# NASCER E CRESCER

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

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

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# EDITORIAL

## 20 YEARS OF SPRING REPORTS - LEARNING PATH

### 20 ANOS DE RELATÓRIOS DE PRIMAVERA - PERCURSO DE APRENDIZAGENS

Pedro Lopes Ferreira[1]

This year we celebrated the 20th anniversary of the Spring Reports of the Portuguese Health Systems Observatory (OPSS). During this time, the Spring Reports addressed a number of issues related to the Portuguese health system, as can be witnessed by reading the annexes to this year's report where the main conclusions and recommendations issued annually by the OPSS are compiled.

For example, issues related to the governance of the health system, the need for an intelligent centre of analysis and for a long-term strategic planning, the importance of distinguishing between the role of the political decision-makers and that of the experts, the financing and financial sustainability of the NHS, the National Health Plan and health regulation were addressed. Above all, the need for the continuity of a consistent political line that has a broad social base of support.

We have analyzed reforms that over the years have been presented to the Portuguese or simply announced, such as the reform of primary health care, the hospital reform and the need for a new internal organization of hospital units, reforms of continuous and palliative care, mental health reform, oral health reform, the management of human resources for health and its professionals, and public health reform to ensure future health and sustainability.

The various care sectors have also not been forgotten during these years. Thus, in addition to the need for better integration of care, we mentioned, for example, the revitalization of the commissioning processes and the need to reduce surgical waiting lists.

More global areas such as the political, economic and financial sustainability of social protection systems, the citizens' access to quality care, a constitutionally right, the access to medicines, the prescription standards, including the use of antibiotics, and the introduction of therapeutic innovation within the NHS have been addressed.

In contextual terms, social inequalities, the aging of the population, the consequent increase in physical, mental and social dependence of citizens and the resurgence of formal caregivers, still somewhat transparent to political power and even to large fringes of society, were addressed. It was also referred the unemployment and the impoverishment of the population, with negative impacts on citizens' health.

During these years, of course, we could not help but talk about the financial, economic and social crisis, the content of the memoranda of understanding with the Troika and, in particular, the impact they have had on health governance in Portugal.

It also advocated greater involvement of citizens in their health system through a higher degree of health literacy and greater appropriation of health information, more investment in health outcomes and, consequently, in the explicitness of value creation for citizens.

Finally, the fragility of the political debate in health was addressed and prospective analyses of health governance and scenarios for the future of the health system Portuguese.

In this year's commemoration report, following a summary of the various conclusions of the previous Spring Reports, the pandemic was addressed in a necessarily preliminary, yet very hot, manner, by making a historical framework and analysing the various decisions taken and the existing pressure forces. Always with the aim of extracting the necessary teachings from this epidemic.

The future of the Portuguese health system and of the NHS has also been addressed, and the recently approved Recovery and Resilience Plan has not been forgotten.

In conclusion, it was argued that smart health governance will have to be based on a strong analytical component and be knowledge sensitive. It is necessary to have a continuous scientific counseling process, transparent and independent of the powers, capable of making a synthesis of the state of the art, in order to write proposals

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for action, and communicated to the community as a whole. This is an issue that has long concerned those who are interested in the quality of public policies. In other words, it is necessary to ensure that political decisions on what interests all citizens are taken on the basis of available knowledge.

**Note:** This text was based on the presentation of the OPSS Spring 2021 Report held at the Oriente Foundation Auditorium in Lisbon on June 23, 2021. The report is available at

https://www.uc.pt/org/ceisuc/Research/Health_Systems/OPSS/RP

OPSS coordinators are currently the Institute of Public Health of the University of Porto, the Center for Health Studies and Research of the University of Coimbra, the National School of Public Health of the New University of Lisbon, the Faculty of Pharmacy of the University of Lisbon, and the University of Évora.

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Neste ano comemoraram-se os 20 anos dos Relatórios de Primavera do Observatório Português dos Sistemas de Saúde (OPSS). Durante este tempo, os Relatórios de Primavera abordaram vários temas relacionados com o sistema de saúde português, conforme se pode testemunhar ao percorrer os anexos do relatório deste ano e onde estão compiladas as principais conclusões e recomendações emitidas anualmente pelo OPSS.

