.039, p = 0.030, respectively). No association was found between the number of previous VDI and the presence of an identifiable trigger (p = 0.147).

There were 48 different drugs used, the most frequent being paracetamol (23.4%), alprazolam (21.9%) and sertraline (20.3%) (Table 3). More than 1 drug was used in 39.1% of VDI, with a maximum of 10 different drugs used simultaneously. The number of different drugs used did not correlate with the number of previous VDI (p = 0.670; r = −0.056). In 10 cases (15.6%) the drug used was part of the adolescents' regular medication.

Physical symptoms were reported in 43 cases (67.2%), the most prevalent were motor impairment/sleepiness (51.2%) and vomiting (18.6%) (Table 4). No adolescents were admitted to the Intensive Care Unit and no deaths were reported. There were 31 patients (48.4%) transferred to a level III hospital for an urgent

Table 1. Socio-demographic characteristics of adolescents admitted to the Pediatric Emergency Department for voluntary drug intoxication

	Total (n = 50)
Age, years	
Mean ± SD	15.6 ± 1.63
Minimum-Maximum	10.9-17.9
Gender, n (%)	
Feminine	38 (76%)
Masculine	12 (24%)
Nationality, n (%)	
Portuguese	45 (90%)
Brazilian	3 (6%)
French	1 (2%)
Cape verdean	1 (2%)
Familial context, n (%)	
Unstable family	32 (64%)
Separated parents	30 (60%)
Institutionalized	4 (6%)

Table 2. Triggers associated with voluntary drug intoxications

Trigger, n (%)	Total (n = 42)
Breakup/conflict with partner	15 (35.7%)
Conflict with family	14 (33.3%)
Conflict with friend	3 (7.1%)
School failure	3 (7.1%)
Anxiety crisis	2 (4.8%)
Cry for attention	2 (4.8%)
Bullying	1 (2.4%)
Terminal organic disease	1 (2.4%)
Sexual abuse	1 (2.4%)

Table 3. Drugs used in voluntary drug intoxications

Drug, n (%)	Total (n = 64)	Drug, n (%)	Total (n = 64)
Paracetamol	15 (23.4%)	Bioflavonoids	1 (1.6%)
Alprazolam	14 (21.9%)	Diazepam	1 (1.6%)
Sertraline	13 (20.3%)	Etinilestradiol + gestodeno	1 (1.6%)
Ibuprofen	11 (17.2%)	Escitalopram	1 (1.6%)
Paroxetine	4 (6.3%)	Fexofenadine	1 (1.6%)
Naproxen	3 (4.7%)	Haloperidol	1 (1.6%)
Trazodone	3 (4.7%)	Levetiracetam	1 (1.6%)
Sodium valproate	3 (4.7%)	Ethyl loflazepate	1 (1.6%)
Zolpidem	3 (4.7%)	Losartan + hydrochlorothiazide	1 (1.6%)
Acetylsalicylic acid	2 (3.1%)	Metamizole	1 (1.6%)
Aripiprazol	2 (3,1%)	Metformin	1 (1.6%)
Clonazepam	2 (3.1%)	Methylphenidate	1 (1.6%)
Fluoxetine	2 (3.1%)	Montelukast	1 (1.6%)
Fluvoxamine	2 (3.1%)	Ondansetron	1 (1.6%)
Lorazepam	2 (3,1%)	Omega-3 supplement	1 (1.6%)
Risperidone	2 (3.1%)	Oxazepam	1 (1.6%)
Amitriptyline	1 (1.6%)	Paracetamol + thiocolchicoside	1 (1.6%)
Aceclofenac	1 (1.6%)	Pantoprazole	1 (1.6%)
Amoxicillin + tlavulanate	1 (1.6%)	Pravastatin	1 (1.6%)
Melatonin + valerian	1 (1.6%)	Prednisolone	1 (1.6%)
Aripiprazole	1 (1,6%)	Quetiapine	1 (1.6%)
Bupropion	1 (1.6%)	Fiber supplement	1 (1.6%)
Chlorphenamine + paracetamol	1 (1.6%)	Topiramate	1 (1.6%)
Cotrimoxazole	1 (1.6%)	Valerian	1 (1.6%)

Child Psychiatry consulting, while 60 (93.8%) were referred for a short-term Child Psychiatry appointment. Three adolescents (4.7%) were admitted as inpatients in a Child Psychiatry Unit.

Pre-COVID Period (PCP) vs. COVID Period (CP)

The characteristics of VDI during PCP and CP are described in table 5. From a total of 64 VDI, 19 occurred in PCP (0.04% of admission to the PED), corresponding to 1.4 VDI per month; and 45 VDI in CP (0.17% of admission to the PED), corresponding to 2.8 VDI per month. There was no statistically significant difference in mean age (p = 0.628), median number of drugs used (p = 0.065) or number of cases at first VDI (p = 0.425). There was a predominance of female gender in both groups, with a tendency to increase the gender gap in CP, although with no statistical significance (57.9% vs. 75.6%, p = 0.158).

We did not observe any statistical difference regarding the presence of an identifiable trigger (p = 0.475), family instability (p = 0.550), existence of previous psychiatric diagnosis or follow-up in Child Psychiatry appointments (p = 0.737, p = 0.107, respectively). However, in CP there was higher coexistence of other SHB (35.3% vs. 64.3%, p = 0.017). We further verified a decrease in transfers to a level III hospital for urgent Child Psychiatry consults (78.9% vs. 35.6%, p = 0.002), with an increase in referrals to Child Psychiatry appointments in our hospital (36.8% vs. 73.3%, p = 0.006).

Table 4. Symptoms associated with voluntary drug intoxication

Symptoms, n (%)	Total (n = 42)
Fatigue/motor impairment/sleepiness	22 (51.2%)
Vomit	8 (18.6%)
Nausea	5 (11.6%)
Slurred speech	4 (9.3%)
Abdominal pain	4 (9.3%)
Headache	3 (7%)
Ataxia	3 (7%)
Diarrhea	2 (4.7%)
Tremor	2 (4.7%)
Dehydration	1 (2.3%)
Miosis	1 (2.3%)
Seizure	1 (2.3%)

Discussion

During the 30 months of the study, we observed 64 cases of VDI, showing a two-fold increase in the number of VDI from 1.4 to 2.8 cases per month in pre-COVID and COVID periods, respectively. Simultaneously, there was a decrease in the number of total admissions to PED, translating to a four-fold increase in representativeness of VDI across causes of admission (0.04% vs. 0.17%). Hill et al. had already reported an increase in admissions to PED for suicide ideation or attempt since the beginning of COVID-19 pandemic[6], with a more marked increase in female gender[6-9]. We also verified this tendency for a greater impact in female gender, although with no statistical significance (57.9% vs. 75.6%, p = 0.158).

Simultaneous to the increasing number of VDI, there was also a more frequent association with other SHB, reinforcing the negative impact of the pandemic period on adolescents' mental health.

Nistor et al. described familial dysfunction and separated parents as risk factors for suicide ideation and attempt in adolescence[15]. In our study, family instability was described in 62.9% of cases, however, contrary to what could be expected, this was not associated with VDI in CP, despite the increased time spent at home with family during that period.

The profile of adolescents admitted for VDI overlapped that previously described in Portuguese and European literature, with pronounced predominance of female gender (85-87% vs. 76.0% in our study)[5,15-18] and mean age of 15 years[5,17]. Almost all VDI happened at home (96% vs. 92.1% in our study)[5], using easily accessible over-the-counter drugs or the adolescents' own medication[8], most frequently paracetamol, followed by benzodiazepines. We also observed a frequent use of other antidepressants, although other studies report anti-epileptic drugs and antibiotics as the most commonly used drugs[15-17]. In most cases (60.9%) only one drug was used in VDI, which was consistent with previous studies (45-52%)[5,17].

Underlying psychiatric illness confers a significant risk, with 78.9% presenting with previous psychiatric diagnosis. This percentage is higher than previous reports by other authors of 50-61% of adolescents with a previous diagnosis, more frequently suicide attempts, eating disorders and depression[5,15]. This group of adolescents with a previous psychiatric diagnosis and follow-up or with other associated SHB reported less frequently the existence of a trigger, suggesting that VDI may happen less as a reactive behavior to adverse life events and more probably as a manifestation of suicidal ideation in the context of their underlying disease.

Consistent with this higher prevalence of previous psychiatric diagnosis, the number of adolescents with previous history of other VDI (40.6%) was also higher than the rate of re-attempted suicide of 34.8% reported by Romero et al., and even higher than previously described in other studies (6-14%)[8], with no significant difference between PCP and CP (p = 0.425). In line with this increase in psychopathology in adolescents, there was an expansion of our hospital's Child Psychiatry Unit, which allowed an increase in the number of short-term appointments for adolescents referred from the PED. This may justify the reduction to half in transfers to a level III hospital for urgent Child Psychiatry consults (p = 0.002), while doubling the referrals to Child Psychiatry appointments in our hospital (p = 0.006) from PCP to PC.

According to Ahmedani et al., within adolescents who died by suicide, 38% were seen by a doctor in the month prior to their death (11% in an Emergency Department), and 77% in the preceding year (28% in an Emergency Department)[19]. Therefore, we emphasize that adolescents at risk of VDI, in addition to the well-established profile already described, are frequent users of health services, creating a window of opportunity for detection of warning signs and early intervention.

Table 5. Comparison between voluntary drug intoxication cases in pre-COVID and COVID periods

	Pre-COVID Period (n = 19)	COVID Period (n = 45)	
Age (years) Mean ± SD	15.7 ± 2.0	15.5 ± 1.5	p = 0.628
Gender, n (%) Female Male	11 (57.9%) 8 (42.1%)	34 (75.6%) 11 (24.4%)	p = 0.158
Number of VDI, n (%) First VDI > 1 VDI	13 (68.4%) 6 (31.6%)	26 (57.8%) 19 (42.2%)	p = 0.425
Number of drugs used, n Median [IQA]	1 [1;1]	1 [1;2]	p = 0.065
Medical history, n (%) Other SHB Previous diagnosis Previous Child Psychiatry consult Trigger Family instability	 6 (35.3%) (n = 17) 13 (76.5%) (n = 17) 10 (52.6%) 11 (61.1%) (n = 18) 13 (68.4%)	 29 (64.3%) (n = 42) 32 (80%) (n = 40) 33 (73.3%) 31 (79.5%) (n = 44) 26 (60.5%) (n = 43)	 p = 0.017 p = 0.737 p = 0.107 p = 0.475 p = 0.550
Referral, n (%) Transferred to level III hospital	15 (78.9%)	16 (35.6%)	p = 0.002

Our study has some limitations. Firstly, generalization of these results is limited due to being a unicentric retrospective study with a small sized sample. Secondly, data was retrieved from clinical record written by different doctors, sometimes with incomplete information that may create a potential bias. Thirdly, the results were not adjusted to adolescents' socioeconomic status, which may be a confounder for psychiatric pathology. Lastly, we compared periods with different lengths (14 vs. 16 months), which results in a methodological error that was partially compensated by presenting number of cases per month rather than absolute numbers, when comparing different periods.

Awards and previous presentations

The present study was presented as an oral communication in the 21º Congresso Nacional de Pediatria, in Braga, in 28 October, 2021. It received the Pierre Fabre/SPP Award for works presented in the aforementioned congress.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Mourouvaye M, Bottemanne H, Bonny G, Fourcade L, Angoulvant F, Cohen JF, et al. Association between suicide behaviours in children and adolescents and the COVID-19 lockdown in Paris, France: a retrospective observational study. Arch Dis Child. 2021;106(9):918-19.
2. Cloutier R, Marshaall R. A dangerous pandemic pair: Covid19 and adolescent mental health emergencies. Am J Emerg Med. 2021;46:776-7.
3. EuroStats. Being young in Europe today. [cited 2022 Mar 26]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=-Being_young_in_Europe_today_-_health#Causes_of_death
4. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS) [online]. Leading Causes of Death Reports, 1981–2020. [cited 2022 Mar. 26]. Available from: www.cdc.gov/injury/wisqars
5. Romero RG, García JG, Ruano EC, Cubells CL, Díez JA, Fernández JP. Intoxicaciones voluntarias como intento de suicidio. An Pediatr. 2020;53(3):213-16.

6. Hill RM, Rufino K, Kurian S, Saxena J, Saxena K, Williams L. Suicide ideation and attempts in a pediatric emergency department before and during COVID-19. Pediatrics. 2021;147(3):e2020029280.
7. von Soest T, Kozák M, Rodríguez-Cano R, Fluit DH, Cortés-García L, Ulset VS, et al. Adolescents' psychosocial well-being one year after the outbreak of the COVID-19 pandemic in Norway. Nat Hum Behav. 2022;6(2):217-28.
8. Mayne SL, Hannan C, Davis M, Young JF, Kelly MK, Powell M, et al. COVID-19 and Adolescent Depression and Suicide Risk Screening Outcomes. Pediatrics. 2021;148(3):e2021051507.
9. Magson NR, Freeman JYA, Rapee RM, Richardson CE, Oar EL, Fardouly J. Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic. J Youth Adolesc. 2021;50(1):44-57.
10. Melhem N, Brent D. Debate: The toll of the COVID- 19 pandemic on children's risk for suicidal thoughts and behaviors. Child and adolescent mental health. 2021;26(3):274-5.
11. Bartek N, Peck JL, Garzon D, VanCleve S. Addressing the Clinical Impact of COVID-19 on Pediatric Mental Health. J Pediatr Health Care. 2021;35(4):377-86.
12. Carney C. Reducing the rise in adolescent suicide during COVID-19. Ment Health Wkly. 2021;31(10):5-5.
13. Fidanci I, Taşar MA, Akıntuğ B, Fidancı İ, Bulut İ. The impact of the COVID-19 pandemic on paediatric emergency service. Int J Clin Pract. 2021;75(9):e14398.
14. Cohen R, Bosk E. Vulnerable youth and the COVID-19 pandemic. Pediatrics. 2020;146(1):e20201306.
15. Nistor N, Jitareanu C, Frasinariu OE, Ciomaga IM, Rugina AL, Streanga V. Epidemiologic profile and triggering factors of voluntary poisoning in teenagers. Medicine (Baltimore). 2017;96(5):e5831.
16. Cachão J, Oliveira I, Raminhos I. Adolescência e Abuso de Substâncias. Nascer e Crescer-Birth and Growth Medical Journal. 2017;26(2): 103-8.
17. Macedo MA, Ramos V, Lanzas D, Baltazar J. Intoxicações medicamentosas voluntárias na urgência pediátrica: uma análise ao período 2017-2018. In Congresso Internacional de Psicologia da Criança e do Adolescente. 2021;11.
18. Nunes I, Monteiro J, Amorim J, Jorge R, Ferreira S, Costa M, et al. Intoxicações voluntárias em adolescentes: casuística do serviço de urgência de um hospital distrital. Acta Pediatr Port. 2014;45:270-4.
19. Ahmedani BK, Simon GE, Stewart C, Beck A, Waitzfelder BE, Rossom R, et al. Health care contacts in the year before suicide death. J Gen Intern Med. 2014;29(6):870-7.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

Pediatric epidermolysis bullosa – psychosocial impact and the importance of palliative care based on 5 clinical cases

Inês Pais-Cunha[1,2a], Paula Guerra[3,4,5b], Alice Porto-Guerra-Vasconcelos[6c], Laura Leite-Almeida[1d], Nuno Gomes[7e], Alberto Mota[5,7,8f], and Irene Carvalho[1g]*

[1]Pediatria Hospitalar, Unidade de Gestão Autónoma da Criança e da Mulher, Centro Hospitalar Universitário de São João; [2]Faculdade de Medicina, Universidade do Porto; [3]Equipa Intra-Hospitalar de Suporte de Cuidados Paliativos Pediátricos da Unidade de Gestão Autónoma da Criança e da Mulher, Centro Hospitalar Universitário de São João; [4]Unidade de Gastroenterologia e Nutrição Clinica Pediatrica, Unidade de Gestão Autónoma da Criança e da Mulher, Centro Hospitalar Universitário de São João; [5]Faculdade de Medicina do Porto, Universidade do Porto; [6]Serviço de Genética Médica, Centro Hospitalar Universitário de São João; [7]Serviço de Dermatologia, Centro Hospitalar Universitário de São João; [8]CINTESIS@RISE. Porto, Portugal

ORCID: [a]0000-0001-5368-0335; [b]0009-0006-5245-2158; [c]0000-0001-9423-956X; [d]0000-0003-2319-1332; [e]0000-0003-4278-3106; [f]0000-0003-2467-4926; [g]0009-0006-6164-8857

Abstract

Introduction and Objectives: Epidermolysis bullosa (EB) is a rare genodermatosis caused by pathogenic variants in several genes leading to epithelial fragility with blisters, erosions and ulcerations following minor trauma. Given the affection of any epithelial-lined organ, it can result in several complications. Our aim was to describe this disease's psychosocial impact in pediatric patients. **Methods:** Case series of pediatric epidermolysis bullosa patients in a tertiary hospital between 2008-2023. Data collection was conducted retrospectively and quality of life assessment was obtained with a cross-sectional questionary. **Results:** We identified five unrelated patients, three of the female gender, aged 3 to 22 years old. All with neonatal symptoms. Genetic testing revealed pathogenic variants characteristic of dystrophic EB subtype in four and junctional EB subtype in one patient. Three patients were followed in psychology and psychiatry consultations. Four patients received pediatric palliative consultations. Three patients responded to quality-of-life questionnaires, two of them with a median score of PedsQL of 47% and one with a DLQI score of 17. Regarding complications, all patients had microcytic anemia requiring iron supplementation. Gastrointestinal symptoms included epigastric pain in three patients and esophageal stenosis needing gastrostomy in one patient. Poor weight gain was detected in four patients. **Discussion and Conclusions:** EB is a complex and heterogeneous disease. Pediatricians should be aware of the complications associated to this disease in order to provide early guidance. Palliative care with social, psychological and spiritual support for patients and their family are essential for the management of this disease.

Keywords: Dermatology. Epidermolysis bullosa. Genetics. Palliative care.

Epidermólise bolhosa em idade pediátrica – impacto psicossocial e a importância dos cuidados paliativos, baseado em 5 casos clínicos

Resumo

Introdução e Objetivos: A epidermólise bolhosa (EB) é uma genodermatose rara causada por variantes patogénicas num dos várias genes que causam fragilidade dos tecidos epiteliais com a formação de bolhas, vesículas e úlceras após trauma *minor*.

***Correspondence:**
Inês Pais-Cunha
E-mail: inespaiscunha@gmail.com

Received: 14-12-2022
Accepted: 07-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):27-33
DOI: 10.24875/PJP.M23000132

Dado poder afetar qualquer órgão epitelial, resulta numa variedade de complicações. O nosso estudo tem como objetivo descrever o impacto psicossocial desta doença em idade pediátrica. **Métodos:** Série de casos de doentes com epidermólise bolhosa diagnosticada em idade pediátrica, num hospital terciário, entre 2008 e 2023. A colheita de dados foi realizada de forma retrospetiva e a avaliação da qualidade de vida foi obtida através da aplicação de um questionário. **Resultados:** Foram identificados cinco pacientes, três do sexo feminino, com idade à data de colheita de dados: 3 a 22 anos. Todos apresentaram sintomas no período neonatal. O estudo genético revelou variantes patogénicas, características to subtipo distrófico em quatro pacientes e característica do tipo juncional num paciente. Três doentes eram seguidos em consulta de psicologia e psiquiatria. Três doentes responderam a questionários de qualidade de vida, dois com score mediano de PedsQL de 47% e um com score de DLQI de 17. Quatro doentes tinham seguimento em cuidados paliativos pediátricos. Relativamente a complicações, todos os doentes apresentaram anemia microcítica com necessidade de ferro suplementar. Sintomas gastrointestinais incluíram dor epigástrica em três doentes e estenose do esófago com necessidade de gastrostomia num doente. Foi identificada má evolução ponderal em quatro pacientes. **Discussão e Conclusão:** A EB é uma doença complexa e heterogénea. Os pediatras devem ter presente as várias complicações associadas à doença de forma a garantir o seu tratamento precoce. A abordagem holistica dos cuidados paliativos integrando o apoio social, espiritual e psicológico do doente e familiares, são essenciais na abordagem da doença.

Palavras-chave: Cuidados paliativos. Dermatologia. Epidermólise bolhosa. Genética.

Keypoints

What is known
- Epidermolysis bullosa is a heterogeneous entity with a broad genetic and phenotypic spectrum.
- Given that any epithelial-lined organ can be affected several complications can arise from this disease.
- There is no curative treatment - symptom control and complications' prevention and management are the main objective of these patient's management.

What is added
- Patients with epidermolysis bullosa had low quality of life scores.
- The majority of our patients received psychological and psychiatric support, and some of them needed treatment with antidepressants.
- Regular follow-up by palliative care specialists should be ensured from the moment of diagnosis, enabling not only pain management, but also guaranteeing a holistic and integrated approach, from pediatric age onwards.

Introduction

Epidermolysis bullosa (EB) is a rare genodermatosis, clinically and genetically heterogeneous[1]. A research group on EB in the United States estimated the incidence (from 1986 to 2002) to be 19.57 per 1,000,000 individuals[2].

EB is characterized by mechanical fragility of the epithelial tissues giving rise to mucocutaneous blistering, erosions and ulcerations secondary to minor trauma[3]. Pathogenic variants in more than 30 genes that encode proteins influencing cellular integrity and adhesion have been associated with EB. Depending on the gene involved, a specific subtype might be expected[3]. There are different subtypes of EB according to the layer of the skin affected: bullosa simplex epidermolysis (intra-epidermal), junctional epidermolysis bullosa (lamina lucida of the basement membrane) and dystrophic epidermolysis bullosa (below the basement membrane). Kindler syndrome, a genodermatosis with a mixed skin cleavage pattern is also an important differential diagnosis to keep in mind. Depending on the phenotypic spectrum, patients can be mildly to severely affected and symptoms can present from birth to early childhood[4].

Any epithelial-lined organ can be involved resulting in a vast array of complications. Depending on the subtype, musculoskeletal system, heart, bone marrow, and oral and esophageal mucosa can also be affected[5]. Regarding epithelial tissues, squamous cell carcinoma and cutaneous infections, which can lead to sepsis, are important causes of morbidity and mortality in these patients[6].

Several studies have showed that chronic dermatologic conditions have an important psychosocial impact on patient's life. In fact, EB patients struggle with altered perception of the body, lack of self-esteem and depression[7,8]. Quality of life (QoL) scores have been reported to be lower in these patients, including studies in children and their caregivers[9], given the challenges that this disease raises. Since there is no curative therapy for EB, an holistic palliative care approach, with wound care and pain management, as well as psychosocial support, is of crucial importance for these patients[10-12].

Although several studies have focused on the adult population, literature regarding challenges in the pediatric EB population is still lacking. Our study aims to describe the psycho-social impact of EB in young patients.

Methods

This article presents a case series of patients with history of epidermolysis bullosa followed diagnosed in pediatric age, in a tertiary hospital between 2008-2023. Data collection was conducted retrospectively and quality of life assessment was obtained with a cross-sectional questionary.

We identified all patients who had a diagnosis of EB from birth to 18 years of age based on ICD9 and ICD10 diagnosis coding (ICD9: 694.8; 694.9; 757.39 and ICD10: Q81 (Q81.0; Q81.1;Q81.2; Q81.8; Q81.9) and L12 (L12.8; L12.9; 2l; L12.30; L12.31; L12.35). After screening, these patients were included if they had a genetic test result compatible with EB.

Clinical data including age, sex, genetic analysis, hospitalizations, hospital consultations, emergency visits and usual medication was collected from paper and electronic clinical records.