A título de exemplo, abordaram-se temas relacionados com a governação do sistema de saúde, a necessidade de um centro inteligente de análise e de planeamento estratégico de longo prazo, a importância de distinguir entre o papel do decisor político e o do técnico especialista, o financiamento e a sustentabilidade financeira do SNS, o Plano Nacional de Saúde e a regulação em saúde. Acima de tudo, a necessidade da continuidade de uma linha política consistente que conte com uma ampla base social de apoio.

Analisaram-se reformas que ao longo dos anos têm sido apresentadas aos portugueses ou pura e simplesmente anunciadas, como é o caso da reforma dos cuidados de saúde primários, da reforma hospitalar e da necessidade de uma nova organização interna das unidades hospitalares, das reformas dos cuidados continuados e paliativos, da reforma da saúde mental, da reforma da saúde oral, da gestão dos recursos humanos da saúde e dos seus profissionais, e da reforma da saúde pública para garantir a saúde e a sustentabilidade futuras.

Os vários setores da prestação de cuidados também não foram esquecidos durante estes anos. Assim, para além da necessidade de uma melhor integração de cuidados, falou-se, por exemplo, da revitalização dos processos de contratualização e da necessidade de redução das listas de espera cirúrgicas.

Abordaram-se áreas mais globais como a sustentabilidade política, económica e financeira dos sistemas de proteção social, o acesso dos cidadãos a cuidados de qualidade, um direito constitucionalmente assegurado, o acesso aos medicamentos, os padrões de prescrição, incluindo a utilização dos antibióticos, e a introdução da inovação terapêutica no âmbito do SNS.

Em termos contextuais abordaram-se as desigualdades sociais, o envelhecimento da população, o consequente acréscimo da dependência física, mental e social dos cidadãos e o ressurgimento dos cuidadores informais, ainda de certo modo transparentes para o poder político e mesmo para grandes franjas da sociedade. Referiu-se também ao desemprego e ao empobrecimento da população, com impactos negativos sobre a saúde dos cidadãos.

Durante estes anos não se pôde obviamente deixar de falar da crise financeira, económica e social, do conteúdo dos memorandos de entendimento com a Troika e, particularmente do impacto que tiveram na governação da saúde em Portugal.

Defendeu-se também um maior envolvimento do cidadão no seu sistema de saúde através de um mais elevado grau de literacia em saúde e de uma maior apropriação da informação de saúde, mais investimento em resultados em saúde e, consequentemente, na explicitação da criação de valor para os cidadãos.

Por fim, abordou-se a fragilidade do debate político na saúde e apresentaram-se análises prospetivas da governação da saúde e cenários para o futuro do sistema de saúde português.

No Relatório deste ano de comemoração, após uma súmula das várias conclusões dos Relatórios de Primavera anteriores, abordou-se de uma forma necessariamente preliminar, e ainda muito a quente, a pandemia, fazendo um enquadramento histórico e analisando as várias decisões tomadas e as forças de pressão existentes. Sempre com o objetivo de extrair os ensinamentos necessários desta experiência pandémica.

Abordou-se também o futuro do sistema de saúde português e do SNS e não foi esquecido o recentemente aprovado Plano de Recuperação e Resiliência.

Em conclusão, defendeu-se que uma governação inteligente da saúde terá de se basear numa forte componente analítica e ser sensível ao conhecimento. É forçoso existir um processo de aconselhamento científico contínuo, transparente e independente dos poderes, capaz de fazer uma síntese do estado da arte e vertê-la em propostas de ação, comunicadas ao conjunto da comunidade. Esta é uma questão que há muito preocupa quem se interessa pela qualidade das políticas públicas. Por outras palavras, há que assegurar que as decisões políticas sobre aquilo que interessa ao conjunto dos cidadãos sejam tomadas com base no conhecimento disponível.

**Nota:** Este texto foi baseado na apresentação do Relatório de Primavera 2021 do OPSS realizada no Auditório da Fundação Oriente, em Lisboa, em 23 de junho de 2021. O relatório está disponível em

https://www.uc.pt/org/ceisuc/Research/Health_Systems/OPSS/RP

São atualmente coordenadores do OPSS o Instituto de Saúde Pública da Universidade do Porto, o Centro de Estudos e Investigação em Saúde da Universidade de Coimbra, a Escola Nacional de Saúde Pública da Universidade Nova de Lisboa, a Faculdade de Farmácia da Universidade de Lisboa, e a Universidade de Évora.

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# ORIGINAL ARTICLE

# ORBITAL COMPLICATIONS IN PEDIATRIC ACUTE SINUSITIS: EIGHT-YEAR EXPERIENCE

## COMPLICAÇÕES ORBITÁRIAS DE SINUSITE AGUDA EM PEDIATRIA: EXPERIÊNCIA DE OITO ANOS

João Fonseca Neves[1], João Filipe Simões[2], Sofia Paiva[1], Felisberto Maricato[1], Luís Filipe Silva[1]

## ABSTRACT

**Objectives:** Acute sinusitis accounts for up to 82% of orbital infection cases. Infection spreads very quickly, especially through the ethmoid sinus, and orbital complications may arise even under antibiotic therapy. The aim of this study was to describe an 8-year hospital experience with these children.

**Methods:** All cases of acute sinusitis with orbital complications admitted to the Department of Otorhinolaryngology of Centro Hospitalar e Universitário de Coimbra between 2010 and 2017 were retrospectively reviewed.

**Results:** Sixty-four patients met the inclusion criteria, with a mean age of 9 ± 4.7 years. Male:female ratio was 1.67:1. Most subjects were admitted in the winter period (57.8%), with 2.9 ± 2.5 days of clinical evolution. The mean Lund Mackay score was 10.6 ± 4.9, with maxillary and ethmoid being the most prevalent involved sinuses (96.4% and 94.6%, respectively), and was inversely correlated with age ($p<0.05$). Preseptal cellulitis was the most common complication (56.3%). Abscesses were identified in 18.7% of patients, but only four (6.25%) required surgery. Seven cases (10.9%) recurred shortly after hospital discharge and required prolonged antibiotic course. All patients recovered well, without further complications.

**Conclusion:** Results showed that orbital complications of sinusitis respond well to high doses of endovenous antibiotherapy and patients tend to recover without local comorbidities. Close monitoring of these patients during the first months after hospital discharge is crucial to prevent early relapse.

**Keywords:** complications; orbital disease; sinusitis

## RESUMO

**Objetivos:** A sinusite aguda é responsável por até 82% dos casos de infeções orbitárias. As infeções propagam-se facilmente, em particular através das células etmoidais, mesmo em crianças sob antibioterapia. O objetivo deste estudo foi descrever a experiência de oito anos de um centro hospitalar com esta patologia.

**Métodos:** Revisão retrospetiva dos casos de sinusite aguda com complicações orbitárias admitidos no Departamento de Otorrinolaringologia do Centro Hospitalar e Universitário de Coimbra entre 2010 e 2017.

**Resultados:** Sessenta e quatro doentes foram incluídos no estudo, com uma idade média de 9 ± 4,7 anos e uma proporção de rapazes:raparigas de 1,67:1. A maioria dos doentes foi internada nos meses de inverno (57,8%), com 2,9 ± 2,5 dias de evolução clínica. O score de Lund Mackay foi de 10,6 ± 4,9, com os seios maxilar e etmoidais mais prevalentemente envolvidos (96,4% e 94,6%, respetivamente), e correlacionou-se

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inversamente com a idade (p <0,05). A celulite pré-septal foi a complicação mais comum (56,3%). Foram identificados abscessos em 18,7% dos doentes, mas apenas quatro (6,25%) necessitaram de tratamento cirúrgico. Sete (10,9%) casos ocorreram logo após a alta hospitalar e exigiram antibioterapia prolongada. Todos os doentes recuperaram bem, sem lesões sequelares.

**Conclusão:** Os resultados obtidos demonstram que as complicações orbitárias da sinusite respondem bem à terapêutica médica e os doentes frequentemente recuperam sem comorbilidades locais. O acompanhamento clínico destes doentes durante os primeiros meses após a alta hospitalar é essencial para evitar recidivas precoces.

**Palavras-chave:** complicações; doença orbital; sinusite

## INTRODUCTION

Acute sinusitis is responsible for up to 82% of cases of orbital infection.[1] Before the widespread use of antibiotherapy, 17% of patients affected by orbital cellulitis died from meningitis and 20% suffered permanent visual loss.[2] Orbital complications can occur either directly through a defect in the lamina papyracea or from an septic emboli.[3] Diagnosis is usually established through the combination of clinical examination and radiologic findings.[4] Chandler's classification (**Table 1**), published fifty years ago, still represents the most complete and popular classification of orbital infection severity.[5]

The best pharmacological modality for these patients remains controversial, and the optimal surgical approach has been debated, especially since the widespread use of endoscopic nasal surgery.[6] The aim of this study was to analyze the outcomes of patients admitted to the Department of Otorhinolaryngology of our institution with orbital complications due to acute sinusitis over an eight-year period.