Regarding genetic testing, three patients underwent Next Generation Sequencing (NGS) gene panel for genes related to EB, with different number of genes testes depending on the date of the test. Patient 5 underwent targeted Sanger sequencing for the genes *LAMA3, LAMB3, LAMC2, COL7A1 and COL17A1.*

Quality of life (QoL) was assessed by tele-consultation using the Pediatric Quality of Life 4 (PedsQL-4) score for patients under 16 years old and the Dermatology Life Quality Index (DLQI) for patients over 16 years old. Both questionaries are validated for the Portuguese population[13,14]. We did not use the C-DLQI score for younger children because it is not validated for our population. For the PedsQL score, higher results mean a higher quality of life. For the DLQI score, 0-1 meant no effect on patient's life; 2-5 small effect on patient's life; 6-10 moderate effect on patient's life; 11-20 very large effect on patient's life and 21-30 extremely large effect on patient's life[15].

Results

Sample characteristics

A total of five patients were identified (numbered 1-5 in Table 1), 60% (n = 3) of the female gender. All of the patients presented with symptoms during the neonatal period and underwent genetic testing (number of genes discriminated in Table 1). For patient 2, the original genetic report was not found, but clinical records refer to a *COL7A1* pathogenic variant. In four patients, *COL7A1* pathogenic or likely pathogenic variants were identified, compatible with the dystrophic epidermolysis bullosa (DEB) subtype. Personal and family history and genetic testing of patients 1 and 3 is suggestive of an autosomal recessive phenotype, patient 4 can either have autosomal dominant DEB or recessive DEB with second variant not found. The allelic status of the variants in patient 1 could not be confirmed. Patient 5 has a homozygous *COL17A1* pathogenic variant, compatible with autosomal recessive junctional epidermolysis bullosa (JEB). None of the patients performed copy number variation analysis in the EB genes. None of the patients had family history of EB.

EB multi-systemic complications

We identified several complications of EB, further described in table 1. All the patients presented with chronic anemia and required iron supplementation. Four patients had gastrointestinal involvement with epigastric pain: three patients were treated with proton pump inhibitors and one patient (patient 3, with DEB) had esophageal stenosis with the need for gastrostomy and posterior parenteral feeding. The same four patients showed poor weight gain with the need for nutritional supplementation. Two patients, with DEB, had corneal leucoma. One of them presented with corneal neo-vascularization and underwent treatment with bevacizumab. Both of them maintained treatment with eye lubricant. Three patients had oral and dental complications with the need for treatment and intervention by stomatology specialists.

One patient, with DEB, had bilateral digital synechia requiring plastic surgery. The first surgery was at 5 years of age and he needed two re-interventions. The median number of hospitalizations for cutaneous infections was 1.5 (0-4).

One death was registered: patient 3, at five years of age, had a prolonged hospitalization due to multiple cutaneous infected lesions and posteriorly developed an infection of the central venous catheter. He died of sepsis in this context (two agents were identified in blood culture: *Acinetobacter baumannii* and *Enterococcus faecalis*).

We did not find any case of squamous cell carcinoma.

EB iatrogenic complications

One patient developed adrenal insufficiency resulting from the prolonged use of topical corticotherapy. This patient was then chronically treated with oral prednisolone.

Table 1. Characteristics and clinical complications of patients with epidermolysis bullosa

	Dystrophic subtype				Junctional subtype
Patients	1	2	3	4	5
Age at the time of data collection (years)	22	12	†	3	18
Sex	M	F	F	M	F
Genetic analyses	NGS panel (21 genes)	NA	NGS panel (8 genes)	NGS panel (22 genes)	Targeted sequencing (5 genes)
Gene	*COL7A1*	*COL7A1*	*COL7A1*	*COL7A1*	*COL17A1*
Genetic variant (s) (hg19)	c. 6527dup p. (Gly2177Trpfs*113)/c. 5009G > A p. (Gly1670Asp)	NA	c. 7006G > A p.(Gly2336Arg)	c. 325_326insCG p.(Glu109Alafs*39)	c. 505 > T p. (Arg169*)
Allelic status	Double heterozygous†	NA	Homozygous†	Heterozygous	Homozygous†
ACGM variant classification	P/LP	NA	LP	P	P
Symptoms in the neonatal period	+	+	+	+	+
Chronic anemia (n = 5)	+	+	+	+	+
Gastrointestinal symptoms (n = 4) Epigastric pain (n = 3) Esophageal stenosis (n = 1)	 + -	 + -	 + +	 - -	 + -
Poor weight gain (n = 4)	+	+	+	-	+
Corneal leucoma (n = 2)	-	+	-	+‡	-
Digital synechia (n = 1)	+	-	-	-	-
Psychology/psychiatry consultations (n = 3)	+	+	-	-	+
Oral/dental complications	+	+	-	-	+
Pediatric palliative care consultation	+	+	-	+	+§
QoL score	-	36%¶	-	58%¶	17**
Number of hospitalization for cutaneous infection	4	1	3	0	1
Iatrogenic complications	+	-	-	-	-
Deaths (n = 1)	-	-	+	-	-

*Non applicable, patient 3 died at 5 years of age, prior to data collection.
†Apparent, since segregation in parents was not performed.
‡Patient also presented with corneal neo-vascularization.
§Chronic pain consultation
¶PedsQL.
**DLQI.
NA: not available; M: male; F: female; P: pathogenic; LP: likely pathogenic.

EB QoL scores; psychological support and palliative care

One patient chose not to participate the QoL questionary. The remaining presented with a median PedsQL score of 47% and a DQLI score of 17. Three patients were followed in psychology and psychiatry consultations, two of them were being treated with antidepressants. Three patients were followed in palliative care consultations since pediatric age and one patient was followed in chronic pain consultation. All of them were medicated with fentanyl or tramadol with paracetamol in case of pain.

Discussion

As previously stated, EB is a heterogeneous entity with a variety of complications. All of our patients presented with symptoms in the neonatal period, which highlights the importance of pediatric care since birth in these patients.

Inevitably, EB's clinical manifestations with different degrees of severities, take a toll on patient's QoL. Although we were only able to analyze 3 of our patients, all of them had an impact on the QoL. Younger patient's PedsQL score was lower than the general population[13] and patient's 5 DLQI score showed that the disease had a very large effect on his life[15]. The majority of our patients were followed in psychology and psychiatry consultations, some of them needing treatment with antidepressants. These findings are a result of the particular combination of a rare disease, with a lifelong hereditary nature, and its disfiguring impact on the skin[8]. Similar to our results, Francesco Margari et al., studied a cohort of 25 patients with EB, including children and adults with different types of EB, and found a high frequency of psychiatric symptoms, in 80% of the population, and a severe impairment of the QoL. This study did not find a correlation between the clinical severity of the condition and the intensity of the psychological disturbances[16]. On the other hand, a cross-sectional study in adult patients with DEB did not show differences in anxiety and depression between patients with DEB and healthy individuals[17]. These apparently conflicting results may be explained by the fact that QoL, emotional and social functioning of patients with EB is not only influenced by the disease itself, but also by the family's support and emotional state as well as the patient's ability to develop coping strategies to accept and overcome EB's challenges[9].

Besides the impact that EB has on patients' wellbeing, it is also important to consider the disease's burden on caregivers and family members. Caregivers of EB patients are faced with the uncertainty of a chronic disease with no definitive treatment and are often concerned about their child suffering pain and being different[18]. Therefore, patients, as well as caretakers, should be given the adequate psychological support at the time of diagnosis. In addition, genetic counseling is also essential to predict prognosis and plan future pregnancies within the family.

Another important result we found was the importance of pain management and palliative care in this population. Almost all of our patients were followed in palliative or chronic pain consultation and follow-up was guaranteed from the time of diagnosis, in pediatric age. Routine management of patients with EB has several painful events. These episodes of pain may trigger the need for pharmacological intervention. Nevertheless, physicians must take into account that these medications may lead to a level of sedation that impairs patients' daily functioning. It is important to discuss the patients' options, which should include pharmacological as well as non-pharmacological approaches such as psychological support, as we mentioned before[19]. In terms of pain medication, in accordance to recent guidelines published on pain management of patients with EB[20], our patients were treated in the outpatient setting with tramadol and fentanyl for acute pain management. Patient 4 used the latter during his hospitalization, in the first months of life, for pain management during the procedures, given its practical intranasal formulation with a rapid onset of action[21]. Along with pain management, palliative consultations guaranteed proper wound management which, in our patients, included home care. Improvement in wound management has lead to a decrease in wound infections as well as systemic infections in patients with EB[6]. In accordance, our cohort had a low median hospitalization of 1.5 (0-4). We encountered a case of iatrogenic adrenal insufficiency due to prolonged topical corticotherapy for skin lesions treatment. This reminds us that the choice to use corticosteroids should be judicious, because even in the topical formulation it can have permanent secondary effects. In fact, treatment should be based essentially on disinfection and wound care[12].

Regarding other complications, chronic anemia was a common feature in our patients, in accordance to previous literature[22,23]. This complication is mainly caused by iron insufficiency due to feeding difficulties and impaired absorption caused by chronic denudation of the epithelial tract. Gastrointestinal ulcerations may also lead to blood loss. In addition, these patients are under a chronic inflammatory state, which contributes to anemia. Treatment should rely on iron supplementation, which can be given orally. In EB patients, this formulation seems to be less efficient due to decreased absorption and secondary gastrointestinal symptoms which affect treatment adherence. Alternatively, intravenous iron supplementation seems to have good results[24]. A. Reimer et al. found that anemia and iron deficiency correlated with low weight in patients with RDEB ($p < 0.001$)[23]. In line with these findings, poor weight gain was also a frequent complication in our group of patients. This results from a variety of factors, namely nutrients' malabsorption and oral cavity lesions which affect chewing and swallowing. In addition, caloric and protein requirements can be up to 50% and 100% higher, respectively, compared with

other children of the same age[6]. In order to provide a holistic and integrated approach to EB patients, treatment of anemia and poor weight gain were also guaranteed in our patient's palliative care consultations. Hemoglobin and iron study analysis, as well as anthropometric evaluations, were performed routinely. It is imperative that these patients are given adequate nutritional supplementation, in order to prevent failure to thrive, poor wound healing and delayed puberty.

Due to the requirement for ongoing chronic care, this disease also carries a significant social and economic impact. A Portuguese ictiosis/rare diseases working group, in a parliamentary hearing in 2014, estimated that direct health treatment costs of the most severe patients could reach 650 € per month, which can be unaffordable for most family budgets[25]. A more recent study with DEB in Europe showed that besides the direct health costs of EB, there are also high direct non-healthcare costs resulting from informal care needs and loss of patient and caregiver's labour productivity[26]. Although in our country, some hospitals co-participate with wound treatment and outpatient care, there is still a lack of specific legislation that protects this disease group which leads to healthcare asymmetry in EB. There is a need to create reference centers and regulations that detail treatment access for this group of patients.

This was a nonrandomized, single-center study, with its inherent limitations. Although we were able to identify variants in genes related to the main subtypes of EB, parental testing was not performed to confirm biallelic status of the recessive forms and accurately determine the inheritance pattern. Additionally, the NGS panel with all the genes reported to date and copy number variation of analyses in these genes could further enlighten the genotype of patients 2 and 4. On the other hand, when assessing patient's QoL we were not able to use the same instrument for different age categories, given the lack of validated pediatric dermatological questionaries for the Portuguese population. Nevertheless, we were able to gather a significant number of patients affected with this rare disease and analyze its vast array of complications and therapeutic approaches.

Conclusion

EB is a complex and heterogeneous disease. Pediatricians should be aware of the vast array of complications associated to this disease in order to provide early guidance. Palliative care consultations are indispensable to manage pain and guarantee multidisciplinary care tailored for these patients. It is essential to provide social, spiritual and psychological support to both patients and their caretakers. Studies of variants segregation in the parents are mandatory to carry out family studies and eventually reproductive options.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Herod J, Denyer J, Goldman A, Howard R. Epidermolysis bullosa in children: pathophysiology, anaesthesia and pain management. Paediatr Anaesth. 2002;12(5):388-97.
2. Fine JD. Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. JAMA Dermatol. 2016;152(11): 1231-8.
3. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), October 2022. World Wide Web URL: https://omim.org/
4. Mariath LM, Santin JT, Schuler-Faccini L, Kiszewski AE. Inherited epidermolysis bullosa: update on the clinical and genetic aspects. An Bras Dermatol. 2020;95(5):551-69.
5. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part II. Other organs. J Am Acad Dermatol. 2009;61(3):387-402; quiz 403-4.
6. Murat-Sušić S, Husar K, Skerlev M, Marinović B, Babić I. Inherited epidermolysis bullosa - the spectrum of complications. Acta Dermatovenerol Croat. 2011;19(4):255-63.
7. Yew YW, Kuan AHY, Ge L, Yap CW, Heng BH. Psychosocial impact of skin diseases: A population-based study. PLoS One. 2020 Dec 31;15(12):e0244765.
8. Dures E, Morris M, Gleeson K, Rumsey N. The psychosocial impact of epidermolysis bullosa. Qual Health Res. 2011;21(6):771-82.
9. Mauritz PJ, Bolling M, Duipmans JC, Hagedoorn M. The relationship between quality of life and coping strategies of children with EB and their parents. Orphanet J Rare Dis. 2021 Jan 30;16(1):53.
10. Bardhan A, Bruckner-Tuderman L, Chapple ILC, Fine JD, Harper N, Has C, et al. Epidermolysis bullosa. Nat Rev Dis Primers. 2020;6(1):78.
11. Cohn HI, Teng JM. Advancement in management of epidermolysis bullosa. Curr Opin Pediatr. 2016;28(4):507-16.

12. Price-Douglas W, Diehl-Svrjcek B. Epidermolysis bullosa: a case study in transport, treatment, and care. Adv Neonatal Care. 2007;7(6):289-94.
13. Lima L, Guerra MP, Lemos MS, Adaptação da escala genérica do inventário pediátrico de qualidade de vida - Pediatric Quality Life Inventory 4.0 - PedsQL, a uma população portuguesa, Revista Portuguesa de Saúde Pública, Vol 8, 2009, 83-95.
14. Fonseca A. Impacto das doenças dermatológicas na qualidade de vida: dermatology life quality index e euroqol 5d – correlação. 5 1 (2017): ISSN 0719-6008.
15. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005 Oct;125(4):659-64.
16. Margari F, Lecce PA, Santamato W, Ventura P, Sportelli N, Annicchiarico G, et al. Psychiatric symptoms and quality of life in patients affected by epidermolysis bullosa. J Clin Psychol Med Settings. 2010 Dec;17(4):333-9.
17. Fortuna G, Aria M, Cepeda-Valdes R, Garcia-Garcia SC, Moreno Trevino MG, Salas-Alanís JC. Role of dystrophic epidermolysis bullosa in anxiety, depression and self-esteem: A controlled cross-sectional study. J Dermatol. 2016 Jan;43(1):70-8.
18. van Scheppingen C, Lettinga AT, Duipmans JC, Maathuis KG, Jonkman MF. The main problems of parents of a child with epidermolysis bullosa. Qual Health Res. 2008 Apr;18(4):545-56.
19. Goldschneider KR, Lucky AW. Pain management in epidermolysis bullosa. Dermatol Clin. 2010 Apr;28(2):273-82.
20. Goldschneider KR, Good J, Harrop E, Liossi C, Lynch-Jordan A, Martinez AE, et al. Dystrophic Epidermolysis Bullosa Research Association International (DEBRA International). Pain care for patients with epidermolysis bullosa: best care practice guidelines. BMC Med. 2014 Oct 9;12:178.
21. Kaushal S, Placencia JL, Maffei SR, Chumpitazi CE. Intranasal Fentanyl Use in Neonates. Hosp Pharm. 2020 Apr;55(2):126-9.
22. Hwang SJE, Daniel BS, Fergie B, Davey J, Murrell DF. Prevalence of anemia in patients with epidermolysis bullosa registered in Australia. Int J Womens Dermatol. 2015;1(1):37-40.
23. Reimer A, Hess M, Schwieger-Briel A, Kiritsi D, Schauer F, Schumann H, et al. Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. Br J Dermatol. 2020;182(6):1437-48.
24. Simpson B, Tarango C, Lucky AW. Clinical algorithm to manage anemia in epidermolysis bullosa. Pediatr Dermatol. 2018;35(5):e319-e20.
25. Debra Portugal Associação Portuguesa de Epidermólise Bolhosa Audição pela Comissão 9º - CS XII Grupo Trabalho Ictiose/Doenças Raras 03 de Abril de 2014 - Documento informativo.
26. Angelis A, Kanavos P, López-Bastida J, Linertová R, Oliva-Moreno J, Serrano-Aguilar P, et al. BURQOL-RD Research Network. Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe. Eur J Health Econ. 2016 Apr;17 Suppl 1(Suppl 1): 31-42.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

ORIGINAL ARTICLE

Campylobacteriosis: from diagnosis to the community intervention, a case-control study

Inês Silva-Costa[1a], João Sousa-Marques[1b], Sara Geitoeira[1c], Catarina Dias[2d], Sara Dias[3e], Lígia M. Ferreira[1f], Sofia Reis[1g], and Cristina Baptista[1h]*

[1]Serviço de Pediatria, Centro Hospitalar Tondela-Viseu E.P.E.; [2]Serviço de Patologia Clínica, Centro Hospitalar Tondela-Viseu E.P.E.; [3]Unidade de Saúde Pública, ACES Dão-Lafões. Viseu, Portugal

ORCID: [a]0000-0002-2940-838X; [b]0000-0002-2845-3357; [c]0000-0002-2298-1327; [d]0000-0002-8094-9827; [e]0009-0002-3494-1039; [f]0000-0003-1098-0420; [g]0009-0002-3667-9241; [h]0009-0002-8154-5920

Abstract

Introduction: Campylobacteriosis is the most frequent cause of acute bacterial diarrhea and its rising incidence in Europe is of concern. Guidelines for etiological investigation in acute infectious diarrhea and their impact on therapeutic conduct and community interventions are yet to be defined. **Materials and Methods:** We viewed 5 years of the Pediatric Emergency Department´s stool cultures. The case group included 207 patients with Campylobacteriosis and the control group 276 patients with a negative stool culture. We evaluated the execution rate of Mandatory Notification and the diligence performed by Public Health Authorities. **Results:** In the case group, the median age was 2 years, 59.90% of patients were males and 68.60% were residents in rural areas. The bloody stool was significantly more frequent in the case group (78.26% vs. 30.80%, OR 8.09) and so was the presence of fever (65.22% vs. 39.86%, OR 2.83). In the case of group, 8.70% were admitted to in-patient facilities. The readmission rate in the subsequent 7 days was 17.87%, 45.95% of which with alterations to the previously chosen therapeutic conduct. The notification was performed in 37.63% of all Campylobacteriosis, translating most frequently isolated cases in the intervention area of the studied Health Authority. The most frequent diligence was sanitary education. In the group of patients whose notification was not performed, reinfection happened twice. **Conclusion:** Campylobacteriosis is in most cases a benign and self-limited disease. The isolation of the agent in the stool culture still plays a role in the management of the therapeutic conduct and the methods of community control.

Keywords: Campylobacteriosis. Diarrhea. Public Health.

Campilobacteriose: do diagnóstico à intervenção comunitária, um estudo de caso-controlo

Resumo

Introdução: A Campilobacteriose é a causa mais frequente de diarreia bacteriana aguda sendo preocupante a sua incidência crescente no espaço europeu. Estão ainda por definir orientações para a investigação etiológica na diarreia infeciosa aguda, o seu impacto no plano terapêutico e nas medidas interventivas na comunidade. **Materiais e Métodos:** Analisámos 5 anos de episódios de urgência com pedido de coprocultura anexo. Obteve-se uma população composta por um grupo caso de 207 culturas positivas para *Campylobacter* e um grupo controlo com 276 culturas negativas. Avaliámos o cumprimento da notificação obrigatória e as diligências efetuadas pela Saúde Pública. **Resultados:** A mediana de idades

***Correspondence:**
Inês Silva-Costa
E-mail: c-ines@hotmail.com

Received: 30-03-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):34-39
DOI: 10.24875/PJP.M23000133

do grupo caso foi 2 anos. Destes, 59,90% eram do sexo masculino e 68,60% provenientes de um meio rural. A diarreia sanguinolenta foi significativamente mais frequente no grupo caso (78,26% vs. 30,80%, OR 8,09) assim como a presença de febre (65,22% vs. 39,86%, OR 2,83). No grupo caso optou-se por internamento em 8,70% dos doentes. A taxa de readmissões a 7 dias foi de 17,87%, 45,95% das quais com alterações do plano terapêutico. Notificaram-se 37,63% das Campilobacterioses, a maioria tratando-se de casos isolados na área de intervenção da Autoridade de Saúde Pública em estudo. A diligência mais comum foi a educação sanitária. No grupo de admissões não notificadas verificaram-se duas reinfeções. **Conclusão:** A Campilobacteriose é na maioria dos casos uma doença benigna e autolimitada e o seu isolamento em coprocultura continua a ter papel na gestão do plano terapêutico e dos métodos para controlo de focos na comunidade.

Palavras-chave: Campilobacteriose. Diarreia. Saúde Pública.

Keypoints

What is known
- Campylobacteriosis is the main cause of bacterial gastrointestinal infections worldwide.
- It usually presents as a self-limited, low morbimortality disease.
- It is a disease of mandatory notification to health authorities.

What is added
- Campylobacter was most frequently isolated in children with bloody diarrhea or fever.
- Notification to Public Health authorities is underperformed.
- Reinfection was more frequent in the group of patients whose notification was not performed.

Introduction

Acute diarrhea is one of the most frequent conditions that cause admission to pediatric emergency departments worldwide. In children without comorbidities and that don´t present severity signs of illness, no etiologic investigation is usually required[1-2].

Campylobacter is the main causative agent of acute bacterial diarrhea in medium-to-high-income countries. It usually presents as self-limited acute gastroenteritis in infants and adolescents. The treatment is mainly supportive and few cases require an antibiotic prescription. Epidemiological studies continue to identify changes in its seasonal pattern, with infections happening earlier than the previously stated summer season. On the other hand, the emergence of antimicrobial resistance is concerning and the incidence of campylobacteriosis is rising parallelly to the implementation of high hygiene and sanitary control standards that are required in European countries[3-5].

Campylobacter is a commensal microorganism found in the gastrointestinal tracts of animals, including birds and cattle, and is prevalent in all avian species destined for human consumption. Water is another known source of contamination and European legislation mandates that natural mineral water sourced from springs and, occasionally, from drilling sources must be free from parasites and pathogens[6,7].

A well-structured surveillance program for campylobacteriosis is essential, as it provides vital information regarding the prevalence of the disease and helps identify common routes of pathogen transmission. Therefore, it is crucial to implement standardized biocontrol methods in the poultry sector and water supply. Patient notification is also of utmost importance as it enables public health authorities to trace the source of infection, thereby reducing community spread and the risk of reinfection[6-8]. Therefore, campylobacteriosis is a mandatory notification disease to Public Health departments that afterward conduct an epidemiological investigation and implement prevention and control measures. A correct and early notification allows more effective community interventions to prevent the short and long-term spread of the infection chain[1,6,7].

Our main purpose was to assess signs and symptoms more likely to be present in patients with campylobacteriosis, comparing to patients with acute infectious diarrhea from another bacteriological agent, and also gage whether there were changes in the chosen therapeutic conduct after requesting the stool culture in the ED. Moreover, we intended to study the practical consequences of notifying the infection in preventing reinfection.

Methods

Study design and sample

A retrospective, case-control study was conducted in the pediatric emergency department (ED) of a level II hospital in Portugal, overviewing all patients who were admitted between the 1st of March 2015 and 31st of March 2020 and for whom a stool culture was requested

and analyzed at our Clinical Pathology Department. The patients were then assessed wether eligible for either case or control group. Stool cultures after April 2020 were excluded, as the COVID-19 pandemic started to spread in Portugal, and Public Health procedures were adapted to face this emergent pandemic.