**Table 1 –** Chandler classification

| Category | Group |
|---|---|
| Inflammatory edema (Preseptal cellulitis) | 1 |
| Orbital cellulitis | 2 |
| Subperiosteal abscess | 3 |
| Orbital abscess | 4 |
| Cavernous sinus thrombosis | 5 |

## MATERIAL AND METHODS

A retrospective review of medical records of all children (age <18 years) diagnosed with orbital complications of acute sinusitis admitted to our hospital department between 2010 and 2017 was conducted. Data retrieved included demographics, clinical signs and symptoms, laboratory study, radiologic evidence of orbital inflammation and sinusitis, treatment with intravenous antibiotic, and surgical intervention.

Stata® 15.0 was used for data descriptive and analytical statistics. Associations between dichotomic variables were assessed with chi-squared test (or Fisher's exact test, when applicable), and continuous measures were compared using a two-sample student t- test. Statistical significance was set at 0.05.

## RESULTS

A total of 64 children were admitted to our institution between January 2010 and December 2017, with a mean age of 9 ± 4.7 (range 1-17) years and predominantly (62.5%) male. Most patients were admitted during winter months (57.8%) and 65.6% were not under any medication on admission (**Table 2**).

Clinical findings are resumed in **Table 3**. Most patients were admitted with rhinorrhea (78.1%) and only 46% presented with fever. Patients with rhinorrhea tended to be admitted earlier to the Emergency Department compared with patients without this symptom (2.6 vs. 4 days, respectively; p=0.05). Ocular signs were uncommon, with ocular pain being the most relevant ophthalmologic sign (31.8%), followed by ophthalmoplegia, diplopia, and proptosis. Computed tomography (CT) scan was performed in 65 (87.5%) patients, with ethmoidal and maxillary being the most commonly affected sinuses (95.6% and 96.4%, respectively; **Table 4**) . Frontal disease was more prevalent in older patients (11.0 ± 4.0 vs. 7.9 ± 4.2; p=0.01). Lund-Mackay score was used for sinusitis radiologic staging, showing a mean value of 10.6 ± 5.0 (range 3-23) and inverse correlation with age (p=0.01). Most (53.8%) patients with proptosis on admission presented abscesses in CT scan (p=0.001). Laboratory findings showed a mild rise in white blood cells (15.5 ± 4.0 x 109/L) and C-reactive protein (10.5 ± 9.0 mg/L; **Table 4**).

Cellulitis was the most prevalent complication in this patient population (**Table 5**). Thirty-six patients (56.3%) developed preseptal

(Chandler type I) and 16 patients postseptal (Chandler type II) cellulitis. Overall, 12 patients (18.8%) presented subperiosteal (n=7) or orbit (n=5) abscesses. Two patients with orbital abscesses developed intracranial complications: cerebral abscess in one patient and cavernous sinus thrombosis in another patient.

Treatment predominantly included high doses of intravenous ceftriaxone combined with other drugs (flucloxacilin, clyndamicine, or metronidazole; **Table 6**). Sixty-one (95.3%) patients received concomitant intravenous corticotherapy. Patients exclusively treated with medical therapy had a lower mean age (8.75 ± 4.8 years; p>0.05). Only four patients, with a mean age of 12.8 ± 3.0 years, required surgical drainage, three of whom with external approach and one with combined approach. Two of these patients presented positive culture, one for Fusobacterium necrophorum and the other for Streptococcus constellatus. The mean length of hospital stay was 8.0 ± 5.5 days (range 2-38), and was longer in patients submitted to surgery (11.3 ± 2.9 vs. 7.8 ± 5.6 days in patients undergoing pharmacotherapy, p >0.05) and in older patients (R=0.2546, p= 0.04).

Seven patients (10.9%) recurred shortly after hospital discharge (mean 10.6 ± 7.3 days) due to relapse of orbital signs and were submitted to a longer period of parenteral antibiotherapy, with full recovery. Programmed adenoidectomy was performed in two of these patients (with five and eight years, respectively), and functional endoscopic sinus surgery was performed in a 13-year-old patient to improve nasal breathing.