The case group included all patients with isolation of a *Campylobacter* species in the stool culture performed through a selective agar base that incubates for up to 5 days in a microfilic environment at 42°C.

The control group included all patients without bacterial isolation in every stool culture performed (*Salmonella* and *Shigella* selective and differential agar, *Campylobacter* selective agar, *Yersinia* selective and differential agar, and the subculture performed in the gram-negative enriched agar). Exclusion criteria for the control group included: patients with inflammatory bowel disease or under immunosuppressive therapy, patients with positive polymerase chain reaction for adenovirus or rotavirus (PCR), or a final diagnosis that was not acute infectious diarrhea.

Data collection

Demographic and clinical variables were collected using the emergency admission records. The distinction between rural and urban areas was performed through the consultation of administrative records from Ministério da Administração Interna, namely "PRODER - Classificação das Freguesias do Continente em Rurais e Não Rurais"[9]. The therapeutic conduct was assessed through electronic medical prescriptions and discharge transcripts.

Notification of campylobacteriosis, epidemiological questionnaires, and the reports of the community interventions performed by Health Authorities were consulted in the archives of the local Public Health Department and Sistema Nacional de Vigilância Epidemiológica (SINAVE®) system.

Data analysis

Statistical Package for Social Sciences (SPSS®) version 26 software was used to analyze the collected data. The quantitative variables were expressed as central tendency measures and the qualitative variables as absolute values and percentages. Given the non-normal distribution of continuous variables, non-parametric tests were used. Values for $p < 0.05$ were considered statistically significant.

Approval by the Ethics Committee of the Hospital and the Public Health Department was obtained before initiating data collection.

Table 1. Qualitative variables

Variable	Control group (n = 276) n (%)	Case group (n = 207) n (%)	*p* value*
Sex (males)	160 (57.97)	124 (59.90)	0.64
Residence (rural area)	169 (61.23)	142 (68.60)	0.09
Vomiting	113 (40.94)	58 (28.02)	< 0.01
Fever	110 (39.86)	135 (65.22)	< 0.01
Abdominal pain	90 (32.61)	69 (33.33)	0.92
Bloody stool	85 (30.80)	162 (78.26)	< 0.01
Epidemiological context	70 (25.36)‡	42 (20.29)†	0.19
Admission to ED < 15 days	72 (26.09)	55 (26.57)	0.19

*Chi-Squared test.
†76 missing data.
‡99 missing data.

Results

During the five-year study period, 1089 stool cultures were requested in the ED. *Campylobacter* was isolated in the culture of 209 patients, two of whom were excluded from the case group due to missing clinical data.

Of the remaining 880 patients, 521 were eligible for the control group. The group of 359 patients not eligible included patients to whom only a certain type of bacteriological subculture was performed and, more infrequently, patients with isolation of another bacteriological agent rather than *Campylobacter*.

Exclusion criteria were then applied, with five patients excluded due to previous history of inflammatory bowel disease or recent immunosuppressive therapy and 240 without a final diagnosis of acute infectious diarrhea, leaving 276 patients to be included in the final control group.

Clinical presentation

The case and control groups were similar in age, sex, and area of residence (Tables 1 and 2).

Vomiting was the only clinical feature significantly more frequent in the control group. On the other hand, fever and bloody stool were more common in the case group, with an odds ratio of 2.83 (IC95% [1.95;4.11]) and 8.09 (IC95% [6.71;10.75]), respectively.

The median number of reported stools per day was significantly different in the extreme age groups, both higher in patients with campylobacteriosis (Table 3).

Table 2. Quantitative variables

Variable	Control group (n = 276) Median (variance)	Case group (n = 207) Median (variance)	*p* value*
Age in years	2.00 (20.18)	2.00 (12.18)	0.37
Illness evolution in days	4.00 (138.05)	3.00 (72.01)	< 0.01
Number of stools per day	5.00 (8.48)	6.00 (12.93)	< 0.01

*Mann Whitney U for independent samples.

Table 3. Median number of stools per day, per age group

Age group	Median number of stools per day (variance)		*p* value*
	Control group (n = 215)†	Case group (n = 165)‡	
≤ 1 year	4.00 (6.02)	6.00 (9.98)	0.02
(1-2) years	5.00 (11.20)	6.00 (10.20)	0.09
(2-4) years	6.00 (5.78)	6.00 (26.05)	0.51
> 4 years	4.00 (9.54)	6.00 (14.34)	0.01

*Mann-Whitney U test for independent samples.
†61 missing data.
‡42 missing data.

From the case group, 18 (8.70%) were admitted to in-patient facilities, in contrast with 39 (14.13%) in the control group. The main reason for in-patient admission was suspected bacteremia and dehydration/electrolytic alterations. Regarding antibiotic treatment, only ceftriaxone was an empirically chosen therapeutic conduct in patients at admission, 4 (22.2%) in the case group and none in the control group.

In the case group, after telephonic contact with caregivers or through readmission in the ED, an antibiotic was prescribed in 34 (16.40%) patients, most frequently azithromycin (52.94%), all because of persistent symptoms.

Recorded readmissions to the ED, due to persistence or recrudescence of symptoms, in the seven subsequent days, were 17.87% in case group and 10.87% in the control group. Readmissions in the control group resulted in the change of management plan in two patients, who collected new stool cultures, both negative. On the other hand, readmissions in the case group resulted in the change of plan 45.95% of the time, most frequently initiating antibiotics.

Community intervention

From the total amount of patients diagnosed with Campylobacteriosis, 186 (89.86%) were residents in the area covered by the local Public Health Authority. Mandatory Notification was performed in 70 cases (37.63%), with a median time between diagnosis and notification of 6 days and a median time between the beginning of symptoms and notification of 13 days.

After epidemiological questionnaires were analyzed, three clusters were confirmed, two of them in family settings and one involving 9 children through contaminated water.

Sanitary education, such as food hygiene and safety procedures, personal hygienic care measures, and veterinary advice, if contact with animals was found as a possible contamination source, was the most frequent diligence, performed by Health Authorities, in 100% of identified cases. Water sample analysis was required in 28 cases: 19 private water sources, six public water fountains, one kindergarten, one private pool, and one water spring. Of the seven public water sources tested (water fountains and water springs), six were considered positive.

There were no reinfections registered in the group of patients who were notified. Furthermore, two patients were reinfected in the group whose notification was not performed, with a time gap of 4 and 10 months each. In our geographical area, for the pediatric population, if 58 notifications are performed, one case of reinfection is prevented.

Discussion

Campylobacteriosis is still a benign and self-limited disease in most cases. In our study, the mean age of diagnosis is compatible with the literature´s description of higher prevalence in preschoolers[2,3]. Bloody stool and fever may be associated with the isolation of *Campylobacter* in the stool cultures, with the first showing a stronger association. Vomiting is the only clinical feature associated with no isolation, which may be because, according to the literature, it is clinically more present when viral agents are involved.

Stool cultures continue to play an important role in the management of acute campylobacteriosis, with a non-neglectable proportion of children requiring antibiotic treatment. A positive stool culture, when children are readmitted for the persistence of symptoms, may lead to more antibiotic prescriptions, although it is not certain if this therapeutic conduct actually changes the natural progression of the disease[1].

Rural areas were not associated with a higher incidence of campylobacteriosis. The same was found in the epidemiological context. The latter needs careful evaluation as the control group might include children infected with viral agents, which also spread frequently in the pediatric population. However, in the case group, the epidemiological context should indicate that cohabitants would more likely be also infected with *Campylobacter*, and that was not found in the data extracted from the public health authorities, as just three outbreaks were confirmed. This might be a limitation of low rates of notification.

Notification to Public Health Authorities is still underperformed in our center, with more than half of the affected individuals without the potential care of public health authorities. However, in every patient whose notification was performed, an investigation was conducted by Health Authorities, which translates into full rates of management if proper reporting by pediatricians is performed. In the group of patients whose infection was notified, the time gap between the beginning of symptoms and the notification date, 13 days, is of note. This may pose difficulties in the management of the infection chain as it delays the investigation of possible contaminated sources that may have been discarded in that period, namely contaminated food. On the other hand, Campylobacter species is thermotolerant and grows at pH between 6.5 and 7.5, which are conditions difficult to maintain stable in natural environments exposed to changes in temperature, humidity, and acidity, increasing the potential of false negative sampling after several days of exposure[6,7]. However, the efficacy of water sampling in our population was very high in public sources, as 6 out of 7 were positive. This should raise awareness of two problems: freshwater consumption implies that no heating is performed to eliminate coliforms and therefore individuals who drink it are more susceptible to infection compared to food that undergoes cooking, and, on the other hand, public water sources should be the ones with higher water quality, compared to private water sources that, by legislation, are not required to undergo frequent testing[6,10].

Reinfection rate in the children whose notification was not performed, with a large period of interval time, showing that although a benign course of infection happened, continuous exposure to the agent is still a risk factor for reinfection. Public health diligence should focus on stopping the primary source to prevent this from happening as more infections and reinfections translate into more bacterial gastroenteritis, more school or work absence, more admission to the emergency departments, and higher rates of Guillain-Barré Syndrome and Reactive Arthritis, which are both known complications of campylobacteriosis[6]. The impact of campylobacteriosis on the overall public health burden of acute gastrointestinal illness remains uncertain. Numerous studies conducted have aimed to calculate the expenses associated with gastrointestinal infections, including campylobacteriosis. In a Swiss study, researchers determined that the average cost of a laboratory-confirmed case of Campylobacteriosis is approximately 975 euros[11]. Therefore, accounting for the number of infected people in our center, the prevention of this infectious disease also translates into a cost-efficient activity as zoonotic diseases are more easily preventable compared to other environmental exposure lead pathologies. The costs associated with undiagnosed cases tend to vary more widely, with most studies focusing on underdiagnosis rather than underreporting.

This study assesses only the pediatric population, and this may pose a bias in the study of community interventions since we do not assess whether adults were also infected/reinfected in the families of children whose notification was not performed. There is still a big group of children, whose area of residence was not the one where the hospital was located, and because of that, we may have lost them for follow-up of readmission to the ED, notification to the public health department, and reinfection.

In conclusion, although campylobacteriosis is mostly a benign infection, it is also a preventable one. Notification to Public Health Authorities should be performed as reinfection is a reality and all cases are readily evaluated after correct reporting, with a considerable rate of potential-changing lead findings. The decrease in incidence may happen after correct notification of every case and if there is a shorter period between the beginning of symptoms and the public health investigation.

Acknowledgments

The results of this investigation were presented in 1ªs Jornadas Digitais de Pediatria, on the 29th of October 2020.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Rodrigues F, Calvino J, Alves AF, Lemos L. Diarreia Aguda por Campylobacter Jejuni. 2006. Acta Med Port;(3),Vol 37. 91-3.
2. Soares AT, Couto C, Romão P, Melo IS, Braga M, Diogo J, et al. Gastroenterite Aguda por Campylobacter Spp: Casuística de uma Urgência Pediátrica [Acute gastroenteritis by Cambylobacter spp: a retrospective study of a paediatric emergency department]. Acta Med Port. 2014 Sep-Oct;27(5):556-60.
3. Borges AC, Pedrosa C, Santos A, Vitorino M, Costa M, Godinho C. Campylobacter jejuni: Gastroenterites Agudas e Infeções Extra-Intestinais. Acta Med Port; 2005;36(4):191-3.
4. Patrick ME, Henao OL, Robinson T, Geissler AL, Cronquist A, Hanna S, et al. Features of illnesses caused by five species of Campylobacter, Foodborne Diseases Active Surveillance Network (FoodNet) - 2010-2015. Epidemiol Infect. 2018 Jan;146(1):1-10.
5. Fitzgerald C, Patrick M, Gonzalez A, Akin J, Polage CR, Wymore K, et al. Multicenter evaluation of clinical diagnostic methods for detection and isolation of *Campylobacter* spp. from the stool. J Clin Microbiol. 2016;54(5):p. 1209-15.
6. Facciola A, Riso R, Avventuroso E, Visalli G, Delia SA, Lagana P. Campylobacter: from microbiology to prevention. J Prev Med Hyg. 2017;58(2):E79-E92.
7. The Institute of Environmental Science and Research Ltd. Notifiable Diseases in New Zealand: Annual Report 2016.
8. Hlashwayo DF, Sigaúque B, Noormahomed EV, Afonso SMS, Mandomando IM, Bila CG. A systematic review and meta-analysis reveal that Campylobacter spp. and antibiotic resistance are widespread in humans in sub-Saharan Africa. PLoS One. 2021 Jan 27;16(1):e0245951.
9. Ministério da Agricultura e do Mar. PRODER - Classificação das Freguesias do Continente em Rurais e Não Rurais. 2020.
10. Bull SA, Allen VM, Domingue G, Jorgensen JA, Frost R, Ure R, et al. Sources of Campylobacter spp. colonizing housed broiler flocks during rearing. Appl Environ Microbiol. 2006;72:645-52.
11. Schmutz C, Mausezahl D, Bless PJ, Hatz C, Schwekglenks M, Urbinello D. Estimating healthcare costs of acute gastroenteritis and human campylobacteriosis in Switzerland. Epidemiol Infect. 2017;145(4):627-41.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

REVIEW ARTICLE

A reviewed approach to vitamin D supplementation in pediatric age in Portugal

Carla Rêgo[1,2,3a], Gonçalo Cordeiro-Ferreira[4b], Maria J. Lages-Fonseca[5c], Mariana Moura-Relvas[6d], Ricardo Ferreira[7e], and Sofia Pinto-da Costa[8f]*

[1]Department of Pediatrics, Hospital CUF, Porto; [2]CINTESIS, Faculdade de Medicina da Universidade do Porto, Porto; [3]ESB, Universidade Católica Portuguesa, Porto; [4]Pediatrics, Hospital Dona Estefânia, Lisbon; [5]General Practice USF Arcos D'Ouro - ACeS Grande Porto VII Gaia, Porto; [6]General Practice, USF Génesis, Odivelas; [7]Pediatric Department, Centro Hospitalar e Universitário de Coimbra, Coimbra; [8]General Practice, USF São João (São João da Madeira), ACeS Aveiro Norte. Portugal

ORCID: [a]0000-0003-1229-8775; [b]0000-0001-6145-0468; [c]0000-0003-4895-4295; [d]0000-0001-6058-507X; [e]0009-0003-2437-7304; [f]0000-0002-4633-0676

Abstract

Vitamin D deficiency is a well-established cause of rickets in children and has been reported as associated to impacts on other systems and organs. Vitamin D deficiency and insufficiency are pediatric worldwide global health problems. Although data on the prevalence of vitamin D deficiency and insufficiency in the Portuguese pediatric population are scarce, data for Portuguese subpopulations and equivalent regions allows us to speculate that the prevalence of vitamin D deficiency in Portugal should be also relevant. The current article focuses on vitamin D supplementation at pediatric age in Portugal reviewing the prevalence data of vitamin D insufficiency/deficiency for Portugal, the main groups and the risk factors for vitamin D deficiency and educational measures and vitamin D supplementation recommendations for different risk factors/groups.

Keywords: Adolescent. Child. Dietary supplements. Vitamin D deficiency.

Revisão à abordagem de suplementação de Vitamina D em idade pediátrica, em Portugal

Resumo

A deficiência de vitamina D é uma causa bem estabelecida de raquitismo em crianças e tem sido associada a compromisso funcional de outros órgãos e sistemas. A deficiência e insuficiência de vitamina D são um problema de saúde global, muito comum em crianças de todo o mundo. Embora os dados sobre a prevalência da deficiência/insuficiência de vitamina D na população pediátrica portuguesa sejam escassos, os dados relativos às subpopulações portuguesas e regiões equivalentes permitem-nos especular que a prevalência da deficiência de vitamina D em Portugal deverá ser relevante. O presente artigo centra-se na suplementação com vitamina D em idade pediátrica em Portugal, revendo os dados de prevalência da insuficiência/deficiência em vitamina D em Portugal, os principais grupos e os factores de risco de deficiência de vitamina D, bem como as medidas educativas e recomendações de suplementação de vitamina D para os diferentes factores/grupos de risco.

Palavras-chave: Adolescentes. Crianças. Deficiência de vitamina D. Suplementação alimentar.

***Correspondence:**
Carla Rêgo
E-mail: carlambssrego@gmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):40-47
DOI: 10.24875/PJP.M23000120

Introduction

Vitamin D plays a key role in bone and muscle health due to its interference in calcium metabolism and consequent role in bone formation. Vitamin D deficiency is a well-established cause of rickets in children and of osteomalacia in adults. Other effects associated with vitamin D deficiency on other organs and systems have also been reported. However, the available literature refers mostly to adult populations and pediatric data are often contradictory or inconclusive[1].

Clinical research on vitamin D has been stimulated by the discovery that many human cell types carry the vitamin D receptor. This receptor may play a role in the regulation of cell proliferation and differentiation, for example, in cells of the immune system as T cells, macrophages or monocytes. In children and adolescents, additional health effects of vitamin D have been proposed due the plethora of vitamin D functions, as well as data from observational studies on the association between vitamin D status and diseases. These additional effects of vitamin D may include prevention of immune-related diseases (asthma, type 1 diabetes mellitus, multiple sclerosis), prevention of infectious diseases (e.g., respiratory infections) and prevention of cardiovascular diseases and cancer. Infants and children with severe vitamin D deficiency and rickets may also present delayed motor development, muscle hypotonia, and weakness[1-3].

Vitamin D deficiency and insufficiency are a global health problem, very common in infants and children worldwide[4,5]. Data on the prevalence of vitamin D deficiency and insufficiency in the Portuguese pediatric population are scarce. However, regional data available for pediatric populations of Portugal[6,7] and data for other Mediterranean countries[2,8], allows us to speculate that the prevalence of vitamin D deficiency in Portugal can be higher.

In this scenario, this review article will focus on vitamin D supplementation in pediatric age in Portugal and will, therefore: 1) review the prevalence data of vitamin D insufficiency/deficiency available for Portuguese pediatric populations and/or other Mediterranean countries; 2) review and document the main groups and the risk factors for vitamin D deficiency and the mechanism responsible for the deficit in each case; 3) review educational measures and vitamin D supplementation recommendations according to the age of the child/adolescent and the presence (or absence) of risk factors/groups.

Vitamin D biomarkers, reference values and prevalence data of vitamin D deficiency/insufficiency in pediatrics in Portugal

Vitamin D, also designated as calciferol, is a pre-hormone obtained by dietary sources but mainly formed by sun exposure of the skin (almost 90% of our needs). In the liver, vitamin D suffers metabolization to an inactive form designated as 25-hydroxyvitamin D [25(OH)D] or calcidiol. This inactive form is activated at the renal level into 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] or calcitriol, which plays a critical role in calcium and mineral homeostasis. 25(OH)D, of the overall circulating vitamin D metabolites, is the established biomarker for assessing vitamin D status, because it is the most abundant form, it has the longest half-life, and it reflects both skin synthesis and dietary intake. Furthermore, it shows greater sensitivity to variations in vitamin D status of individuals, serving not only as a status indicator of this micronutrient but also as the main storage form in the body[6,9].

Definition of vitamin D status and reference values are not consensual between different committees or societies. For children, the Direção-Geral da Saúde (DGS - the Portuguese General Directorate for Health) establishes vitamin D deficiency for plasmatic concentration of 25(OH)D lower than 12 ng/mL (30 nmol/L) and insufficiency when plasmatic concentration lies between 12-20 ng/mL (30-50 nmol/L). For adult age, established values are different and vitamin D deficiency was defined for plasmatic concentration of 25(OH)D lower than 20 ng/mL (50 nmol/L) and insufficiency if it lies between 20-30 ng/mL (50-75 nmol/L)[10].

On the other hand, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) does not use the concept of insufficiency and define deficiency and severe deficiency of vitamin D for plasmatic concentration of 25(OH)D between 10-20 ng/mL (25-50 nmol/L) and lower than 10 ng/mL (25 nmol/L), respectively[1].

Considering the reference values of DGS and ESPGHAN, there is no consensus on the characterization of adequate vitamin D levels, particularly with regard to cut-off points for defining insufficiency/deficiency. However, it is agreed that serum levels below 20 ng/mL (50 nmol/L) indicate children at risk. While describing the prevalence of vitamin D deficiency in the following paragraphs, plasmatic values of 25(OH)D are used to avoid ambiguous classification.

As previously mentioned, data on the prevalence of vitamin D deficiency in Portuguese pediatric populations are very limited. A study conducted in a northern region of Portugal (Porto region) (n = 67; 5-18 years), showed that 41.8% presented serum values of 25(OH)D between 10 ng/mL and 20 ng/mL, and 6% below 10 ng/mL, indicating that almost half of the sample (47.8%) suffered from vitamin D deficiency/insufficiency[5]. A study done to assess vitamin D levels and cardiometabolic risk factors

in the same region showed mean serum vitamin D levels below the recommendations (16.52 +/–5.72 ng/mL) (514 subjects) for adolescents (13 years old)[7].

In adults, a study conducted to give an overall epidemiological picture of vitamin D status in the Portuguese population (n = 3092) estimated 25(OH)D levels < 20 ng/ml and < 30 ng/ml to affect 66.6%, and 96.4% of the population, respectively, with strong geographical and seasonal variation[3].

A recent systematic review on pediatric populations covering over 107 studies (representing 630,093 individuals) showed that in the Southern Europe and Eastern Mediterranean regions, more than one-third of the studies reported mean 25(OH)D levels < 20 ng/mL across all population subgroups, but especially among neonates/infants and adolescents[8]. A study conducted in Spain (a neighbor country of Portugal) in the sunny region of Valencia (n = 169) with children aged under two, found 8.3% with plasmatic levels of 25(OH)D under 20 ng/mL[2].

Risk groups and factors for vitamin D deficiency in the pediatric populations

This section identifies groups of children/adolescents with a higher predisposition or risk of developing vitamin D deficiency/insufficiency, also identifying the mechanism that leads to the possible deficiency. All the information is summarized in table 1.

Endogenous production of vitamin D after exposure to natural sunlight is the most important source of vitamin D. Thus, lack of natural sunlight exposure is one of the most relevant risk factors for vitamin D deficiency, with the geographic location (latitude) having an important role[11]. Lack of sun exposure is associated with lifestyle (clothing habits, cultural and religious habits, sedentarism and long indoor permanence) but may also be associated with conditions or pathologies that impair sun exposure. For example, dark-skinned individuals (photo-type V) require about 3 to 5 times more time of sun exposure to synthesize the same amount of vitamin D, in comparison to a person with a photo-type II[12]. Conditions such solar urticaria, vitiligo or chemical photosensitivity (for example, acne under isotretinoin) have strong indication to avoid sun exposure. Last, but not least, the use of high protection factor sunscreen (above 30) significantly reduces the capacity for vitamin D synthesis (~ 95%, when used in the recommended amount and frequency)[13].

Vitamin D deficiency is also a consequence of reduced dietary intake of vitamin D or of variabilities in absorption/distribution/metabolization/excretion of the vitamin, in a variety of different situations in children and adolescents.

Preterm newborns have a high risk of vitamin D deficiency due to maternal vitamin D supply deprivation (early birth inhibits the fetus to store adequate levels of vitamin D obtained essentially via maternal source) and potential exposure to additional risk factors such as long-term parenteral nutrition use, intolerance to human milk fortifiers and formulas and neonatal cholestasis[14]. A study showed that about 65% of preterm infants with less than 32 weeks of gestation had vitamin D deficiency and associated with this deficiency, an increased risk of prematurity-related bone disease (which affects up to 55% of preterm infants weighing < 1000 g)[15].