**Table 2 –** Epidemiological characteristics of the study population

| | | |
|---|---|---|
| **Age (years), Mean ± standard deviation (range)** | | 9 ± 4.7 (1-17) |
| **Gender** | **Male, n (%)** | 40 (62.5) |
| | **Female, n (%)** | 24 (35.5) |
| **Season** | **Spring, n (%)** | 13 (20.3) |
| | **Summer, n (%)** | 7 (10.9) |
| | **Autumn, n (%)** | 7 (10.9) |
| | **Winter, n (%)** | 37 (57.8) |
| **Antibiotherapy on admission, n (%)** | | 22 (34.4) |

**Table 3 –** Clinical findings

| | |
|---|---|
| **Headache, n (%)** | 27 (42.6) |
| **Rhinorrhea, n (%)** | 50 (78.1) |
| **Fever, n (%)** | 29 (46.0) |
| **Periorbital edema, n (%)** | 64 (100) |
| **Proptosis, n (%)** | 8 (13.0) |
| **Ocular pain, n (%)** | 20 (31.8) |
| **Ophthalmoplegia, n (%)** | 12 (19.7) |
| **Diplopia, n (%)** | 9 (15.5) |

**Table 4 –** Imaging and laboratory study

| | | |
|---|---|---|
| **CT scan** | Ethmoidal, n (%) | 53 (94.6) |
| | Maxillary, n (%) | 54 (96.4) |
| | Frontal, n (%) | 34 (60.7) |
| | Sphenoidal, n (%) | 24 (42.9) |
| | Lund-Mackay Score, mean ± standard deviation (range) | 10.6 ± 5.0 (3-23) |
| **Laboratorial evaluation** | Leucocyte count (x$10^9$/L), mean ± standard deviation (range) | 15.5 ± 4.0 (9-25) |
| | C-reactive protein (mg/L), mean, ± standard deviation (range) | 10.5 ± 9.0 (1-36) |

**Table 5 –** Orbital complications

| | |
|---|---|
| **Preseptal cellulitis, n (%)** | 36 (56.3) |
| **Postseptal cellulitis, n (%)** | 16 (25.0) |
| **Subperiosteal abscess, n (%)** | 7 (10.9) |
| **Orbital abscess, n (%)** | 5 (7.8) |

**Table 6 –** Medical therapy

| | | |
|---|---|---|
| **Intravenous antibiotherapy** | ceftriaxone plus flucloxacillin, n (%) | 4 (6.3) |
| | ceftriaxone plus flucloxacillin plus metronidazol, n (%) | 2 (3.1) |
| | ceftriaxone plus clindamycin, n (%) | 15 (23.4) |
| | cefuroxime plus clindamycin, n (%) | 1 (1.6) |
| | cefuroxime, n (%) | 9 (14.1) |
| | cefuroxime plus metronidazol (%) | 2 (3.1) |
| | amoxicillin/clavulanate acid, n (%) | 7 (10.9) |
| | ceftriaxone, n (%) | 22 (34.4) |
| | ceftriaxone plus vancomycin, n (%) | 2 (3.1) |
| **Intravenous corticotherapy, n (%)** | 61 (95.3) | |

## DISCUSSION

Ethmoid sinuses are separated from the orbit by the lamina papyracea, a paper-thin layer that contains many perforations for nerves and blood vessels, as well as some natural dehiscences.[7] Ethmoidal and maxillary sinuses are usually the only cavities present in childhood, and complicated sinus infections mainly result from disease in these sinuses. The orbit is a cone-shaped structure lined by periosteum and surrounded by paranasal sinuses. The orbital septum is a thin connective tissue membrane that separates the superficial portion of the lids (preseptal region) from the deeper orbital structures (postseptal region). Preseptal infection usually only results in cellulitis. However, postseptal infection can evolve from cellulitis to an abscess collection, either intraconal (orbital), extraconal (SPA), or intracranial (directly or through cavernous sinus thrombosis).[8-9] Sinus involvement and orbital extension can be difficult to predict based only on clinical examination, and account for the high number of patients (87.5%) evaluated with CT scan in the present study. Patients in this retrospective cohort were slightly older (mean age of 9 ± 4.7 years) compared with other studies,[1,10-13] what may explain the high prevalence (60.7%) of frontal sinus involvement found. In agreement with the results obtained, other authors have also reported a strong statistical correlation between ophthalmoplegia and proptosis and presence of orbital abscesses.[1,2,7,12] Gonçalves R et al. investigated a group of 110 children and found that ophthalmoplegia ($p < 0.001$) and proptosis ($p < 0.001$) were significant features for post-septal infections.[7] Although abscess volume was not measured in the present study, bigger abscesses are more prone to surgical drainage, with abscesses larger than 1.250 $mm^3$ likely requiring surgical drainage, according to Todman MS and colleagues.[12-15]