Children who did not comply with the universal supplementation of 400 IU per day of vitamin D in the first year of life are also considered a risk group for vitamin D deficiency. The importance of universal, early and regular supplementation is related to: 1) increased vitamin deficiency in the general population and in pregnant women; 2) often unknown status of vitamin D deficiency in pregnant women; 3) reported vitamin D deficiency in the first month of life (both for mother and child), particularly in breastfeeding (around 50% in the woman [insufficiency plus deficiency] and 80% in the newborn [deficiency])[16]; 4) medical recommendation to avoid direct sun exposure of children in the first year of life (due to higher risk of skin cancer and premature skin aging)[17]. As this avoidance of direct sun exposure is recommended at least until 2 years old, some scientific societies recommend the universal supplementation until 18-24 months of age[18].

A study that interviewed caretakers of approximately 1% of the Portuguese children with ages comprised between 12-36 months, showed lack of compliance of vitamin D supplementation in the first year of life in about one-third of the cases (31.7%)[15], although universal supplementation of vitamin D is recommended by DGS and ESPGHAN for this period[9]. In the United States of America prevalence of lack of compliance of recommendations is almost the same, with nearly one third of infants not meeting American Academy of Pediatrics (AAP) recommendations[19].

Breastfeeding infants are also at risk of vitamin D deficiency since breast milk contains very low amounts of vitamin D. Considering an intake of 150 ml/kg/day, the amount of vitamin D obtained by a breastfeeding an infant through breast milk is only 30 IU/day[20].

Obese children and adolescents are also at a higher risk of vitamin D deficiency because vitamin D, a fat-soluble vitamin, is sequestered by the higher amount of adipose tissue[11] and because body and serum volume are higher in these individuals, causing a dilution effect[21].

Table 1. Summary of risk groups for vitamin D deficiency, associated mechanism and recommendations

Risk groups	Mechanism		Recommendation
Children/adolescents living in lifestyle contexts with limited sun exposure: – Clothing habits – Cultural/religious habits – Sedentarism – Long indoor permanence	Limited sun exposure reduces the endogenous production of vitamin D (which is the most important source of vitamin D).	Low endogeneous production	Educational measures. If educational measures are not successful/possible, supplement with 600 IU/day of vitamin D (autumn-spring). Routine 25(OH)D determination not recommended.
Children/adolescents with conditions or pathologies which do not allow for sun exposure, e.g: – Children/adolescents with high phototypes – Children/adolescents with solar urticaria, vitiligo and chemical photosensitivity	Dark-skinned individuals require about 3 to 5 times more time of sun exposure to synthesize the same amount of vitamin D, in comparison to person with a lower phototype. Limited sun exposure reduces the endogenous production of vitamin D.	Low endogeneous production	
Children/adolescents with use of high protection factor sunscreen (above 30)	Sunscreen (above 30) significantly reduces the capacity for vitamin D synthesis (~ 95%, when used in the recommended amount and frequency).	Low endogeneous production	
Pre-term newborns	Maternal vitamin D supply deprivation. Other factors such as: – Long-term parenteral nutrition use – Intolerance to human milk fortifiers and formulas – neonatal cholestasis	Low intake Low reserve Low absorption	Supplementation with 800-1000 IU/day of vitamin D.
Infants in the 1st year of life Children who did not comply with the universal supplementation in 1st year of life	Maternal vitamin D deficiency. Unknown status of vitamin D in pregnant women. Reported vitamin D deficiency in the first month of life (both for mother and child). Recommendations to avoid direct sun exposure of children in the first year of life.	Low intake Absence of cutaneous synthesis	Universal supplementation with 400 IU/day of vitamin D.
Breastfeeding infants	Breast milk contains very low amounts of vitamin D.	Low intake	If in the 1st year of life, universal supplementation with 400 IU/day of vitamin D.
Obese children/adolescents	Vitamin D is sequestered by the higher amounts of adipose tissue. Dilution effect to higher body and serum volume.	Distribution variability	Consider supplementing with 600 IU/day of vitamin D at least from autumn to spring.
Children/adolescents following certain diets (such as veganism or macrobiotics). Nutritionally inadequate diets	Low intake due to dietary restrictions or inadequate diet.	Low intake	
Children/adolescents with a known history of congenital or acquired metabolic disorders of calcium and vitamin D metabolism	Deficiencies in enzymes responsible for metabolization to the active for of vitamin D (p.e. 1α-hydroxylase deficiency). Vitamin D resistance (receptor defect).	Impaired metabolism Receptor deficiency	Determine 25(OH) D basal levels. If levels are deficient supplement with 600 IU/day (vitamin D deficiency) 1000-2000 IU/day (severe vitamin D deficiency)

(Continues)

Table 1. Summary of risk groups for vitamin D deficiency, associated mechanism and recommendations *(continued)*

Risk groups	Mechanism		Recommendation
Children/adolescents with chronic diseases, such as:			Always respect the maximum allowed daily doses for vitamin D: – 1000 IU/day: < 6 months – 1400 IU/day: 6-12 months – 2000 IU/day: 12 months-12 years – 4000 IU/day: > 12 years Conduct a new 25(OH)D determination after 3-6 months and adjust supplementation if necessary. Adapt supplementation to specific situations: – In hepatic cholestasis: 1300-2200 IU/day – In liver failure: supplement with 25(OH)D – In chronic kidney disease: supplement with 25(OH)2D (as in congenital or acquired metabolic disorders or chronic diseases)
Malabsorption syndromes	Cause reduction the intestinal absorption of vitamin D.	Low absorption	
Inflammatory bowel disease	Might be associated to reduced absorption and increased excretion of vitamin D.	Low absorption Increased excretion	
Hepatic cholestasis	Causes absorption disturbances of vitamin D.	Low absorption	
Liver failure	Compromises the first hydroxylation mechanism, which converts vitamin D into 25(OH)D.	Impaired metabolism	
Chronic kidney disease	Causes increased urinary excretion of 25(OH)D, before it is converted into the active form of vitamin D.	Increased excretion	
Adolescent/children under chronic/prolonged treatments with:			
Anticonvulsants – Antiretrovirals	These drugs increase the metabolism of 25(OH)D and 1,25(OH)2D.	Increased metabolization	
Systemic corticoids	Antagonize the effect of vitamin D and can lead to hypocalcemia.	Antagonization mechanism	
Anti-fungals	Inhibit the enzymes responsible for metabolization to the active for of vitamin (hydroxylases).	Impaired metabolization	
Children/adolescents health conditions or tests suggestive of vitamin D deficiency: – Bone disease (rickets) – Non-traumatic fractures – Known history of vitamin D deficiency – Low 25(OH)D levels – Low urinary calcium excretion in 24h urine – Elevated parathyroid hormone or bone alkaline phosphatase levels – Bone mass compromise for age (z score for bone mineral density (BMD) < –2)	-	-	Nutritional rickets in children 12 months-10 years: 2000 IU/day for 3 months. Low 25(OH) D levels: Vitamin D deficiency: 600 IU/day Severe vitamin D deficiency: 1000-2000 IU/day

Another risk groups for vitamin D deficiency are children and adolescents following certain diets (such as veganism or macrobiotics or inadequate diets), which include limited sources of vitamin D (see list of foods with high vitamin D content in Table 2)[11,22,23].

Children/adolescents with a known history of congenital or acquired metabolic disorders of calcium and vitamin D metabolism are also a risk group. Examples include changes that compromise the availability of the active form of vitamin D (1.25$(OH)_2$D or calcitriol) such as deficiency in 1α-hydroxylase, the enzyme responsible for the second hydroxylation of 25(OH)D (calcidiol) into 25$(OH)_2$D (calcitriol). Another risk group includes individuals with hereditary resistance to vitamin D, which is characterized by a defect in vitamin D receptors. In these individuals, vitamin D levels are normal, calcitriol levels are high, yet there is resistance to vitamin D action due to unavailability/deficiency of its receptors[24].

Several chronic pathologies may be linked to vitamin deficiency due to disrupted absorption, metabolization

or excretion mechanisms. Examples include: 1) malabsorption syndromes, in which the intestinal absorption of vitamin D is reduced; 2) inflammatory bowel disease, which might be associated to reduced absorption and increased excretion of vitamin D; 3) hepatic cholestasis, which impairs vitamin D absorption; 4) liver failure, which might compromise the first hydroxylation mechanism, and which converts vitamin D into 25(OH)D; 5) chronic kidney disease which causes increased urinary excretion of 25(OH)D before it is converted into the active form of vitamin D[11,25].

Chronic or prolonged treatments with specific drugs might also be a risk factor for vitamin deficiency in children or adolescents. These include: 1) anticonvulsants and antiretrovirals, since these drugs increase the metabolism of 25(OH)D and 1,25(OH)2D; 2) systemic corticoids, which antagonize the effect of vitamin D and can lead to hypocalcemia; 3) anti-fungals, which inhibit the enzymes responsible for metabolization to the active for of vitamin (hydroxylases)[11,26]. Additionally, children/adolescents with health conditions or tests suggestive of vitamin D deficiency should also be considered at risk. These include children/adolescents with bone disease, non-traumatic fractures or with a known history of vitamin D deficiency, and indicators, such as low urinary calcium excretion in 24h urine, elevated parathyroid hormone or bone alkaline phosphatase levels and bone mass compromise for age (z score for bone mineral density (BMD) < –2)[10].

Table 2. Vitamin D content in food[11,22,23]

Food	Amount of food	Vitamin D content/IU*
Salmon (wild)	100 g	600-1000
Salmon (farmed)	100 g	100-250
Sardines (tinned)	100 g	300
Sardines (fresh)	100 g	280-320
Mackerel (wild)	100 g	104
Mackerel (tinned)	100 g	250
Herring (fresh)	100 g	215
Tuna (fresh)	100 g	292
Tuna (tinned)	100 g	236
Codfish	100 g	44
Eggs† (chicken bred with sun exposure)	1 egg	148
Eggs† (aviary chicken)	1 egg	32
Shitake mushrooms (dried)	100 g	1660
Cow milk	100 g	4
Yogurt	100 g	2,4
Cheese (varies according to type of cheese)	100 g	6,8-80

*The amount of vitamin D reported for each type of food may vary in the literature.
†Vitamin D exists in egg yolk.

Educational measures for the prevention of vitamin D deficiency in children and adolescents

Health education directed at pediatric age and their caregivers will be essential to prevent vitamin D deficiency/insufficiency and is an attempt to avoid pharmacological measures. Educational measures include recommendations about diet and sun exposure.

Nutritional advice should include the recommendation to ingest foods rich in vitamin D, such as: 1) oily fish (e.g. salmon, sardines, mackerel, herring, tuna, codfish); 2) eggs (yolk); 3) mushrooms; 4) dairy products (e.g. milk, yogurt, cheese), preferably fortified. However, the practice of food fortification in Portugal is not very common and, when available, fortified products contain relatively low amounts of vitamin D. Table 2 lists vitamin D-rich foods and their respective content of vitamin D[11, 22,23].

Dermatologic recommendations about sun exposure should include advice about moderate and regular exposure to natural sunlight for short periods, taking into consideration the dermatology recommendations for the prevention of neoplasms. Infants (< 12 months) and young children at least until 2 years old must avoid direct sun exposure[27]. An adequate exposure for vitamin D production seems to correspond to exposing face, hands and part of the arms, without the use of sunscreen, for 10 to 15 minutes a day (before the skin turns red), two or three days a week, in spring, summer and autumn[22].

Vitamin D supplementation recommendations according to the age of the child/adolescent and the presence (or absence) of risk factors/groups

The recommendations described in this section are summarized in table 1. For children/adolescents with low sun exposure, educational measures should be implemented (diet and sun exposure) and the levels of 25(OH)D should not be determined regularly. Supplementation should be considered from autumn to spring, especially if educational measures are not successful. Supplementation should be conducted according to established daily doses, namely 600 IU/day from

the 2nd year of life, always respecting the maximum allowed daily doses of 2000 IU/day for children aged from 12 months to 10 years and 4000 IU/day for children older than 10 years[1,28,29].

Vitamin D supplementation is already recommended in certain groups or clinical framings. In preterm newborns the recommended supplementation is 800-1000 IU/day. In preterm newborns with rickets or with high alkaline phosphatase levels, higher doses of vitamin D are recommended, with a maximum of 1000 IU/day[20]. In term infants a universal prophylactic supplementation is recommended during the first year of life with 400 IU/day of vitamin D[10, 20]. Those with dark skin or living in a high latitude (> 40º) may need a higher dose (800 IU/day)[30]. Children aged from 12 months to 10 years with confirmed diagnosis of nutritional rickets (based on a clinical history, physical examination, biochemical tests and confirmed by radiological study) should be supplemented with 2000 IU/day during 3 months. When vitamin D deficiency is confirmed by determination of 25(OH)D levels, children/adolescents should be supplemented with 600 IU/day. In severe deficiency supplementation of 1000-2000 IU/day should be implemented[10].

Other groups should also be considered for supplementation. For obese children/adolescents and children/adolescents following low vitamin D diets (veganism, macrobiotics or nutritionally inadequate diets) a supplementation of 600 IU/day, at least from autumn to spring, may be considered. In the case of obese children/adolescents, higher doses may be needed due to the sequestration of vitamin D in the adipose tissue[11]. In the case of weight loss, vitamin D liberation from the adipose tissue should be taken into account for dose adjustment.

For children/adolescents with: 1) a known history of metabolic disorders of calcium and vitamin D; 2) chronic diseases that disturb vitamin D absorption, metabolism and excretion; 3) under chronic or prolonged treatment with drugs that interfere in vitamin D availability; 4) known history of vitamin D deficiency and with other health conditions or tests indicative of vitamin D deficiency[10], the clinician should start by evaluating 25(OH) D basal levels. The initial supplementation should be defined according to the basal level of 25(OH)D. Children/adolescents should be supplemented with 600 IU/day (for vitamin D deficiency) and 1000-2000 IU/day (for severe vitamin D deficiency) always considering the maximum allowed daily dose: 1000 IU/day for children < 6 months; 1400 IU/day for children 6-12 months; 2000 IU/day for children aged from 12 months to 12 years; 4000 IU/day for children > 12 years[28,29]. The doses should be readjusted, if necessary, after a new evaluation of 25(OH)D levels and comparison with the basal levels, 3-6 months after the initial evaluation. In certain diseases, the supplementation should be done by resorting to alternative ways. In the case of renal failure, the supplementation should be conducted with $25(OH)_2D$ or calcitriol, due to the accelerated excretion mechanism of 25(OH)D under these conditions. In the case of liver failure, the supplementation should be done directly with 25(OH)D or calcidiol, since as described above, the hydroxylation mechanism from vitamin D to 25(OH)D is impaired. Micellar or hydro-soluble formulations should be preferred. In hepatic cholestasis, vitamin D absorption is disturbed and, therefore, supplementation with higher doses is recommended (1300-2200 IU/day)[20].

Conclusions

Vitamin D plays a key role in bone and muscle health. Other effects associated with vitamin D deficiency on other systems and organs have also been reported. There is no consensus on the characterization of vitamin D status compromise, particularly with regard to cut-off points for defining insufficiency/deficiency. However, it is agreed that serum levels below 20 ng/mL (50 nmol/L) indicate individuals at risk.

Data on the prevalence of vitamin D deficiency and insufficiency in the Portuguese pediatric population are non-existent. However, regional data and data for other Mediterranean countries allows us to speculate that the prevalence of vitamin D deficiency is a relevant challenge in our country.

Vitamin D supplementation should be universal in the first year of life, and there is epidemiological and scientific support for extending this recommendation to the end of the second year. It is mandatory to check this accomplishment during all clinical interviews. In the child health consultation, particular attention should be given to the early identification of children/adolescents at risk, in order to diagnose early and prevent vitamin D deficiency/insufficiency. Health education directed at pediatric age and their caregivers will be essential to prevent vitamin D deficiency/insufficiency and is an attempt to avoid pharmacological measures. Educational measures include recommendations about diet and sun exposure. There are risk groups in which prophylactic supplementation should be considered, in the autumn, winter and spring months. Plasmatic 25(OH)D determination and supplementation is recommended only in well-defined pathological situations.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. Vitamin D in the healthy European paediatric population. J Pediatr Gastroenterol Nutr. 2013; 56(6):692-701.
2. Togo A, Maciá DE, Segura SB, Díaz NS, Martínez CV. Is there vitamin D deficiency in children in a sunny Mediterranean city?. An Pediatr (Engl Ed) 2016; 84(3), 163-9.
3. Duarte C, Carvalheiro H, Rodrigues AM, Dias SS, Marques, A, Santiago T, et al. Prevalence of vitamin D deficiency and its predictors in the Portuguese population: a nationwide population-based study. Arch Osteoporos. 2020;15(1):1-11.
4. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18(2):153-65.
5. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? The Journal of Steroid Biochemistry and Molecular Biology. 2014, 114 (Part A): 138-145.
6. Ferreira S, Tomada I, Carreiro E, Poínhos R, Rêgo C. Défice de Vitamina D: Comorbilidade da Obesidade Pediátrica ou Consequência do Estilo de Vida?. Acta Pediatr Port 2016; 47(1): 38-45.
7. Cabral M, Araújo J, Teixeira J, Barros H, Martins S, Guimarães JT, et al. Vitamin D levels and cardiometabolic risk factors in Portuguese adolescents. Int J Cardiol. 2016; 220: 501-7.
8. Manios Y, Moschonis G, Lambrinou CP, Tsoutsoulopoulou K, Binou P, Karachaliou A, et al. A systematic review of vitamin D status in southern European countries. Eur J Nutr. 2018;57(6): 2001-36.
9. El Hajj Fuleihan G, Bouillon R, Clarke B, Chakhtoura M, Cooper C, McClung M, et al. Serum 25 hydroxyvitamin D levels: variability, knowledge gaps, and the concept of a desirable range. J Bone Miner Res. 2015;30(7):1119-33.
10. Prevenção e tratamento da deficiência de vitamina D, Norma da Direcção Geral da Saúde nº 004/2019 (14.08.2019).
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
12. Chen TC, Chimeh F, Lu Z, Mathieu J, Person K, Zhang A, et al. Factors that influence the cutaneous synthesis and dietary sources of vitamin D. Arch Biochem Biophys. 2007;460(2):213-17.
13. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr. 2005;135(2):317-22.
14. Kołodziejczyk-Nowotarska A, Bokiniec R, Seliga-Siwecka J. Monitored Supplementation of Vitamin D in Preterm Infants: A Randomized Controlled Trial. Nutrients. 2021;13:3442.
15. Kołodziejczyk A, Borszewska-Kornacka MK, Seliga-Siwecka J. Monitored supplementation of Vitamin D in preterm infants (MOSVID trial): study protocol for a randomised controlled trial. Trials. 2017;18(1):1-8.
16. Rego C, Nazareth M, Lopes C, Graça P, Pinto E. Suplementação vitamínica e mineral em Portugal durante o primeiro ano de vida. Resultados do EPACI Portugal 2012. Acta Pediatr Port. 2016;47(3):211-20.
17. Grupo Português de Dermatologia Pediátrica Sociedade Portuguesa de Dermatologia e Venereologia. Proteção Solar Infantil. [Internet]. 2019 [cited 2023 March 16]. Available from: https://www.spdv.pt/op/document/?co=641&h=fed59&in=1
18. Vidailhet M, Mallet E, Bocquet A, Bresson JL, Briend A, Chouraqui JP, et al. Turck D, Comité de nutrition de la Société française de pédiatrie. Vitamin D: Still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics. Archives de Pédiatrie. 2012;19(3):316-28.
19. Simon AE, Ahrens KA. Adherence to Vitamin D Intake Guidelines in the United States. Pediatrics. 2020;145(6):e20193574.
20. Soares E, Pereira-da-Silva L, Cardoso M, Castro MJ. Vitaminas, Minerais e Oligoelementos por Via Entérica no Recém-Nascido. Revisão do Consenso Nacional. Acta Pediatr Port. 2015;46(2):159-69.
21. Vranić L, Mikolašević I, Milić S. Vitamin D deficiency: consequence or cause of obesity? Medicina. 2019;55(9):541.
22. Aliberch RM, Gómez SO, Mendoza MB, Garcia-Algar O. Vitamina D: fisiopatología y aplicabilidad clínica en pediatría. An Pediatr (Barc). 2012;77(4):279.
23. Brennan D. What Foods Are Highest in Vitamin D?. Medecinenet [Internet]. 2021 Mar [cited 2023 March 17]. Available from: https://www.medicinenet.com/what_foods_are_highest_in_vitamin_d/article.htm
24. Malloy PJ, Feldman D. Genetic disorders and defects in vitamin D action. Rheumatic Disease Clinics. Endocrinol Metab Clin North Am. 2012;38(1):93-106.
25. Li XX, Liu Y, Luo J, Huang ZD, Zhang C, Fu Y. Vitamin D deficiency associated with Crohn's disease and ulcerative colitis: a meta-analysis of 55 observational studies. J Transl Med. 2019;17(1):1-19.
26. Glass AR, Eil C. Ketoconazole-induced reduction in serum 1, 25-dihydroxyvitamin D. J Clin Endocrinol Metab. 1986;63(3):766-9.
27. Sociedade Portuguesa de Dermatologia e Venereologia. Proteção Solar Infantil. [Internet]. 2023 [cited 2023 March 16]. Available from: https://www.spdv.pt/_cuidados_com_a_pele
28. EFSA Panel on Dietetic Products, Nutrition and Allergies (EFSA NDA Panel), Turck D, Bresson JL, Burlingame B, Dean T, Fairweather Tait S., et al. Update of the tolerable upper intake level for vitamin D for infants. EFSA Journal. 2018;16(8):5365.
29. EFSA Panel on Dietetic Products, Nutrition and Allergies (EFSA NDA Panel). Scientific opinion on the tolerable upper intake level of vitamin D. EFSA Journal. 2012;10(7):2813.
30. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Pediatrics. 2008;122(2):398-417.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

CASE REPORT

A rare presentation of Sturge-Weber syndrome: when a port-wine stain is not the key – case report

Miguel Labrusco[1a], Inês Martins[1b], Sara I. de Almeida[1c], Sofia Quintas[2d], and Paulo Oom[1e]*

[1]Paediatric Department; [2]Neurodevelopment Service, Paediatric Department. Hospital Beatriz Ângelo, Loures, Portugal

ORCID: [a]0000-0003-4979-0632; [b]0000-0003-4249-5542; [c]0000-0002-9332-122X; [d]0000-0001-8115-1852; [e]0000-0002-5329-8782

Abstract

Sturge-Weber syndrome (SWS) is a sporadic congenital vascular disorder which typically presents with a facial port-wine stain and capillary malformations affecting the brain and eye. We present the case of a 15-month-old boy admitted to the paediatric emergency department with right arm palsy and focal clonic seizure on the right side of the body, without a facial nevus. Brain MRI revealed leptomeningeal angiomatosis suggestive of SWS. Despite the absence of the characteristic facial port-wine stain, diagnosis of SWS remains clinical and must be suspected whenever there are focal seizures associated with focal neurological deficits. In this case report we describe the clinical presentation, imaging findings and management of this rare presentation of SWS. We are reporting this case as few patients have been described in the literature.

Keywords: Case report. Facial nevus. Focal seizures. Leptomeningeal angiomatosis. Sturge-Weber syndrome.

Uma apresentação rara do síndrome de Sturge-Weber: quando a mancha de vinho do porto não é a chave – relato de caso

Resumo

A Síndrome de Sturge-Weber (SWS) é um distúrbio vascular congénito esporádico, que se apresenta tipicamente por mancha facial de vinho do porto e malformações capilares com envolvimento cerebral e ocular. Apresentamos o caso de uma criança de 15 meses, do sexo masculino, admitida no Serviço de Urgência Pediátrica com paresia do membro superior direito e convulsão clónica focal no hemicorpo direito, sem mancha facial. A RMN cranioencefálica revelou angiomatose leptomeníngea sugestiva de SWS. Apesar da ausência da mancha de vinho do porto facial característica, o diagnóstico de SWS permanece clínico e deve ser suspeitado sempre que hajam convulsões focais associadas a défices neurológicos focais. Neste case report, descrevemos a apresentação clínica, imagiológica e abordagem desta rara forma de apresentação de SWS. Relatamos o caso atendendo ao escasso número de doentes descritos na literatura.

Palavras-chave: Angiomatose leptomeníngea. Case report. Convulsões focais. Mancha facial. Síndrome Sturge-Weber.

***Correspondence:**
Miguel Labrusco
E-mail: mptl@campus.ul.pt

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):48-52
DOI: 10.24875/PJP.M23000122

Keypoints

What is known

- SWS is a sporadic congenital vascular disorder which typically presents with a facial port-wine stain and capillary malformations affecting the brain and eye.
- SWS can be divided in 3 different types, depending on the affected region.
- Neurologic manifestations include seizures, focal neurological deficits, behavioural anomalies and progressive intellectual impairment of variable degree.

What is added

- Focal seizures and stroke-like events in infancy must raise suspicion of SWS, even in the absence of a facial port-wine stain.
- SWS without facial port-wine stain is rare and in these cases the diagnosis can be made upon typical brain imaging findings.
- Characteristic MRI findings include leptomeningeal enhancement, compatible with leptomeningeal angiomatosis.

Introduction

Sturge-Weber syndrome (SWS) is a sporadic, congenital, neurocutaneous disorder, typically presenting in infancy with a facial port-wine birthmark, ipsilateral leptomeningeal capillary malformations and vascular eye abnormalities[1]. The essential pathologic components are the trigeminal and leptomeningeal angiomatosis. Clinically, SWS can be divided in 3 different types: type 1, with the classic manifestation of facial port-wine stains and intracranial leptomeningeal angioma, type 2, with facial angioma without evidence of intracranial disease and type 3, with isolated leptomeningeal angioma[2]. Few reports describe this last variant, in which no facial nevus is observed[2-9]. In such cases, the presenting symptoms are typically seizures in up to 80% of patients, most commonly focal seizures[4,8]. The diagnosis depends on imaging findings such as leptomeningeal angiomatosis in brain magnetic resonance imaging (MRI) and intracranial calcifications in computed tomography (CT)[4].

In this case report, we present a rare case of a patient with leptomeningeal angiomatosis without an associated facial port-wine birthmark.

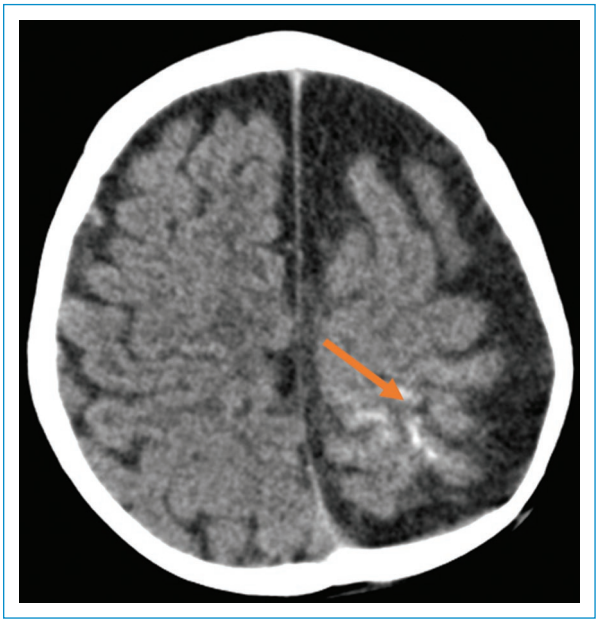

Figure 1. CT image with left cerebral atrophy with associated subcortical calcifications (arrow).

Case presentation

A previously healthy 15-month-old boy, with unremarkable family history, was admitted to the paediatric emergency department (PED) due to sudden onset right brachial palsy after waking up from a nap. Upon arrival at the PED, he presented clonic movements of the right hemibody with impaired awareness, without fever. The seizure was terminated after intravenous diazepam. In the post-ictal period, he maintained right hemiparesis and deep tendon hyperreflexia. There was no history of current or recent infection, trauma, medication or drug intoxication or other symptoms preceding this presentation. Physical exam revealed a borderline normal psychomotor development and preferential use of his left hand. Laboratory blood evaluation – hemogram, C-reactive protein and procalcitonin, had no alterations. Lumbar puncture was performed, and the cerebrospinal fluid (CSF) had no alterations.

Initial brain CT scan revealed left brain atrophy, most prominent on the fronto-parietal and temporal level, with associated subcortical calcifications on the fronto-temporal-occipital regions (Fig. 1).

He was admitted in the paediatric ward and started antiseizure medication (ASM) with levetiracetam as well as antibiotic and antiviral therapy with ceftriaxone and acyclovir while waiting for results from CSF cultures and virologic exam. One day after admission he started fever (tympanic temperature of 39.7°C every six hours), which progressively improved with sustained apyrexia

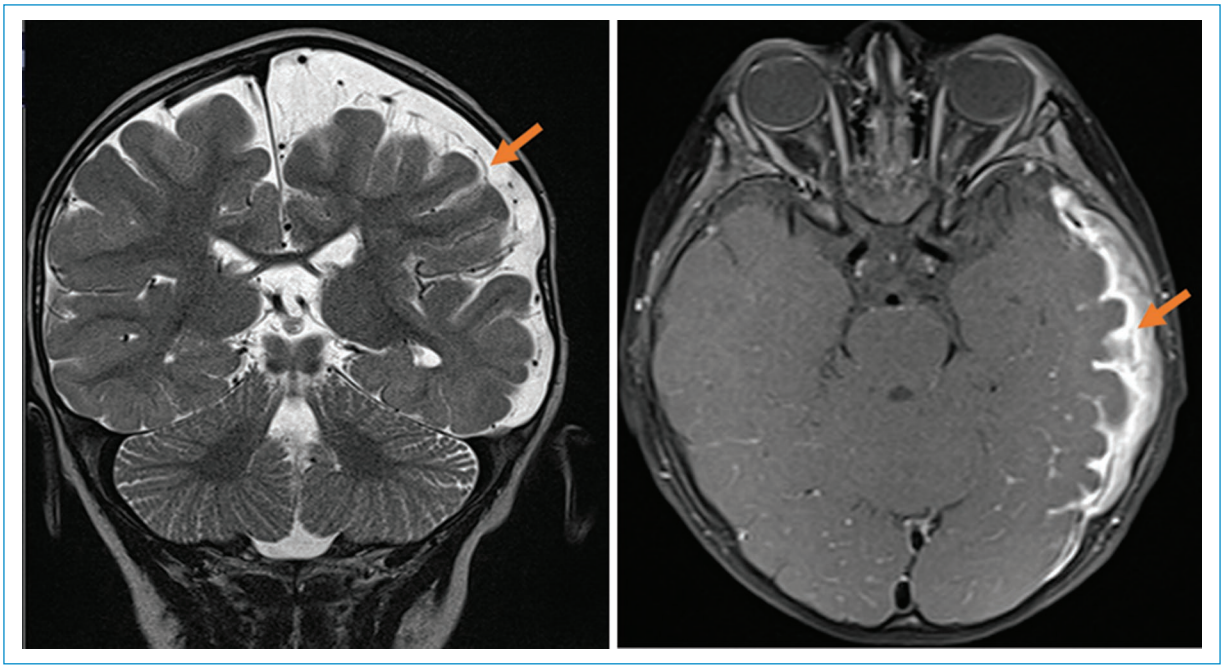

Figure 2. Coronal (left) and transverse (right) plane of MRI images with left cerebral atrophy, involving the frontoparietal and temporal regions. Marked leptomeningeal enhancement compatible with leptomeningeal angiomatosis (see arrow).

since day four of admission. Recent infection with Epstein-Barr virus and cytomegalovirus were ruled out. CSF and blood cultures were negative and so the antibiotic and antiviral were discontinued.

On the fourth day after admission, he had another focal clonic seizure, localized to the right hemibody, which stopped spontaneously after two minutes, followed by no clear post-ictal status or focal deficits. Subsequently, carbamazepine was added to levetiracetam showing a good response without significant side effects.

Electroencephalographic study disclosed an asymmetry of the basal activity (slower and minor amplitude on the left hemisphere, except for the occipital region), and no clear epileptiform activity. Brain MRI (Fig. 2) revealed left cerebral atrophy, involving the frontoparietal and temporal regions. Marked leptomeningeal enhancement compatible with leptomeningeal angiomatosis was suggestive of Sturge-Weber type III syndrome. These findings prompted the introduction of acetyl-salicylic acid (ASA). Ophthalmologic observation was normal.

At clinical discharge, he was apyretic and with no seizures for over 24 hours. He maintained ASM with carbamazepine and ASA. The child is undertaking occupational therapy with improved neurodevelopment.

Discussion

The diagnosis of Sturge-Weber syndrome should be elicited whenever the association of facial nevus and seizures are present[6]. However, rare variants of leptomeningeal angioma without the cutaneous lesion have been described[2-9].

In this case report, we presented a case of a previously healthy, 15-month-old male, with normal psychomotor development, admitted in the PED with sudden right brachial palsy, followed by homolateral focal motor seizures. Upon examination, there was no visible facial nevus. A CT scan reported left cerebral hemiatrophy associated with subcortical fronto-temporo-occipital calcifications, compatible with Sturge-Weber syndrome (Fig. 1). MRI study also revealed fronto-parietal leptomeningeal enhancement, compatible with leptomeningeal angiomatosis (Fig. 2).

Leptomeningeal angiomatosis can be confirmed histologically or by typical radiographic findings associated with suggestive clinical presentation[2]. Even though trigeminal and leptomeningeal angiomatosis are classic pathologic components of SWS, in our patient there was no evidence of trigeminal angiomatosis. The reason behind the absence of this facial nevus in such cases remains unclear.

Encephalofacial angiomatosis has been classified in three types, the present case is in accordance with type 3, in which an isolated leptomeningeal-brain angioma without facial nevus is present[10]. Leptomeningeal angioma is most commonly found in the occipital region. Case reports where this region is spared are rare[7].

SWS is caused by mosaic mutations in the GNAQ gene on fetal ectodermal tissues. Mutations occurring on earlier stages in embryogenesis may affect a greater variety of precursor cells, resulting in SWS[11]. The developmental process that leads to the meningeal angioma is postulated to result from an incomplete degeneration and subsequent maturation of the primitive cephalic venous plexus in the first trimester of development[2,7,12].

The slower blood flow caused by the angiomatosis can lead to stasis and consequent hypoxia, with subsequent cortical atrophy and changes in the vessel wall and ground substance that result in calcification, with characteristic hyperdensity found in neuroimaging, particularly in CT[2,4,12]. This finding should elicit other causes of cerebral calcification such as celiac disease, encephalitis, purulent meningitis, ossifying meningoencephalopathy or leukemia[4]. Leptomeningeal angiomas are readily identifiable with gadolinium-enhanced MRI, which is particularly useful for an early diagnosis, prior to the characteristic calcifications[7,13].

Non-specific findings can also be documented on electroencephalography, such as an asymmetric basal activity, with decreased voltage or slowing on the affected side[4], as was the case of our patient. When such electroencephalographic findings are associated with a typical facial nevus, this diagnosis should be suspected[2].

Neurologic manifestations include seizures, which are characteristically focal motor or generalized tonic-clonic, particularly in younger children, focal neurological deficits, including hypoxic-ischemic events and hemianopsia, behavioural anomalies and progressive intellectual impairment of variable degree[2-4].

The diagnosis of this condition is clinical. Genetic testing is available, however, the somatic, mosaic variants responsible for this pathology arise post-zygotically and only affected tissues will contain them, which limits the diagnostic efficiency[14,15].

There is no specific treatment for SWS[16], and management of neurologic manifestations is often difficult. Carbamazepine, oxcarbamazepine and levetiracetam are acceptable first-line options[17] for focal seizures.

Refractory epilepsy, particularly when associated with clinically significant hemiparesis, visual field loss and developmental delay, may benefit from surgical intervention such as hemispherectomy[18].

Low-dose aspirin beginning in infancy may also be beneficial, as antithrombotic therapy may prevent the progression of hypoxic-ischemic neuronal injury[19]. Some authors suggest the potential benefit of pre-symptomatic ASM treatment combined with aspirin, particularly in children with high risk for seizures[20], but these data still need validation.

The prognosis and clinical course are highly variable and it is unclear if the age of onset has influence, and some children experience intractable seizures, mental retardation, and recurrent stroke-like episodes[13].

This case highlights the variable clinical presentation of SWS, and the importance of its suspicion when presented with focal seizures and neurological deficits such as hemiparesis, even in the absence of facial nevus.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. De la Torre AJ, Luat AF, Juhász C, Ho ML, Argersinger DP, Cavuoto KM, et al. A Multidisciplinary Consensus for Clinical Care and Research Needs for Sturge-Weber Syndrome. Pediatr Neurol. 2018: 84;11-20.
2. Aydin A, Cakmakçi H, Kovanlikaya A, Dirik E. Sturge-Weber syndrome without facial nevus. Pediatr Neurol. 2000; 22(5):400-402.
3. Ambrosetto P, Ambrosetto G, Michelucci R, Bacci A. Sturge-Weber syndrome without port-wine facial nevus. Report of 2 cases studied by CT. Childs Brain. 1983; 10(6):387-92.
4. Dilber C, Tasdemir HA, Dagdemir A, Incesu L, Odaci E. Sturge-Weber syndrome involved frontoparietal region without facial nevus. Pediatr Neurol. 2002;26(5):387-90.
5. Comi AM, Fischer R, Kossoff EH. Encephalofacial angiomatosis sparing the occipital lobe and without facial nevus: on the spectrum of Sturge-Weber syndrome variants? J Child Neurol. 2003;18(1):35-38.
6. Gururaj AK, Sztriha L, Johansen J, Nork M. Sturge-Weber syndrome without facial nevus: a case report and review of the literature. Acta Paediatr. 2000;89(6):740-43.

7. Wong SW, Kyaw L, Ong LC, Zulfiqar AM. Sturge-Weber syndrome without facial nevus: an unusual cause of neonatal seizures. J Paediatr Child Health. 2011;47(4):237-9.
8. Pascual-Castroviejo I, Pascual-Pascual SI, Viaño J, Martinez V, Coya J. Sturge-Weber syndrome without facial nevus. Neuropediatrics. 1995;26(4):220-2.
9. Martínez-Bermejo A, Tendero A, López-Martín V, Arcas J, Royo A, Polanco I, et al. [Occipital leptomeningeal angiomatosis without facial angioma. Could it be considered a variant of Sturge-Weber syndrome?]. Rev Neurol. 2000;30(9):837-41.
10. Roach ES. Neurocutaneous syndromes. Pediatr Clin North Am. 1992; 39(4):591-620.
11. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368(21):1971-9.
12. Ganesh, A., Al-Mujaini A. Sturge-Weber Syndrome without Facial Nevus. Sultan Qaboos Univ Med J. 2014;14(2):e155-6.
13. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a review. Pediatr Neurol. 2004;30(5):303-10. DOI: 10.1016/j.pediatrneurol.2003.12.015
14. Gürsoy S, Erçal D. Genetic Evaluation of Common Neurocutaneous Syndromes. Pediatr Neurol. 2018;89:3-10.
15. Lalonde E, Ebrahimzadeh J, Rafferty K, Richards-Yutz J, Grant R, Toorens E, et al. Molecular diagnosis of somatic overgrowth conditions: A single-center experience. Mol Genet Genomic Med. 2019;7(3):e536.
16. Singh AK, Keenaghan M. Sturge-Weber Syndrome. [Updated 2021 May 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459163/
17. Kaplan EH, Kossoff EH, Bachur CD, Gholston M, Hahn J, Widlus M, et al. Anticonvulsant Efficacy in Sturge-Weber Syndrome. Pediatr Neurol. 2016;58:31-6.
18. Bianchi F, Auricchio AM, Battaglia DI, Chieffo DRP, Massimi L. Sturge-Weber syndrome: an update on the relevant issues for neurosurgeons. Childs Nerv Syst. 2020;36:2553-70.
19. Bay MJ, Kossoff EH, Lehmann CU, Zabel TA, Comi AM. Survey of aspirin use in Sturge-Weber syndrome. J Child Neurol. 2011;26(6):692-702.
20. Day AM, Hammill AM, Juhász C, Pinto AL, Roach ES, McCulloch CE, et al. Hypothesis: Presymptomatic treatment of Sturge-Weber Syndrome With Aspirin and Antiepileptic Drugs May Delay Seizure Onset. Pediatr Neurol. 2019;90:8-12.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

CASE REPORT

Maxillary dentigerous odontogenic cyst: the sinusitis simulator – case report

Joana Faustino[1a], Catarina Brito[2], Fernando Canavarros[3], António Trigueiros[3], and Paulo Oom[4b]*

[1]Pediatric Department, Hospital Dona Estefânia, Lisbon; [2]Neuroradiology Department, Hospital Beatriz Ângelo, Loures; [3]Otolaryngology, Head and Neck Department, Hospital Beatriz Ângelo, Loures; [4]Pediatric Department, Hospital Beatriz Ângelo, Loures. Portugal

ORCID: [a]0000-0003-4015-5624; [b]0000-0002-5329-8782

Abstract

Cell degeneration of the enamel's starry reticulum gives rise to the primary cyst before the mineralized tissue is formed. This cyst appears in place of a normal, un-erupted or supra-numerous teeth and is frequently observed among young people in middle age. A 17-year-old boy, born and resident in Portugal, 2 months before hospitalization starts complaints of nasal obstruction on the right, and later the left, with progressive worsening and pain located in the dental arch and gums and appearance of swelling gingival pain with chewing in the last two weeks. On clinical examination there was a painful swelling of the right cheek, without any other inflammatory signs. Attached to the upper right maxillary dental arch there was a soft, vascularized and painful mass of 3 cm in diameter. Blood tests found hemoglobin 15.3 g/dL (reference: 10.3-13.5 g/dL), leukocytes 9110/uL (reference: 6-16/uL) and c-reactive protein 0.05mg/dL (reference: < 0.5 mg/dL). Computed tomography and magnetic resonance imaging described a 49x45x44 mm right maxillary odontogenic cyst, with an erosion and thinning of the external, posterior, and anterior wall of the maxillary sinus and left deviation of the nasal septum. The diagnosis of odontogenic cyst was made and the cyst was making an orbital compression and involving almost all maxillary sinuses. He was submitted to a videoendoscopic technique associated a Caldwell-Luc technique. This combined technique promotes a better view and control all borders of the lesion. The surgery completely removed the lesion and the supernumerary tooth. The follow up was done without complications. It is important, to bear in mind that in the presence of complaints associated with the sinuses and oral cavity, the need to exclude non-surgical pathology requires the performance of a detailed objective examination.

Keywords: Dentigerous cyst. Mouth. Sinusitis.

Quisto dentígero odontogénico: o grande simulador – relato de caso

Resumo

A degeneração celular do esmalte dá origem ao quisto primário antes da formação do tecido mineralizado. Este quisto aparece no lugar de um dente normal, não irrompido ou supranumerário e é frequentemente observado na segunda década de vida. Os quistos dentígeros podem ser diferenciados dos queratocitos, amelobrastos, friboontomas, fibromas, calcificação epitelial, tumores odontogénicos e adenomatoides e ameloblastomas. Apresentamos um adolescente de 17 anos, natural e residente em Portugal, previamente saudável. Queixas de obstrução nasal com agravamento progressivo e dor localizada à arcada dentária e gengiva direita com 2 meses de evolução. Ao exame objetivo apresentava tumefação dolorosa na hemiface direita, sem outros sinais inflamatórios.

***Correspondence:**
Joana Faustino
E-mail: joanamotafaustino@gmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):53-57
DOI: 10.24875/PJP.M23000123

Anexa à arcada dentária direita, objetivava-se uma massa mole, vascularizada e dolorosa com cerca de 3 cm de diâmetro. Laboratorialmente apresentava hemoglobina de 15,3 g/dL (referência: 10,3-13,5 g/dL), leucócitos de 9110/uL (referência: 6-16/ul) e proteína C-reativa 0,05 mg/dL (referência: < 0,5 mg/dL). A tomografia computorizada e a ressonância magnética descreveram um quisto odontogénico do maxilar superior direito de 49x45x44mm, com erosão e afinamento da parede externa, posterior e anterior do seio maxilar e desvio esquerdo do septo nasal, com extensão intrassinusal, com compressão da órbita e envolvimento de quase a totalidade do seio maxilar. Procedeu-se à videoendoscopia associada à técnica de Caldwell-luz para a remoção do quisto, para otimização da análise da extensão da lesão. Na presença de queixas associadas aos seios da face e cavidade, importa excluir patologia cirúrgica através de um exame objetivo detalhado e minucioso, uma vez que poderá ter implicações prognósticas e terapêuticas.

Palavras-chave: Patologia da cavidade oral. Quisto odontogénico. Sinusite.

Keypoints

What is known
- Odontogenic cyst is not a rare disease, but at pediatric age is not so common.
- The patients present with slow-growing asymptomatic mass in mandible.
- It is obligatory to make this diagnosis when we are presented with sinusitis complaints.
- The treatment and follow-up are not consensual.

What is new
- Videoendoscopic technique associated a Caldwell-Luc technique can help to have a minimal sinuous wall damage.
- A multidisciplinary team is crucial to make the correct diagnosis, treatment, and follow-up.

Introduction

The embryologic process of tooth development is secondary to the invagination of oral epithelium into the jaws. This process has the main challenge to give rise to a tooth, but the odontogenic epithelium has the potential to persist after failing to break down following tooth eruption[1] and, when stimulated, may be the origin of cysts or tumors of odontogenic origin[2].

Odontogenic cysts (OCs) are intraosseous pathological cavities lined by an odontogenic epithelium and filled with fluid or semifluid content[3-5]. They comprise of up to 90%[1] of jaw cysts and are classified, according to the World Health Organization (WHO), as inflammatory or developmental[6]. The inflammatory group consists mainly of radicular and inflammatory collateral cysts, and the developmental group are dentigerous cysts (DTGs) and odontogenic keratocysts (OKCs). Immunohistochemistry is needed to make a final diagnosis[7,8].

It most commonly affects the anterior mandible, but other regions of the jaw can also be affected[8]. The patients present with slow-growing asymptomatic mass in the mandible[7,8] that is usually an incidental radiographic finding, and most frequently in middle age[8]. However, when secondarily infected they can present with inflammatory signs due to compression of a neurovascular bundle[1,7-9].

Radiologically, the lesion may be unilocular or multilocular with borders that, although generally well defined, may occasionally show loss of cortical integrity[10].

Histologically, they have a non-keratinized epithelium with a superficial layer of cuboidal or columnar cells[11].

The maxillary odontogenic cyst is a rare entity, namely in the pediatric population, that can simulate a respiratory tract infection, such as sinusitis. it can have an aggressive clinical course, behavior and recurrence rate. It is often mis-diagnosed.