Management of these patients remains a critical issue. Several studies reported a high percentage of patients successfully treated with medical therapy only,[4,11,14,16,17] in agreement with findings from this study. Parenteral therapy should include broad-spectrum agents, with some authors recommending maintaining it for up to 2–3 weeks.[18] Itzhak Brook recommended an association with a beta-lactam/beta-lactamase inhibitor (e.g., ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam), a carbapenems (e.g. imipenem, meropenem), or a third-generation cephalosporin (e.g. ceftriaxone, cefotaxime) and metronidazole or clindamycin to cover anaerobic bacteria.[19] In this study, patients were preferentially treated with high doses of ceftriaxone, associated with metronidazole or clindamycin in cases of high suspicion of abscess.

Improvement can be assessed by clinical (decrease of ocular edema, erythema, and discomfort) and laboratory progress, with serial CT scans not recommended, for not being a reliable indicator of clinical improvement.[5,9,12] In this study, all patients requiring surgery were above nine years of age. However, results in the literature remain inconclusive regarding age as a potential risk factor for surgical therapy. The odds ratio for requiring surgical treatment increase by 1.5 with each year of age above 5 ($p=0.004$, 95% CI 1.33-1.89), according to a study by Ryan J et al.[14,17] However, another study reported that age was not a predictor of surgical intervention,[13] in agreement with results from the present study. Sciarretta et al. proposed that surgical treatment should be guided by Chandler system score (**Table 1**), as stage I and stage II are usually best managed with medical therapy

and other stages usually require surgical approach to clear the purulent collection.[1] Regular evaluation of these patients is critical, as failure to improve after the first 48 hours likely reflects treatment failure and need for surgical intervention.[2]

## CONCLUSION

This eight-year experience indicates that early diagnosis and prompt institution of appropriate intravenous antibiotic therapy in hospitalized children with orbital complications of acute sinusitis can lead to favorable clinical outcomes without surgical intervention in most children. All patients should be closely monitored with serial ophthalmologic examination, and any deterioration should lead to timely drainage.

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# ORIGINAL ARTICLES

## DRAVET SYNDROME – EXPERIENCE OF A NEUROPEDIATRIC UNIT

### SÍNDROME DE DRAVET – EXPERIÊNCIA DE UMA UNIDADE DE NEUROPEDIATRIA

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## ABSTRACT

**Introduction:** Dravet syndrome (DS) is a rare and complex genetic epilepsy syndrome. The first seizures are generally induced by fever in the first year of life of a previously healthy child, and the condition is typically associated with impaired psychomotor development.

The authors present a clinical review of DS patients followed at a Neuropediatric Unit of a level III Pediatric Hospital.

**Material and methods:** Retrospective study of pediatric patients with DS followed at a Neuropediatric Unit between 2001 and 2019.

**Results:** Twenty-two patients were diagnosed and followed in this institution. The median (interquartile range [IQR]) age at first seizure was 4.5 (4-5.75) months, which was described as generalized tonic-clonic, focal seizure, or focal to bilateral tonic-clonic seizure, and 95% of patients had fever during this first episode. Neuroimaging and first electroencephalogram (EEG) were normal in all patients. SCN1A gene mutations were detected in 21 (95%) patients. All patients underwent multiple antiepileptic drug (AED) regimens. Psychomotor development was delayed in 20 (91%) patients, and 13 (59%) presented ataxia. At the end of follow-up, the median (IQR) age was 19 (8-23) years, with no reported deaths.

**Discussion:** The characteristics of the first DS seizures are crucial for diagnosis, which can be supported by genetic sequencing, with most patients presenting an SCN1A gene mutation. Neuroimaging and EEG are typically normal at disease onset, but most patients present EEG abnormalities over time. Seizure management can be challenging, requiring a combination of multiple AEDs.