The optimal treatment remains unclear. Extensive cysts involving the orbital or the inferior orbital nerve call for a conservative strategy[12]. It consists of either decompression or marsupialization as a single modality or followed by cyst enucleation[3]. Even though cysts are usually treated by enucleation, they may grow extensively to involve the maxillary sinus cavity[13]. The surgery treatment can be accomplished with or without curettage and peripheral ostectomy[14]. It is important to notice that segmental resection, which provides free margin excision, may result in high mobility and cosmetic damages[15]. Segmental resection has the lowest recurrence rate because of the elimination of adjacent daughter cysts and surrounding mucosa. However, it has a high morbidity, including the loss of dentition, oroantral communication, chronic sinusitis and a need for extensive re-construction[13]. Namely, intervention of cysts found in the maxillary sinus may lead to oroantral fistula formation and chronic rhinosinusitis[16]. There are advantages when performing transnasal endoscopic sinus surgery such as avoidance of extensive tooth extraction and oroantral communication, better control of orbital floor and infraorbital

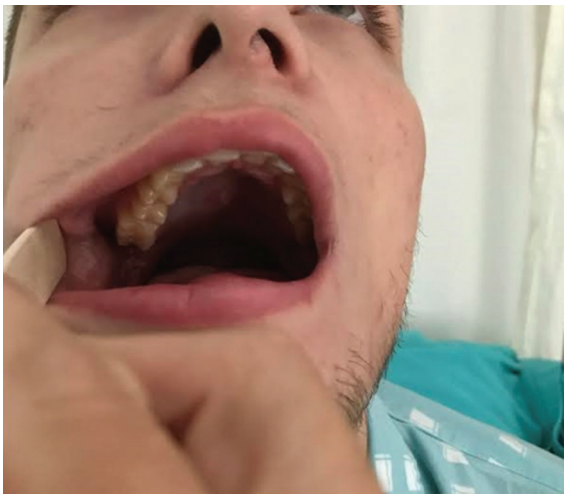

Figure 1. Gingival swelling on first superior right molar.

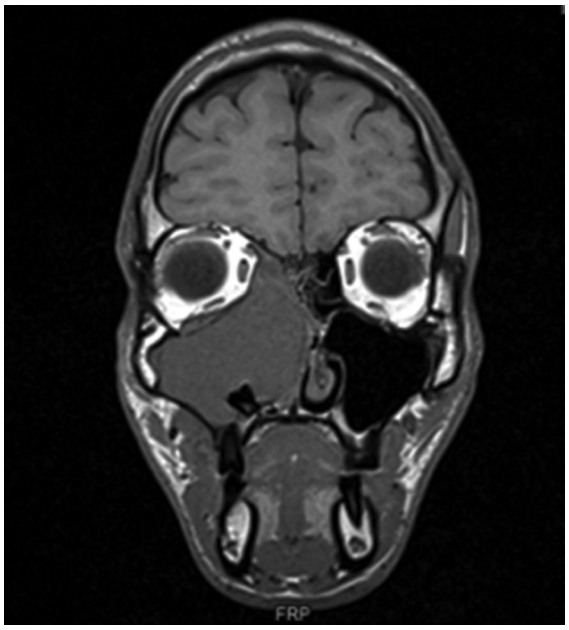

Figure 2. Right maxillary odontogenic cyst with erosion and thinning of the external, posterior and anterior wall of the maxillary sinus and left deviation of the nasal septum.

nerves, avoidance of transoral incisions and less post operative cheek swelling[13].

The aim of this article is to show the importance of keeping in mind the differential diagnosis of upper respiratory tract infection, especially in pediatric age. This article reports a 17-year-old male with an odontogenic cyst who was admitted to the emergency department with swelling and pain in the upper right gingival area for two months.

Case report

A 17-year-old male, presented at the emergency department with a progressive bilateral nasal obstruction, local pain and change of skin color on arch and gums along with gingival swelling for 2 months (Fig. 1). On clinical examination, there was a painful swelling of the right cheek without any other inflammatory signs. Attached to the upper right maxillary dental arch there was a soft, vascularized, and painful mass of 3 cm in diameter. Blood tests found hemoglobin 15.3 g/dL (reference: 10.3-13.5 g/dL), leukocytes 9110/uL (reference: 6-16/uL) and c-reactive protein 0.05mg/dL (reference: < 0.5 mg/dL). Computed tomography and magnetic resonance imaging described a 49x45x44 mm right maxillary odontogenic cyst with an erosion and thinning of the external, posterior, and anterior wall of the maxillary sinus and left deviation of the nasal septum (Fig. 2). The diagnosis of odontogenic cyst was made. The patient was proposed to a video-endoscopic technique associated to a Caldwell-Luc technique with intrasinusal extension.

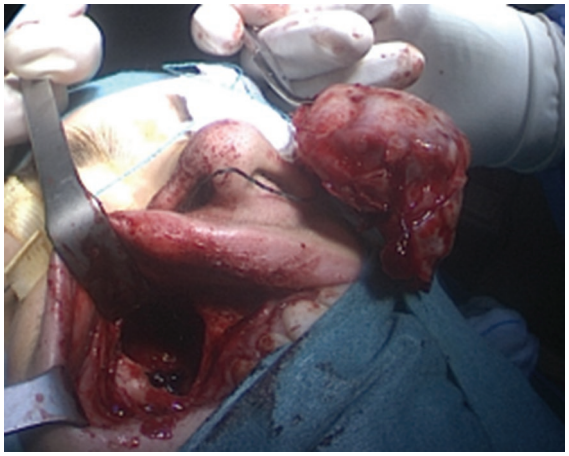

Figure 3. Excised odontogenic cyst - Caldwell-Luc approach.

The cyst was causing orbital compression and involved almost completely the maxillary sinus. This combined technique promotes a better view and control all borders of the lesion. The lesion and the supernumerary tooth were completely removed during surgery. This endoscopic approach provides a better control of the sinus (Fig. 3). Pathological examination was

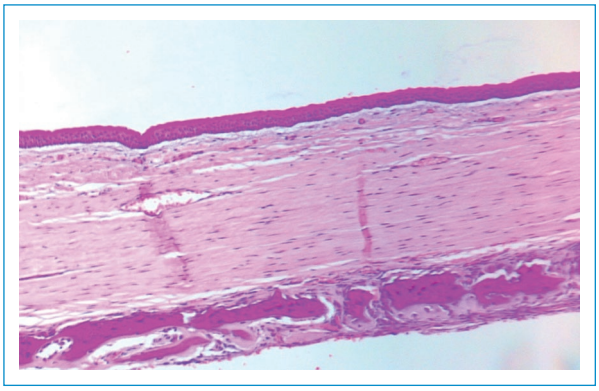

Figure 4. Non-keratinized pavement epithelium cyst with fibrous wall and without bone erosion.

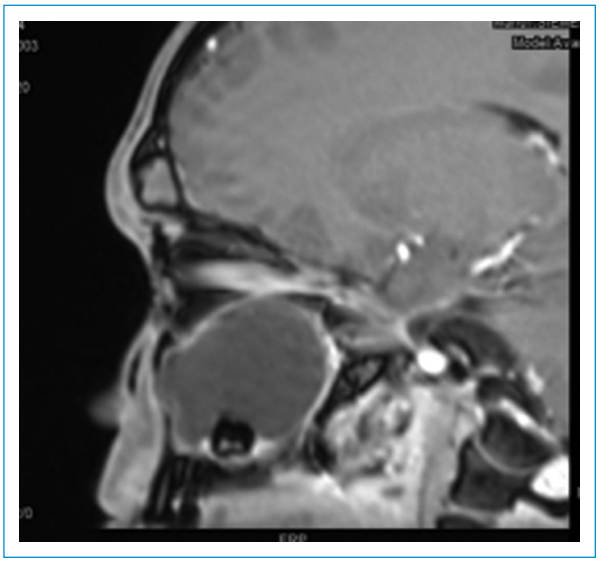

Figure 5. Odontogenic cyst around the crown of the teeth.

compatible with a dentigerous odontogenic cyst surrounded by non-keratinized epithelium (Fig. 4). The follow-up was done without complications.

Discussion

Pediatric odontogenic cysts occur more frequency in middle age, and are rare in pediatric age. Dentigerous cyst accounts for 24% of cases[1,5] (Fig. 5). They are usually asymptomatic[5-8,10-13], unless if secondarily infected, like in the present case, with nasal obstruction and pain, which made a good exam important to make the differential diagnosis of upper respiratory tract infection.

Odontogenic cysts can mimic several tumors or vascular disease and can lead to consequences such as pathologic fractures[5]. The diagnosis is based on its distinct clinical and radiographic characteristics; TC is helpful to characterize correctly.

The treatment is not linear, because extraction of mandibular molar can have a significant statical and tooth impact. The choice of treatment should take into account various factors, including the patient's age, size and location of the cyst, soft tissue involvement, history of treatment and the histological variant of the lesion. The goal is to choose the treatment modality that will completely eradicate the lesion with the lowest possible risk of recurrence and the least morbidity. In the present case, considering the age and associated symptoms, the videoendoscopic technique associated to a Caldwell-Luc technique with intrasinusal extension was the option.

Some recommendations describe that these patients should be kept under follow-up for a minimum of 3 years[17], but no guidelines were previously made and more knowledge is necessary.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Shanti RM, Alawi F, Lee SM, Henderson AJ, Sangal NR, Adappa ND. Multidisciplinary approaches to odontogenic lesions. Curr Opin Otolaryngol Head Neck Surg. 2020 Feb;28(1):36-45.
2. Hormozi E, Fard VN, Naseri MA, Jahromi NH, Keshani F. Comparison of immunohistochemical expression of CD10 in keratocystic odontogenic tumor and ameloblastoma. Dent Res J (Isfahan). 2016 Mar-Apr;13(2):110-6.

3. Daley TD, Wysocki GP, Pringle GA. Relative incidence of odontogenic tumors and oral and jaw cysts in a Canadian population. Oral Surg Oral Med Oral Pathol. 1994 Mar;77(3):276-80.
4. Shear M, Speight P. Cysts of the Oral and Maxillofacial Regions. 4th ed. Hoboken: John Wiley & Sons; 2018.
5. Rajendra Santosh AB. Odontogenic Cysts. Dent Clin North Am. 2020 Jan;64(1):105-119.
6. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, editors. WHO Classification of Head and Neck Tumours. 4th ed. Volume 9. Lyon: IARC Press; 2017.
7. Shah AA, Sangle A, Bussari S, Koshy AV. Glandular odontogenic cyst: A diagnostic dilemma. Indian J Dent. 2016 Jan-Mar;7(1):38-43.
8. Krishnamurthy A, Sherlin HJ, Ramalingam K, Natesan A, Premkumar P, Ramani P, Chandrasekar T. Glandular odontogenic cyst: report of two cases and review of literature. Head Neck Pathol. 2009 Jun;3(2):153-8.
9. Rajendra Santosh AB, Ogle OE. Odontogenic Tumors. Dent Clin North Am. 2020 Jan;64(1):121-138.
10. Tambawala SS, Karjodkar FR, Yadav A, Sansare K, Sontakke S. Glandular odontogenic cyst: A case report. Imaging Sci Dent. 2014 Mar;44(1):75-9.
11. Shear M, Speight PM. Cysts of the Oral and Maxillofacial Regions. John Wiley & Sons; 2008.
12. Deboni MC, Brozoski MA, Traina AA, Acay RR, Naclério-Homem Mda G. Surgical management of dentigerous cyst and keratocystic odontogenic tumor in children: a conservative approach and 7-year follow-up. J Appl Oral Sci. 2012 Mar-Apr;20(2):282-5.
13. Safadi A, Kleinman S, Gigi D, Wengier A, Oz I, Abergel A, et al. Surgical management of odontogenic cysts involving the maxillary sinus- a retrospective study. J Craniomaxillofac Surg. 2020 Aug;48(8):800-807.
14. Poudel P, Srii R, Chaurasia N, Upadhyaya C. Glandular odontogenic cyst-Report of a rare case. Clin Case Rep. 2020 Jan 7;8(2):351-354.
15. Chandra S, Reddy ES, Sah K, Srivastava A. Maxillary Glandular Odontogenic Cyst: An Uncommon Entity at an Unusual Site. Arch Iran Med. 2016 Mar;19(3):221-4.
16. Cedin AC, de Paula FA Jr, Landim ER, da Silva FL, de Oliveira LF, Sotter AC. Tratamento endoscópico do cisto odontogênico com extensão intra-sinusal [Endoscopic treatment of odontogenic cyst with intra-sinusal extension]. Braz J Otorhinolaryngol. 2005 May-Jun;71(3):392-5.
17. Chandolia B, Bajpai M, Arora M. Glandular Odontogenic Cyst. J Coll Physicians Surg Pak. 2017 Mar;27(3):S23-S25.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

CASE REPORT

Methimazole as a rare cause of hepatitis in childhood: a case report

Íris Santos-Silva[1a], Vânia Benido-Silva[2b]*, Catarina Chaves[3c], Sandra Ferreira[4], Isabel Gonçalves[4d], and Alice Mirante[5e]*

[1]Pediatric Department, Unidade Local de Saúde da Guarda, Guarda; [2]Endocrinology Department, Centro Hospitalar Universitário de Santo António, Porto; [3]Endocrinology Department, Centro Hospitalar do Tâmega e Sousa, Porto; [4]Pediatric Hepatology and Liver Transplant Unit, Hospital Pediátrico do Centro Hospitalar Universitário de Coimbra, Coimbra; [5]Pediatric Endocrinology Department, Centro Hospitalar Universitário de Coimbra, Coimbra. Portugal

ORCID: [a]0000-0002-8138-8056; [b]0000-0002-8206-7414; [c]0000-0002-9655-1231; [d]0000-0001-9219-8787; [e]0000-0003-4138-8622

Abstract

Hyperthyroidism is an endocrine disorder whose treatment of choice is methimazole, due to the low risk of adverse reactions. Drug-induced liver injury by methimazole is rare, especially in pediatric age, but when it occurs it is potentially serious. We present a case report of drug-induced liver injury due to methimazole in a 12-year-old boy diagnosed with hyperthyroidism due to Graves' disease. The patient had signs and symptoms of thyrotoxicosis, but not clinical findings related to the liver condition. After the discontinuation of treatment and ablative therapy with Iodine^{131}, there was an excellent clinical and analytical evolution, with recovery of cytocholestasis to almost normal values. Thus, early recognition of this serious adverse effect through frequent monitoring of liver enzymes along with thyroid function is essential to avoid unfavorable outcomes.

Keywords: Case report. Children. DILI. Methimazole. Thyroid.

Metimazol como causa rara de hepatite na infância: um caso clínico

Resumo

O hipertiroidismo é um distúrbio endócrino cujo tratamento de escolha é o metimazol, pelo baixo risco de reações adversas. A hepatite tóxica secundária a este fármaco é rara, sobretudo na idade pediátrica, mas quando ocorre é potencialmente grave. Apresentamos um caso clínico de hepatite tóxica aguda por metimazol num rapaz de 12 anos com diagnóstico de hipertiroidismo por doença de graves. Clinicamente, o doente apresentava sinais e sintomas compatíveis com tireotoxicose, mas nenhuma manifestação relacionada com a condição hepática. Após a suspensão do tratamento e realização de terapêutica ablativa com Iodo^{131}, verificou-se uma evolução clínica e analítica favoráveis, com a recuperação da citocolestase para valores praticamente normais. Assim, o precoce reconhecimento deste efeito adverso grave através da monitorização frequente das enzimas hepáticas em conjunto com a função tiroideia é imprescindível para evitar uma evolução desfavorável.

Palavras chave: Caso clínico. Criança. Hepatite. Metimazol. Tiróide.

Correspondence:
Íris Santos-Silva
E-mail: irissantossilva.92@gmail.com
Vânia Benido-Silva
E-mail: vania.benido@hotmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):58-63
DOI: 10.24875/PJP.M23000124

Keypoints

What is known

- DILI by methimazole is a rare but potentially serious condition in pediatric age, characterized mainly by a cholestatic pattern.
- If DILI occurs, MMI is immediately discontinued and a definitive therapy (RAI or surgery) is performed.

What is new

- This is a very rare case of MMI-induced liver injury with a hepatocellular histological pattern, developed in a young boy.
- Other underlying hepatobiliary pathologies should be firstly excluded and liver dysfunction due to hyperthyroidism itself may be considered.

Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism in children (99%), however it is rare, acounting for approximately 1 to 5% of cases diagnosed in all ages. This condition can occur at any pediatric age, but the peak in prevalence tends to be during adolescence. It is more commonly associated with autoimmune diseases and in children with a family history of autoimmune thyroid disease (1st degree inherited forms account for 15 to 20% of cases)[1]. Treatments for GD include anti-thyroid drug (ATD), ablative radioactive iodine (RAI) therapy and surgery. Methimazole (MMI) is the first-line treatment in pediatric age due to the lower risk of adverse effects/toxicity, such as severe drug-induced liver injury (DILI), compared with propylthiouracil (PTU)[2,3].

Drug-induced hepatotoxicity or DILI consists in an acute or chronic injury caused by natural or manufactured drugs[4,5]. The true incidence is difficult to estimate, but a recent prospective study showed an incidence of 19.1/100,000[6]. DILI was divided into three types: hepatocellular, cholestatic and mixed type, according to the pattern of liver injury. This classification can provide a useful framework to find a differential diagnosis[5]. It covers a spectrum from asymptomatic elevation in liver enzymes or mild symptoms to acute liver failure, and mostly occurs between 5 to 90 days after the medication start[4,5,7]. Since there are no specific biomarkers, to make the diagnosis of DILI it is necessary to have a clinical suspicion and exclude other causes (infection, autoimmune, biliary obstruction, alcohol, ischemia, Wilson disease)[5,7]. Treatment begins with discontinuation of the injury drug, and the prognosis for recovery is usually favorable[4].

DILI by MMI is a rare condition[7,8]. A retrospective study, with 18,558 patients, showed a 1.4% prevalence of DILI by MMI and a median time to the development of DILI of 25 days[3]. According to the same authors, age was a risk factor for the development of this complication, being the rate of severe DILI by MMI in patients less than 20 years old of 0.84%, which was significantly increasing over the older age groups[3].

Case report

A 12-year-old boy, with no relevant medical past history, was admitted in an emergency room with complaints of tiredness, palpitations, diarrhea, hyperkinetic behavior and eyelid edema with 1 year of evolution and increase in the thyroid volume for 1 month. He has a family history of toxic thyroid adenoma (paternal aunt) and GD (paternal grandmother). Objectively, tachycardia (heart rate = 125 bpm) was confirmed. Blood tests showed thyroid stimulating hormone (TSH) < 0.01 uU/mL (Reference Range [RR]: 0.67-4.16), free thyroxine (fT4) 4.86 ng/dL (RR: 0.86-1.40), free triiodothyronine (fT3) > 20 pg/mL (RR: 3.30-4.80), thyroid-stimulating hormone receptor antibodies (TRABs) 37 U/L (RR: < 1); anti-thyroperoxidase antibody (Anti-TPO) > 1300 U/mL (RR: < 60), anti-thyroglobulin antibody (Anti-TG) 0.7 U/mL (RR: < 4.5); aspartate aminotransferase (AST) 55 U/L (RR: 8-60) and alanine aminotransferase (ALT) 98 U/L (RR: 7-46). A thyroid ultrasonography was performed and revealed a diffuse enlargement of the thyroid gland with heterogeneity suggestive of inflammation. The study was complemented with a ^{99}Tc thyroid scintigraphy which showed a gland with greatly increased projection and uptake surface, an aspect compatible with diffuse glandular hyperfunction. Taking into account these results, the diagnosis of hyperthyroidism due to GD was confirmed and treatment with methimazole (7.5mg, twice a day; 0,28 mg/kg/day) and propranolol (10mg, 3 times a day) was started.

One month later, he went to the first pediatric endocrinology appointment. His physical examination revealed exophthalmos, a palpable, homogeneous thyroid with evident goiter. He weighed 54.5 kg and his Tanner pubertal stage was external genitalia: 2, pubic hair: 2. Cardiac and pulmonary auscultation were normal. Analytical control after 1 month of starting medication showed mild cytolysis AST 35 U/L (RR: < 35) ALT 61 U/L (RR: 9-25) and gamma-glutamyl transferase (GGT) 79 U/L (RR: 3-32).

After 2.5 months of treatment for GD, the patient reports an improvement in tiredness and palpitations, but the analytic study reveals a marked rise of liver

enzymes (AST 1054 U/L [RR: < 35], ALT 971 U/L [RR: 9-25], GGT 222 U/L [RR:3-22]), despite of normal liver synthesis function. Thyroid and hepatic blood tests evolution is shown in table 1.

At this time, an urgent pediatric hepatology appointment was requested and the dose of methimazole was reduced (5mg, twice a day; 0.18 mg/kg/day). Two days later, methimazole was discontinued and etiologic study was performed. Systemic and liver autoimmunity study and hepatitis virus serology were negative; coagulation study, immunoglobulins, alpha 1 antitrypsin, ceruloplasmin and ferritin were normal. Total bile acids were elevated 179.4 μmol/L (RR: 0-6) and treatment with ursodeoxycholic acid was started. A liver biopsy was also performed which showed acute hepatitis, mostly lobular, rich in polymorphonuclear neutrophils, associated with acidophilic necrosis and absence of signs of acute or chronic cholestasis. A drug-induced liver injury by methimazole was the most probable diagnosis and in two weeks, liver enzymes (LFTs) dropped to almost normal levels (AST 38 U/L [RR: < 35]), (ALT 60 U/L [RR: 9-25]). Three weeks later he underwent definitive treatment of GD with ablative RAI^{131}I.

Two months after ablative RAI^{131}I (11.9 mCi), the physical examination was similar, there was an improvement in thyroid function (TSH 0.012 uU/mL [RR: 0.67-4.16] and fT4 0.51 ng/dL [RR: 0.86-1.40]) and LFTs remained slightly increased (AST 41 U/L [RR: < 35], ALT 61 U/L [RR: 9-25]). This minimal cytolysis pattern remained stable and always with values close to normal, throughout all the follow-up (Table 1). In January 2022, 6 months after RAI^{131}I, hyperthyroidism relapsed (TSH < 0.004 uUI/mL; T4L 1.65 ng/dL; T3L 10.0 pg/mL) and the patient was re-submitted to radioactive iodine treatment (9.9 mCi) in March 2022. Consequently, after 1 month, an iatrogenic hypothyroidism was established and replacement with levothyroxine 100ugr was initiated. In the last follow-up, in August 2022, he was clinically euthyroid, with stability of hepatic cytolysis and cholestasis parameters, but with analytical hypothyroidism (TSH 34 uUI/mL, T4L 0.70 ng/dL). The levothyroxine dose was titrated to 112ug and active surveillance was maintained.

Discussion

Antithyroid drugs (ATD), including MMI and PTU, have been frequently and safely used for more than six decades to treat hyperthyroidism due to GD[8]. Despite their undoubted clinical benefits, there are some common mild side effects associated with these drugs, including cutaneous reactions (skin rash and urticaria), transient mild leukopenia and arthralgia, that may resolve without the need to suspend treatment or after to change to another ATD[8,9]. Rare but major side effects are also described in 0.1 to 0.5% of patients receiving these drugs and include agranulocytosis, myeloperoxidase antineutrophil cytoplasmic antibody-related vasculitis and severe hepatotoxicity[9,10].

ATD-induced liver injury is a rare but serious complication, classified as a DILI. The insult may occur suddenly, with an unpredictable and unreproducible nature and it is not dose dependent[11]. PTU-induced liver injury occurs especially in pediatric patients, being the 3rd main cause of DILI in young people under 20 years old and responsible for hepatic failure in up to 1 in 2000 children exposed[2,9,11]. For that reason, PTU is no longer recommended to treat GD in childhood, and caution should be taken in adults[9]. MMI-induced liver injury develops in approximately 0.1-0.2% of patients, usually in the early treatment stages, especially within the first 3 months, and is most often associated with a cholestatic analytical and histopathological pattern[8,12,13]. Female gender and older age seem to be two factors that increase susceptibility to develop hepatic complications in patients taking MMI, being quite rare to occur in childhood[14].

This is a very rare case of MMI-induced liver injury since it was developed in a pediatric age boy after 1 month of starting therapy. There are few similar cases published in the literature, but all in adulthood[15,16]. In 2010, a study evaluated the hepatotoxicity profiles of PTU and MMI in children in over 40 years of experience, and only one case of MMI-induced liver injury at age < 17 years was reported[2].

In this case, blood tests showed a clear predominance of hepatic cytolysis pattern and the liver biopsy revealed mild inflammatory infiltrate almost exclusively polymorphonuclear neutrophils, associated with acidophilic necrosis and absence of signs of acute or chronic cholestasis. These findings make this case even more unusual, considering that MMI-induced liver injury is generally related to a cholestatic process, which is characterized by mild periportal inflammation, intracanalicular cholestasis and preservation of hepatocellular structures[4,11]. However, in 2014 Yang J. et al, in a retrospective study of 90 cases of ATS-induced liver injury over 13 years in China, demonstrated that MMI caused mostly hepatocellular injury (43.1%), followed by the cholestatic (35.3%) and mixed (21.6%) patterns[10]. Also, in 2019, Suzuki N, et al. verified a higher frequency of hepatocellular findings (93.9%) in MMI-induced liver injury group[3].

DILI is a challenging diagnosis as there are no specific tests available and so it can mimic any acute or chronic hepatobiliary condition[4,7]. Therefore, it is

Table 1. Thyroid and hepatic blood tests evolution during follow-up

	22/3/2021*	26/4/2021	7/6/2021	11/6/2021	28/6/2021	19/7/2021	13/08/2021	25/01/2022	11/08/2022
Leukocytes	4.6 x 10^9/L (RR: 4.5-13.5)	6.7 x 10^9/L (RR: 4.5-13.0)	5.5 x 10^9/L (RR: 4.5-13.0)	5.9 x 10^9/L (RR: 4.5-13.0)	5.4 x 10^9/L (RR: 4.5-13.0)	-	-	-	-
Eosinophils	0.14 x 10^9/L (RR: 0.04-0.40)	0.34 x 10^9/L (RR: 0.02-0.65)	0.11 x 10^9/L (RR: 0.02-0.65)	0.11 x 10^9/L (RR: 0.02-0.65)	0.09 x 10^9/L (RR: 0.02-0.65)	-	-	-	-
TSH	< 0.01 UI/mL (RR: 0.67-4.16)	< 0.004 uUI/mL (RR: 0.7-4.17)	< 0.004 uUI/mL (RR: 0.7-4.17)	-	-	< 0.004 uUI/mL (RR: 0.7-4.17)	0.012 uUI/mL (RR: 0.7-4.17)	< 0.004 uUI/mL (RR: 0.7-4.17)	34 uUI/mL (RR: 0.7-4.17)
FT4	4.86 ng/dL (RR: 0.86-1.40)	0.70 ng/dL (RR: 0.89-1.37)	1.00 ng/dL (RR: 0.89-1.37)	-	-	1.80 ng/dL (RR: 0.89-1.37)	0.51 ng/dL (RR: 0.89-1.37)	1.65 ng/dL (RR: 0.89-1.37)	0.70 ng/dL (RR: 0.89-1.37)
FT3	> 20.0 pg/mL (RR: 3.30-4.80)	5.1 pg/mL (RR: 2.89-4.33)	5.1 pg/mL (RR: 2.89-4.33)	-	-	8.3 pg/mL (RR: 2.89-4.33)	-	10 pg/mL (RR: 2.89-4.33)	-
TRABs	37U/L (RR: < 1)	67 U/L (RR: < 1)	38 U/L (RR: < 1)	-	-	33 U/L (RR: < 1)	33 U/L (RR: < 1)	-	140 U/L (RR: < 1)
TSI	-	33 U/L (RR: 0.1)	31 U/L (RR: 0.1)	-	-	24 U/L (R: 0.1)	30 U/L (RR: 0.1)	-	-
Anti-TG	0.7 UI/mL (RR: < 4.5)	-	-	-	-	-	-	-	-
Anti-TPO	> 1300 U/mL (RR: < 60)	717 UI/mL (RR: < 5.6)	638 UI/mL (RR: < 5.6)	-	-	-	5471 UI/mL (RR: < 5.6)	-	-
AST	55 U/L (RR: 8-60)	35 U/L (RR: < 35)	1054 U/L (RR: < 35)	520 U/L (RR: < 35)	38 U/L (RR: < 35)	-	41 U/L (RR: < 35)	37 U/L (RR: < 35)	36 U/L (RR: < 35)
ALT	98U/L (RR: 7-46)	61 U/L (RR: 9-25)	971 U/L (RR: 9-25)	602 U/L (RR: 9-25)	60 U/L (RR: 9-25)	-	61 U/L (RR: 9-25)	61 U/L (RR: 9-25)	78 U/L (RR: 9-25)
GGT	-	79 U/L (RR: 3-22)	222 U/L (RR: 3-22)	270 U/L (RR: 3-22)	76 U/L (RR: 3-22)	-	27 U/L (RR: 3-22)	32 U/L (RR: 3-22)	39 U/L (RR: 3-22)
ALP	-	-	-	494 U/L (RR: 141-460)	422 U/L (RR: 141-460)	-	-	313 U/L (RR: 141-460)	281 U/L (RR: 141-460)
Total proteins	5.8 g/dL (RR: 5.7-8.2)	-	-	6.6 g/dL (RR: 5.7-8.0)	-	-	-	-	-
Albumin	4.1 g/dL (RR: 3.2-4.8)	-	-	4.1 g/dL (RR: 3.7-5.6)	-	-	-	-	-
PT	-	-	-	12.9s (RR: 10-14.1)	-	-	-	-	-

*Date when methimazole therapy was started. 9/6/2021: date when methimazole therapy was stopped. 28/4/2022: date when levothyro x ine therapy was started.
ALP: alkaline phosphatase; ALT: alanine aminotransferase; Anti-TG: anti-thyroglobulin antibody; Anti-TPO: anti-thyropero x idase antibody; AST: aspartate aminotransferase; FT3: free triiodothyronine; FT4: free thyro x ine; GGT: gamma-glutamyl transferase; PT: prothrombin time; TRABs: thyroid-stimulating hormone receptor antibodies; TSH: thyroid stimulating hormone; TSI: thyroid- stimulating immunoglobulin.

necessary to rule out other underlying liver diseases that may present with the same clinical characteristics and analytical findings such as viral hepatitis, autoimmune liver disease, alcohol abuse, ischaemia, sepsis and biliary obstruction[4,7]. Some studies report a coexistence between Graves´ disease and other autoimmune diseases (10%), referring to autoimmune hepatitis as one of the most common[17]. In other studies, the prevalence of Graves' disease in autoimmune hepatitis ranged between 1.8 to 6%[18,19]. In our patient, the diagnosis of MMI-induced liver injury was assumed after a complete etiological investigation, in which systemic, autoimmune, viral or hepatic deposit diseases were excluded. In addition, the temporal relationship of the hepatic cytolysis and the introduction of MMI favored this diagnosis. Liver biopsy is not mandatory for MMI-induced hepatitis confirmation, however in this case it was performed and contributed to classify this complication based on histologic findings, excluding other etiologies[4].

In the analytical evaluation carried out in the first hospital appointment, the patient already had a mild elevation of transaminases, which probably was related to a prolonged thyrotoxicosis state. Abnormal liver blood tests associated with hyperthyroidism are well described in the literature and can make the establishment of correct diagnosis even more difficult[17]. The reported prevalence of this relationship varies largely from 11% to 78% and there are several proposed underlying mechanisms[17,20]. A mitochondrial-dependent pathway is activated by a high thyroid hormone level which induce hepatic cell apoptosis and oxidative stress[11,17,20,21]. Also, in hyperthyroidism caused by GD, TRABs can act and stimulate the hepatocytes TSH receptors, inducing a direct inflammatory injury[18]. Finally, serum ALP concentration derived from accelerated bone turnover which results from hyperthyroidism may remain very high for a long time, even after the introduction of pharmacological therapy with ATD[3].

When this diagnosis is made, treatment involves immediate discontinuation of MMI and maintenance of regular clinical and analytical surveillance with supportive therapy. Thus, recovery of most liver panel changes is achieved[4]. Some authors argue that chronic liver disease may occur after DILI, particularly in those presenting a mixed phenotype of this condition[7].

After discontinuing MMI, it is mandatory to choose an alternative and definitive treatment to control hyperthyroidism[1,9,11]. In childhood, and especially with a DILI, substitution for PTU is not recommended[9]. Therefore, one of two options, RAI or thyroidectomy, should be chosen according to patients age, goiter size and parents and/or patient opinion[9]. RAI is the best alternative in children of > 10 years-old and surgery should be considered in patients of < 5 years-old or in the presence of very large goiter in children between 5 and 10 years-old[1]. In this 12-year-old boy, after three weeks of MMI suspension, he underwent ablative RAI with success.

In conclusion, MMI-induced liver injury with a hepatocellular histological pattern is a very rare condition in childhood, but it needs to be promptly identified so that recovery of liver function is possible[4,11]. Other underlying hepatobiliary pathologies that may mimic this diagnosis should be firstly excluded and the possibility of blood liver test alterations due to hyperthyroidism itself may be considered[4]. At this age, the alteration of the MMI by PTU is not an option and the performance of the definitive treatment for thyrotoxicosis control is imperative[1,9].

Our case reflects the benign course of this potentially serious clinical condition when it is promptly recognized and the aggressive agent is removed. Our patient showed a marked drop in transaminase to near normal levels two weeks after MMI was discontinued. At the same time, considering the high bile acid levels, treatment with ursodeoxycholic acid was done. Since the discontinuation of the MMI, the patient maintained a cytolysis and cholestasis values at the upper limit of normal throughout the follow-up period. Therefore, we intend to alert to the importance of frequent monitoring of liver enzymes along with thyroid function to avoid unfavorable outcomes. If DILI occurs, it is imperative to discontinue MMI and definitive therapy for GD should be performed.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Leger J, Oliver I, Rodrigue D, Lambert AS, Coutant R. Graves' disease in children. Ann Endocrinol (Paris). 2018;79(6):647-55.
2. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab. 2010;95(7):3260-7.
3. Suzuki N, Noh JY, Hiruma M, Kawaguchi A, Morisaki M, Ohye H, et al. Analysis of Antithyroid Drug-Induced Severe Liver Injury in 18,558 Newly Diagnosed Patients with Graves' Disease in Japan. Thyroid. 2019;29(10):1390-8.
4. Francis P NV. Drug Induced Hepatotoxicity. 2021 Mar 23:StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;.
5. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR, Practice Parameters Committee of the American College of G. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021;116(5):878-98.
6. Bjornsson ES, Bergmann OM, Bjornsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013; 144(7):1419-25, 25 e1-3; quiz e19-20.
7. Hussaini H. FE. Idiosyncratic drug-induced liver injury: an update on the 2007 overview. Expert Opin Drug Saf. 2014 Jan;13:67-81.
8. DS. C. Antithyroid Drugs. The New England Journal of Medicine. 2005;352:905-17.
9. Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7(4):167-86.
10. Yang J, Li LF, Xu Q, Zhang J, Weng WW, Zhu YJ, et al. Analysis of 90 cases of antithyroid drug-induced severe hepatotoxicity over 13 years in China. Thyroid. 2015;25(3):278-83.
11. Heidari R, Niknahad H, Jamshidzadeh A, Abdoli N. Factors affecting drug-induced liver injury: antithyroid drugs as instances. Clin Mol Hepatol. 2014;20(3):237-48.
12. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab. 2007;92(6):2157-62.
13. KA. W. Methimazole-induced hepatotoxicity. Endocr Pract. 2002;8.
14. IAU-JU Huang MJ LY. Clinical associations between thyroid and liver diseases. Journal of Gastroenterology and Hepatology. 1995 June;10:344-50.
15. Zou H, Jin L, Wang LR, Braddock M, Cai WW, Zheng MH. Methimazole-induced cholestatic hepatitis: two cases report and literature review. Oncotarget. 2016 Jan 26;7(4):5088-91.
16. Zeng J, Luo F, Lin Z, Chen Y, Wang X, Song Y. Rash and cholestatic liver injury caused by methimazole in a woman with Turner syndrome and Graves's disease: a case report and literature review. BMC Endocr Disord. 2021;21(1):179.
17. Yorke E. Hyperthyroidism and Liver Dysfunction: A Review of a Common Comorbidity. Clin Med Insights Endocrinol Diabetes. 2022;15: 11795514221074672.
18. Teufel A, Weinmann A, Kahaly GJ, Centner C, Piendl A, Wörns M, et al. Concurrent autoimmune diseases in patients with autoimmune hepatitis. J Clin Gastroenterol. 2010 Mar;44(3):208-13.
19. Malik R, Hodgson H. The relationship between the thyroid gland and the liver. QJM. 2002 Sep;95(9):559-69.
20. Scappaticcio L, Longo M, Maiorino MI, Pernice V, Caruso P, Esposito K, et al. Abnormal Liver Blood Tests in Patients with Hyperthyroidism: Systematic Review and Meta-Analysis. Thyroid. 2021;31(6): 884-94.
21. SY L. Liver Enzymes Are Commonly Elevated in Untreated Hyperthyroidism and Improve after Correction of the Hyperthyroidism. Clinical Thyroidology. 2021;33(2):70-3.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

IMAGES IN PEDIATRICS

An unusual manifestation of severe edema in nephrotic syndrome

Uma manifestação rara de edema grave na síndrome nefrótica

Maria Garrotes[1a], Marina Mota[2b], Sofia Deuchande[1c], Rita Theias-Manso[3d], Patrícia Costa-Reis[4e], and Ana Rita-Sandes[4f]*

[1]Pediatrics Department, Hospital de Cascais Dr. José de Almeida, Cascais; [2]Pediatrics Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon; [3]Surgical Pathology Department, Hospital Prof. Dr. Fernando Fonseca, Lisbon; [4]Pediatric Nephrology and Kidney Transplantation Unit, Pediatrics Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon. Portugal

ORCID: [a]0009-0002-3829-2793; [b]0000-0001-9435-2207; [c]0000-0002-8319-8635; [d]0000-0002-6863-7468; [e]0000-0002-7174-8302; [f]0000-0003-1121-1092

Keypoints

What is known
- Ascites is a common finding in nephrotic syndrome.
- Adherence to treatment is important to prevent nephrotic syndrome complications.

What is added
- Transudation of ascitic fluid through the abdominal wall is a rare complication of nephrotic syndrome.
- The treatment of transudation of ascitic fluid and skin lesions is challenging and improvement may take several weeks.

Ascites is a common finding in nephrotic syndrome due to transudation from the intravascular compartment to the peritoneal space[1]. We report on a rare complication in a child with severe ascites.

A 4-year-old girl with frequent relapsing nephrotic syndrome presented at the emergency department with abdominal pain. She was being treated with alternate day prednisolone 40mg/m^2, with poor adherence to this medication.

The patient had anasarca, normal blood pressure, tachycardia, and poor peripheral perfusion. Hypoalbuminemia (< 0.6 g/dL), nephrotic range proteinuria (urine protein/creatinine ratio 2.31 g/g) and dyslipidemia were identified. The inflammatory markers were normal. The patient was admitted to the hospital and treated with prednisolone 60mg/m^2/day and, also, albumin, due to the hypovolemic crisis.

In the following days the ascites increased and the abdominal pain intensified. The inflammatory markers raised. On the ultrasound, debris were found in the ascitic fluid, and a presumptive diagnosis of spontaneous bacterial peritonitis was made. Ceftriaxone was started. The ascites intensified, causing abdominal wall distension with skin disruption, and abdominal stria appeared. Transudation of ascitic fluid through the abdominal wall occurred (Fig. 1). Topical fusidic acid, zinc oxide ointment and povidone iodine dressings on the abdominal wall skin were started. After two weeks, the edema decreased and there was progressive skin healing (Fig. 2).

After four weeks of intravenous prednisolone, nephrotic range proteinuria persisted. A kidney biopsy was performed and focal segmental glomerulosclerosis was identified. Tacrolimus and weaning of prednisolone were started. A next-generation sequencing study for genetic causes of nephrotic syndrome was done and

***Correspondence:**
Maria Garrotes
E-mail: mariamgarrotes@gmail.com

Received: 02-12-2022
Accepted: 09-10-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):64-65
DOI: 10.24875/PJP.M23000431

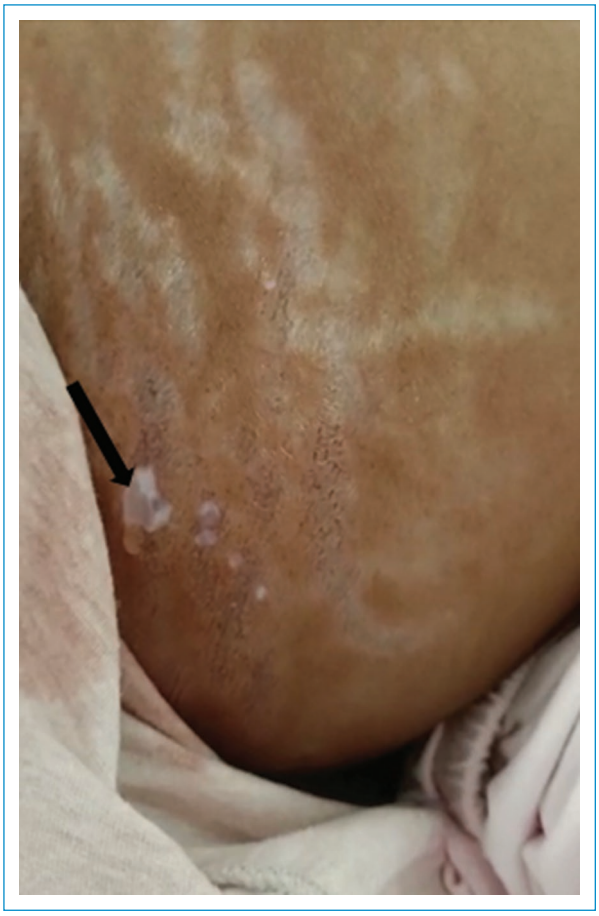

Figure 1. Transudation of fluid through the abdominal wall.

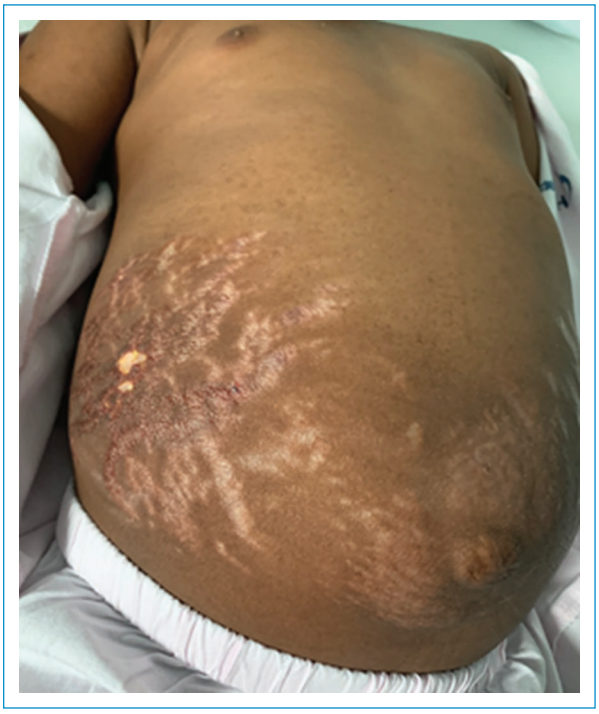

Figure 2. Progressive healing of the skin of the abdominal wall.

no mutations were found. There were no relapses in the two years of follow up.

Hypovolemic crises, spontaneous bacterial peritonitis and, very rarely, transudation of ascitic fluid through the abdominal wall are possible complications of nephrotic syndrome. The treatment of the latter is challenging, and it takes several weeks to improve. Adherence to treatment is a major issue in the care of children with nephrotic syndrome[2,3].

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Kallash M, Mahan JD. Mechanisms and management of edema in pediatric nephrotic syndrome. Pediatr Nephrol. 2021;36(7):1719-30;
2. Starcea IM, Bogos RA, Scurtu G, Munteanu M, Russu R, Lupu VV, et al. Pathological and Evolutive Correlations in Steroid Resistant Nephrotic Syndrome in Children. Int J Gen Med. 2022 19;15:4187-93;
3. Hilmanto D, Mawardi F, Lestari AS, Widiasta A. Disease-Associated Systemic Complications in Childhood Nephrotic Syndrome: A Systematic Review. Int J Nephrol Renovasc Dis. 2022;15:53-62.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

IMAGES IN PEDIATRICS

Ectopic ovary – an unexpected finding

Ovário ectópico – um achado inesperado

Paulo Santos-Correia[1a] and Alexandra Tavares-Ferreira[2b]*

[1]Hospital de São José; [2]Hospital Dona Estefânia. Centro Hospitalar e Universitário de Lisboa Central, Lisbon, Portugal

ORCID: [a]0000-0003-2902-3022; [b]0000-0002-2428-7320

Keypoints

What is known

- Ectopic ovary is a rare gynaecologic abnormality which can be congenital or acquired.
- The diagnose of ectopic ovary is usually difficult since most patients are asymptomatic.

What is added

- Ectopic ovary should be suspected in young patients with an absent pelvic ovary, namely in those with concurrent congenital renal defects.

A 14-year-old girl, with a prenatal diagnose of left pelvic multicystic dysplastic kidney, presented in our department for a follow-up ultrasound. The patient has been followed in our hospital by a paediatric nephrologist since birth. Previous ultrasounds reported a normal right kidney and a left pelvic multicystic dysplastic kidney, with no signs of vesicoureteral reflux on cystography.

She had no symptoms and no relevant family history. Urine and blood analysis were normal.

Physical examination was unremarkable, revealing developed secondary sexual characteristics.

Regarding the gynaecological history, the patient experienced menarche three months before this appointment. She reported that these first cycles were regular, with slight dysmenorrhea.

During an ultrasound examination, an elongated, well-circumscribed and hypoechogenic structure was depicted on the left flank, presenting with some small cystic images (Fig. 1). The left ovary was not depicted on its usual location (and it was never documented on previous ultrasounds).

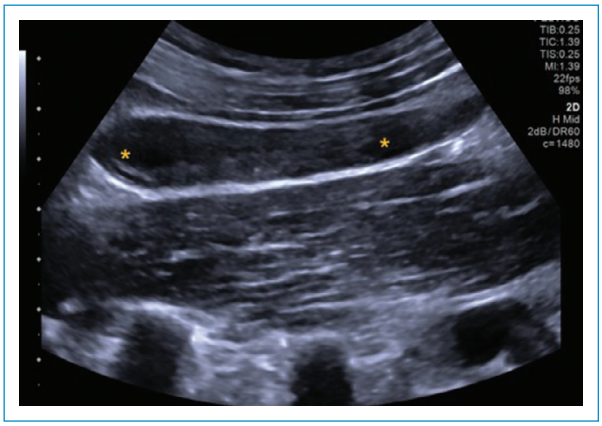

Figure 1. Ultrasound image showing an elongated, well-circumscribed and hypoechogenic structure of the left flank, with some small cystic images (*).

A complementary MR was performed for further characterization, showing an elongated, well-circumscribed structure on the left flank, measuring 84 mm of greatest

***Correspondence:**
Paulo Santos-Correia
E-mail: paulocorreia05@gmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):66-68
DOI: 10.24875/PJP.M23000126

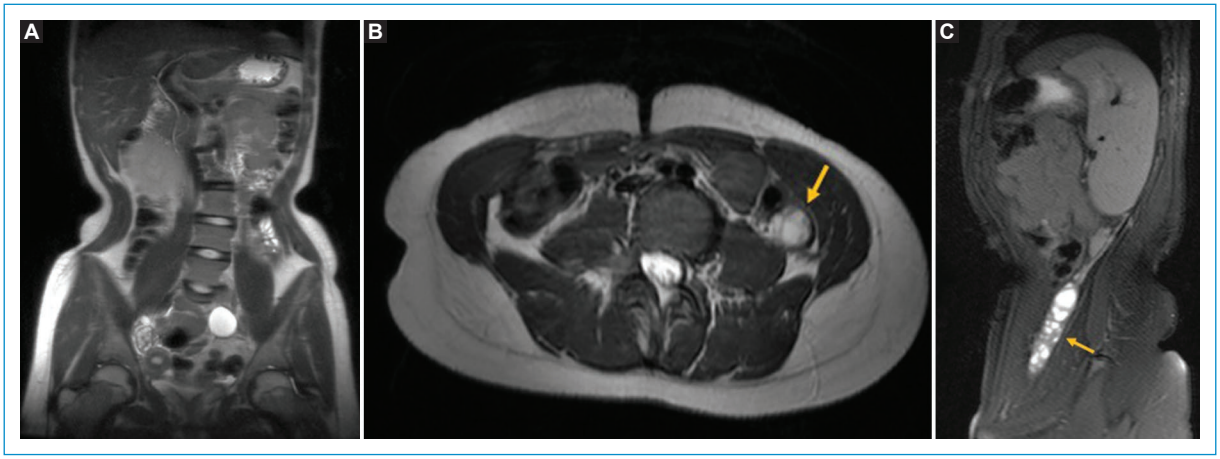

Figure 2. Ectopic ovary. Coronal **(A)**, axial **(B)** T2-weighted and sagittal **(C)** fat-suppressed T2-weighted images showing an elongated, well-circumscribed structure on the left flank (yellow arrow). The right ovary is identified on the pelvis (black arrow) as well as the pelvic multicystic dysplastic kidney (*). An unicornuate uterus is also depicted (yellow arrow-head).

longitudinal diameter. This structure presented with multicystic appearance, resembling an ovary with follicles, the largest being 14 mm (Fig. 2). These imaging findings were consistent with a left ectopic ovary.

Pelvic assessment confirmed the absence of the left ovary (Figs. 2 and 3) and depicted a right deviated uterine cavity, probably an unicornuate uterus lacking a rudimentary horn (Fig. 2). According to the European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) with consensus on the classification of female genital tract congenital anomalies, this anomaly was classified as U4bC0V0 (Fig. 4)[1].

The MR also confirmed the presence of a left pelvic multicystic dysplastic kidney and depicted a normal right kidney in the standard location (Fig. 3).

Ectopic ovary is a rare gynaecologic abnormality, characterized to be located above the level of the common iliac vessels, with less than 50 cases reported in the literature since 1959[2,3]. The estimated prevalence of ectopic ovaries among gynaecologic admissions sets between 1:29 0000 to 1:93 0000[2,4].

They can be classified as congenital or acquired, the later accounting for most cases. In fact, Lachman and Berman found that almost 50% of the reported cases since 1959 were diagnosed in patients with previous pelvic surgery, making our case even rarer[5].

The diagnose of ectopic ovary is difficult since most patients are asymptomatic. However, patients can present with menstrual irregularities, infertility or abdominal pain[3]. Ectopic ovaries can also have an acute presentation (eg. mimicking an appendicitis), or mimic intraperitoneal tumours[3,4].

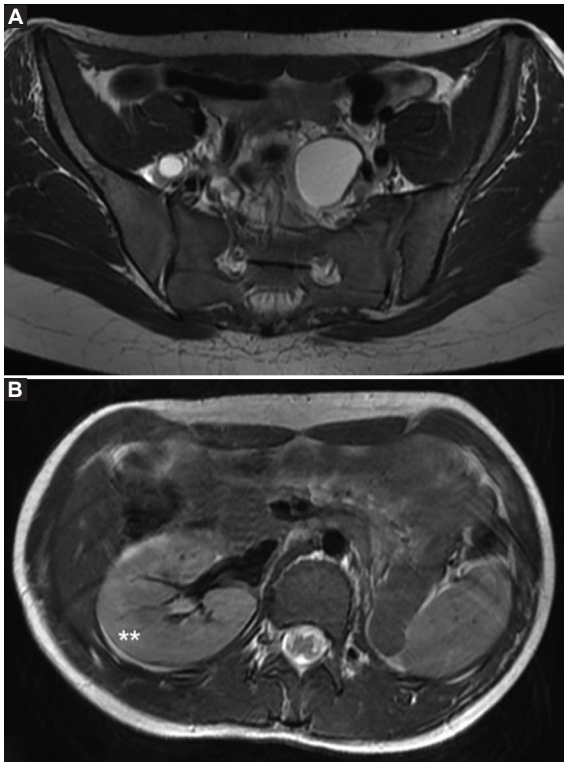

Figure 3. Additional findings. Axial T2-weighted image of the pelvis **(A)** shows a cystic lesion on the left (*) corresponding to the multicystic dysplastic kidney. A normal right ovary is depicted (arrow). Axial T2-weighted image of the upper abdomen **(B)** reveals a normal right kidney (**) and an absent left kidney.

Associations with renal abnormalities have been described, given their common embryologic origin[3].

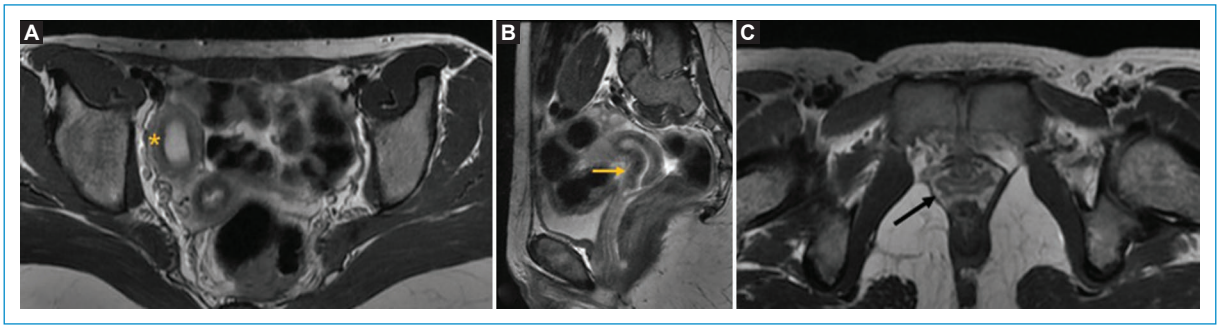

Figure 4. Uterine malformation. Axial T2-weighted image of the pelvis **(A)** shows a right deviated, unicornuate uterus (yellow star), without a rudimentary horn. Sagittal T2-weighted image of the pelvis **(B)** reveals an unilateral cervix (yellow arrow). Axial T2-weighted image of the pelvis at a lower level **(C)**, depicts a normal vagina (black arrow).

The diagnosis can be made by ultrasound, but MR is the best imaging modality to assess ectopic ovaries, given its excellent soft tissue contrast and its ability to diagnose concurrent uterine and renal anomalies.

Given its low prevalence, there are not many published studies concerning ectopic ovary management; however, whenever treatment is required, surgery remains the gold-standard[3,4]. The best management option should be achieved by a multidisciplinary board[4].

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Grimbizis GF, Gordts S, Sardo AS, Brucker S, Angelis C, et al. The ESHRE/ESGE consensus on the classification of female genital tract. 2013;28(8):2032-44. (PMID:23771171)
2. Watkins BP, Kothari SN. True ectopic ovary: a case and review. Arch Gynecol Obs. 2004;(269):145-6. (PMID: 14557889)
3. Kollia P, Kounoudes C, Veloudis G, Giannakou N, Gourgiotis S. True ectopic ovary in the right iliac fossa mimicking acute appendicitis and associated with ipsilateral renal agenesis. J Obstet Gynaecol Res. 2014;40(3):858-61. (PMID: 24320118)
4. Pan J, Wang S, Wang H, Fan Z. A Rare Ectopic Ovary Mimicking Colon Sigmoideum Mesenchymoma Presenting as an Intestinal Mesenchymoma. Front Oncol. 2019;9(580):1-4. (PMID: 31334114)
5. Lachman MF BM. The ectopic ovary: A case report and review of the literature. Arch Pathol Lab Med. 1991;(115):233-4 (PMID: 2001159)

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

IMAGES IN PEDIATRICS

Hereditary multiple osteochondromas

Osteocondromatose múltipla hereditária

João R. Nunes-Pires[1a], Violeta Florova[1b], and Teresa Alves-da Silva[2c]

[1]Unidade de Saúde Familiar São Martinho de Alcabideche, ACES Cascais; [2]Orthopedics Department, Hospital de Cascais. Lisbon, Portugal

ORCiD: [a]0000-0002-4291-3022; [b]0000-0002-6843-1080; [c]0000-0003-1007-6570

Keypoints

What is known

- Hereditary multiple osteochondromas is characterized by osteocartilaginous formations in the growth plates of long or flat bones, which stabilize at puberty.
- Complications include tendon/nerve/vascular compression, short stature, pathological fractures and malignancy. Surgical intervention is rarely needed.

What is added

- Awareness about hereditary multiple osteochondromas is important in the differential diagnosis of bone tumors.

A three-year-old boy's mother reports the appearance of painless swelling at the right tibia's proximal end, with one year of evolution, without previous trauma or local/systemic inflammatory signs, namely fever or lymphadenopathy. There was no family history of similar malformations. An X-ray (Fig. 1) revealed "exostotic formations on the distal end of the external surface of the peroneal diaphysis, external femoral supracondylar region and proximal metaphyseal-diaphyseal region of the tibia". An ultrasound highlighted a "procidence of the tibial anterior tuberosity of the proximal end, without cortical discontinuity". Further studies included a full-length X-ray of the lower limbs (Fig. 2) that showed multiple exostotic formations in both femurs, tibias and fibulas. For better characterization, an MRI was performed (Fig. 3), which identified several other metaphyses' osteochondromas along the lower limbs and signs of malignancy were excluded.

The most likely hypothesis –hereditary multiple osteochondromas– is characterized by osteocartilaginous formations in the growth plates (metaphyses) of long or flat bones, due to a deleterious variant in *EXT1* or *EXT2* tumor suppressor genes[1]. It results from autosomal dominant transmission and its prevalence is 1:50.000[2]. There is no gender difference regarding prevalence, but male subjects can have a more pronounced disease. The formations appear and increase in size and number during the first decade, stabilizing at puberty with the closure of growth plates. However, the number, size and location of osteochondromas vary[3]. Generally asymptomatic and symmetric, the predominant locations are the femur (30%), tibia (20%), radius/ulna (13%) and fibula (13%); hands are also commonly affected[4]. The diagnosis is based on radiological findings of at least two osteochondromas of the juxta-epiphyseal region of long bones and, in the majority of patients, a positive family history or a documented mutation in one of the *EXT* genes, if available. Almost 10% of affected individuals have no family history. Clinical and radiological findings can be supplemented with histological

***Correspondence:**
João R. Nunes-Pires
E-mail: joaorpiresmd@gmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):69-71
DOI: 10.24875/PJP.M23000127

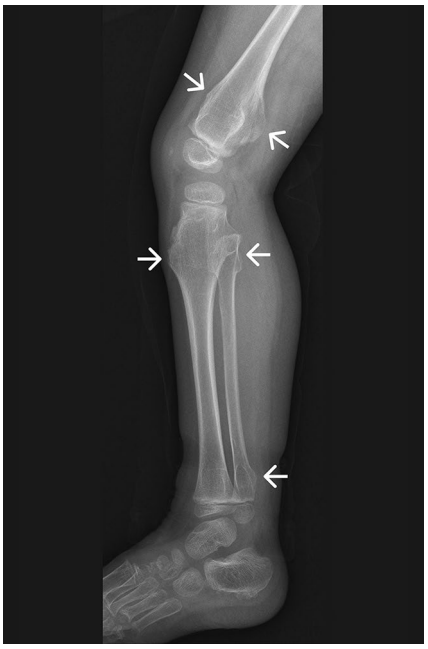

Figure 1. Right lower limb X-ray showing exostotic formations on the distal femur, proximal tibia and distal fibula (white arrows). Note the typical sessile lesions on the surface of the bone which point away from the joint. There is an associated widening of the diametaphysis resulting in an erlenmeyer flask deformity.

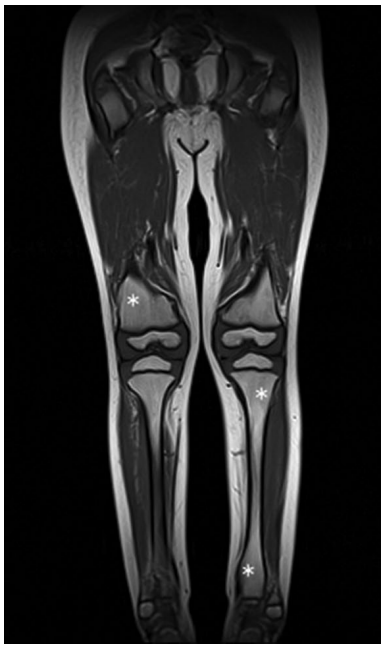

Figure 3. MRI coronal plane of the lower limbs showing multiple exostotic formations (white asterisks), highlighting the shape of the osteochondromas and its continuity from the cortical bone. This allows a direct study of the cartilage cap and the soft tissues surrounding the lesions

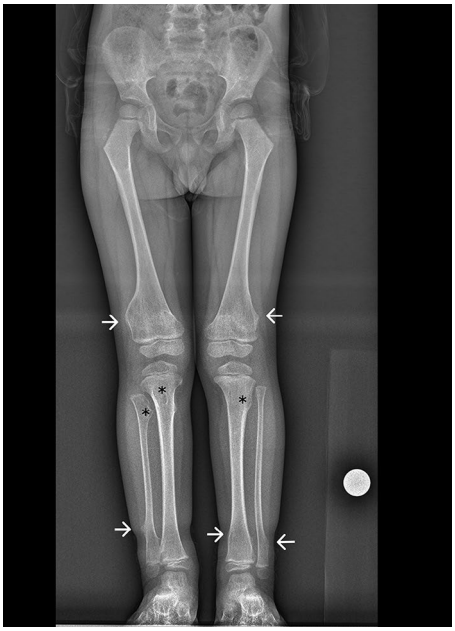

Figure 2. Lower limbs full-length X-ray showing multiple exostotic formations in both femurs, tibias and fibulas (white arrows and black asterisks). Note the characteristic metaphysis widening.

evaluation of the osteochondromas, although not mandatory for diagnosis[4,5]. Complications include tendon/nerve/vascular compression, functional impairment, short stature, fractures and malignancy (1-5%). Surgery may be necessary if any complications arise[1-3]. Differential diagnoses such as simple or aneurysmal cyst, metachondromatosis (most frequently small osteochondromas in the hands and feet, predominantly in digits and toes, that point towards the adjacent growth plate and tend to spontaneously decrease in size or regress), enchondromatosis (predominantly unilateral cartilaginous medullary tumors of short tubular bones), periosteal chondroma (typically includes bone cortex erosion), osteoid osteoma, osteoblastoma and chondroblastoma (usually later and symptomatic onset) must be excluded[2,5].

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Pannier S, Legeai-Mallet L. Hereditary multiple exostoses and enchondromatosis. Best Pract Res Clin Rheumatol. 2008;22:45.
2. Bovée JV. Multiple osteochondromas. Orphanet J Rare Dis. 2008;3:3.
3. Jurik AG. Multiple hereditary exostoses and enchondromatosis. Best Pract Res Clin Rheumatol. 2020;34:101505.
4. Wuyts W, Schmale GA, Chansky HA, Raskind WH. Hereditary Multiple Osteochondromas. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews®; NCBI Bookshelf. 2000. Accessed May 14, 2023. https://www.ncbi.nlm.nih.gov/books/NBK1235/.
5. Bovée JVMG, Hogendoorn PCW. Multiple Osteochondromas. In: Fletcher CDM, Unni KK, Mertens F, editors. World Health Organization of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. Lyon: IARC Press; 2002. p. 360-362.

PORTUGUESE JOURNAL OF PEDIATRICS

PERMANYER

Check for updates

IMAGES IN PEDIATRICS

A non-classic presentation of OHVIRA syndrome

Uma apresentação não-clássica do síndrome OHVIRA

Filipa da Costa-Cascais[1a], Ana Barbosa-Rodrigues[2b], Inês Vermelho-Lourenço[3c], and Rita Marques-Martins[4d]*

[1]Serviço de Pediatria, Hospital Garcia de Orta, Almada; [2]Serviço de Pediatria, Centro Hospitalar Universitário Lisboa Norte, Lisbon; [3]Serviço de Ginecologia e Obstetrícia, Hospital Beatriz Ângelo, Loures; [4]Serviço de Pediatria, Hospital Garcia de Orta, Almada. Portugal

ORCID: [a]0000-0002-5492-831X; [b]000-0002-0033-7047; [c]0000-0003-4630-829X; [d]0000-0003-0237-8093

Keypoints

What is known

- OHVIRA syndrome is a rare urogenital malformation, characterized by uterus didelphys, obstructed hemivagina and ipsilateral renal agenesis.
- It typically presents with progressive and severe dysmenorrhea, but it can also be diagnosed due to acute abdominal pain.

What is added

- OHVIRA syndrome should be a differential diagnosis in acute abdominal pain in female patients, especially adolescents.
- Patients with absent or dysplastic kidney should be routinely investigated for uterovaginal abnormalities, in order to prevent potentially severe complications.

Description

A 13-year-old female adolescent was admitted to the Pediatric Emergency Department with abdominal pain and occasional vomiting, for three days. Her past medical history included a dysplastic right kidney. She had her menarche at the age of 12 years and she had regular menses, without dysmenorrhea. She was haemodynamically stable and physical examination revealed a tender and guarding abdomen in the right iliac region, without any other findings. An initial investigation was performed to exclude acute appendicitis. Laboratory evaluation showed mild leucocytosis ($12.8x10^9$/uL), elevated C-protein reactive (11 mg/dL, for a normal value of < 0.2 mg/dL) and haemoglobin of 12.0 g/dL. Abdominal and pelvic ultrasound revealed two uterine cavities and a tubular image of 15.8 x 8.7 x 8.3 cm, located in the vaginal canal, filled with what seemed to be hematic content. Magnetic resonance image (MRI, Figs. 1 and 2) with contrast was performed and it reported uterus didelphys and two probable hemivaginas, the right one obstructed, with a resultant hematometrocolpos. A dysplastic right kidney and an ectopic right ureter was also evident, with a distal implantation in the right hemivagina. These findings suggested the diagnosis of OHVIRA (obstructed hemivagina and ipsilateral renal agenesis/anomalies) syndrome. The patient underwent an incision in the vaginal septum, with drainage of the accumulated blood and partial resection of the septum, to prevent obstruction of the hemivagina in the future. The procedure went without complications, and she was discharged home the day after. Since then, she has been pain free. After one year of the procedure, the hemivagina is still unobstructed.

***Correspondence:**
Filipa da Costa-Cascais
E-mail: filipa.c.cascais@gmail.com

Received: 11-11-2023
Accepted: 13-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):72-74
DOI: 10.24875/PJP.M23000128

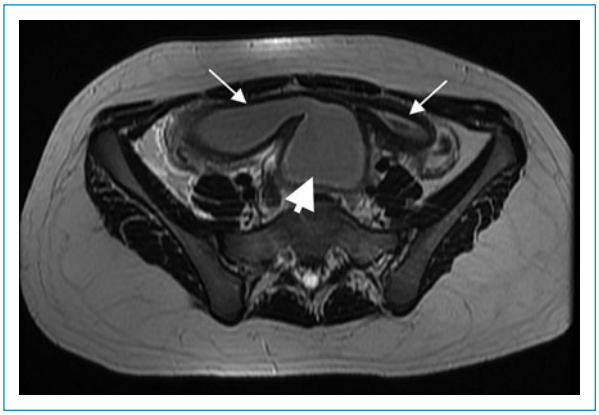

Figure 1. Axial section of magnetic resonance image of the pelvis with contrast showing uterus didelphys, with two uterine cavities (arrows) and what was assumed as the right obstructed hemivagina (large arrow), with an hematometrocolpos.

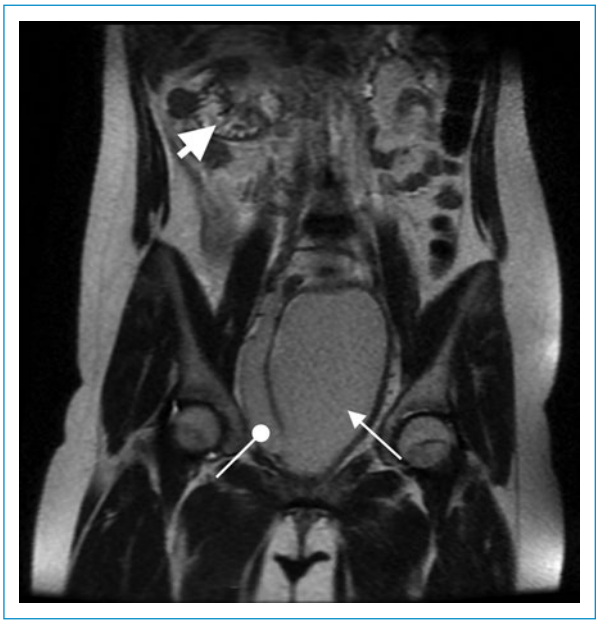

Figure 2. Coronal section of magnetic resonance image of the pelvis with contrast showing what was assumed as the right obstructed hemivagina (arrow), with a distal implantation of an ectopic right ureter (round arrow). Dysplastic right kidney is also shown (large arrow).

OHVIRA syndrome (or Herlyn-Werner-Wunderlich syndrome) is a rare urogenital malformation, occurring in only 5% of all Müllerian duct abnormalities[1]. It is typically characterized by uterus didelphys, obstructed hemivagina, due to a vaginal septum, and ipsilateral renal agenesis, although other renal findings, like dysplastic kidneys and ectopic ureters, are possible[1-4].

The diagnosis, in most of the cases, is delayed until puberty, and it is usually made due to progressive and severe dysmenorrhea, with or without a pelvic mass, which happens because the obstructed hemivagina causes an increasing hematometrocolpos[2-4]. Less frequently, some cases present with urinary retention or acute abdominal pain, like in our patient[2,3]. MRI is the gold standard for anatomic characterization and final diagnosis, although ultrasonography may have an important initial role[1-4].

The treatment of choice is surgical, most of the cases with a resection of the vaginal septum, and it is extremely important for symptom relieve and prevention of long-term complications. An obstructed hemivagina leads to a retrograde flow of the blood into the uterine cavity, which can lead to endometriosis and pelvic adhesions. Other complications, like impaired fertility, pregnancy complications and pelvic infections can also occur[1-3].

This case is important to remind that OHVIRA syndrome should be a differential diagnosis in acute abdominal pain, although it is not the classic presentation. Furthermore, it is also a diagnosis to bear in mind when facing patients with absent or dysplastic kidney, and some authors recommend investigation of uterovaginal abnormalities in such cases to allow early recognition and treatment[2].

Awards and presentations

This case was presented at the 21th National Congress of Pediatrics that took place between 27th and 29th October 2021, Braga, Portugal.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

References

1. Girardi Fachin C, Aleixes Sampaio Rocha JL, Atuati Maltoni A, das Chagas Lima RL, Arias Zendim V, Agulham MA, et al. Herlyn-Werner-Wunderlich syndrome: Diagnosis and treatment of an atypical case and review of literature. *Int J Surg Case Rep.* 2019;63:129-34.
2. Jha S, Abdi S. Diverse Presentations of OHVIRA Syndrome: A Case Series. *Clin Pediatr (Phila).* 2021;60(1):6-8.
3. Gungor Ugurlucan F, Bastu E, Gulsen G, Kurek Eken M, Akhan SE. OHVIRA syndrome presenting with acute abdomen: a case report and review of the literature. *Clin Imaging.* 2014;38(3): 357-9.
4. Angotti R, Molinaro F, Bulotta AL, Bindi E, Cerchia E, Sica M, et al. Herlyn–Werner–Wunderlich syndrome: An "early" onset case report and review of Literature. *Int J Surg Case Rep.* 2015;11: 59-63.