**Conclusion:** DS is a progressive disease associated with poor cognitive and motor skill outcomes, resulting in great morbidity. Early diagnosis can help avoid unnecessary studies, optimize the therapeutic strategy, allow genetic counseling, and improve long-term outcomes.

**Keywords:** Dravet syndrome; SCN1A gene; severe myoclonic epilepsy in infancy

## RESUMO

**Introdução:** A síndrome de Dravet (SD) é uma síndrome epilética genética rara e complexa. As primeiras crises são habitualmente induzidas por febre no primeiro ano de vida de crianças previamente saudáveis e a doença está tipicamente associada a atraso no desenvolvimento psicomotor.

Os autores apresentam uma revisão clínica de doentes com SD seguidos numa Unidade de Neuropediatria de um Hospital Pediátrico de nível III.

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**Material e métodos:** Estudo retrospetivo de doentes pediátricos com SD seguidos numa Unidade de Neuropediatria entre 2001 e 2019.

**Resultados:** Vinte e dois doentes foram diagnosticados e seguidos na instituição. A mediana de idades aquando da primeira crise foi de 4.5 meses (intervalo interquartil [IQR] 4-5.75 meses), que foi descrita como tónico-clónica generalizada, focal ou focal com evolução para tónico-clónica bilateral, e 95% dos doentes apresentaram febre associada. O estudo de neuroimagem e o primeiro eletroencefalograma (EEG) foram normais em todos os doentes. Vinte e um doentes (95%) tinham mutação no gene SCN1A. Todos os doentes foram submetidos a múltiplos esquemas de antiepiléticos. Verificou-se atraso do desenvolvimento psicomotor em 20 (91%) doentes e 13 (59%) apresentaram ataxia. No final do período de seguimento, a mediana (IQR) de idades foi de 19 (8-23) anos, não tendo sido reportadas mortes.

**Discussão:** As características das primeiras crises de SD são essenciais para o diagnóstico, o qual pode ser apoiado por estudo genético, com a maioria dos doentes a apresentar mutações no gene SCN1A. Na apresentação, o estudo de neuroimagem e EEG são tipicamente normais, mas a maioria dos doentes apresenta alterações no EEG ao longo do tempo. As crises podem ser de difícil controlo e requerem o uso de múltiplos antiepiléticos.

**Conclusão:** A SD tem um carácter progressivo e está associada a mau prognóstico cognitivo e motor, resultando em grande morbilidade. O diagnóstico precoce pode evitar investigação desnecessária, ajudar a otimizar a estratégia terapêutica, permitir o aconselhamento genético e melhorar os resultados a longo prazo.

**Palavras-chave:** epilepsia mioclónica grave da infância; gene SCN1A; síndrome de Dravet

## INTRODUCTION

Dravet syndrome (DS) is a genetic epilepsy syndrome characterized by a variety of drug-resistant seizures. It has an estimated incidence between 1:15700 and 1:40000 live births and affects both genders equally.[1–4] It was first described in 1978 by Charlotte Dravet under the name of "severe myoclonic epilepsy in infancy", and several classification reviews have been proposed since.[5] In 1989, it was classified by the International League Against Epilepsy (ILAE) as an antiepileptic drug-resistant seizure entity.[6] The first seizure is typically induced by fever in the first year of life of a previously healthy child and often leads to severe motor and cognitive impairment. It can emerge with temperature-sensitive seizures, including generalized tonic-clonic and unilateral clonic seizures, but other seizure types may follow. Electroencephalogram (EEG) and neuroimaging, including magnetic resonance imaging (MRI), are frequently normal at disease onset, making diagnosis challenging, with some abnormalities only becoming evident during the course of the disease.[1,5,7]

Most (70-85%) DS patients present heterozygote loss-of-function mutations in the voltage-gated sodium channel type I alpha subunit gene SCN1A on chromosome q2.[1,2,8] More than 700 mutations randomly distributed along the SCN1A gene have been identified, with most being *de novo* mutations, although familial or germline mutations are found in 5-10% of cases.[1,9]

DS diagnosis is clinical, and even though genetic testing for SCN1A mutations is recommended, it is not required for diagnosis.[1,10]

The authors present a clinical review of DS patients diagnosed at a Neuropediatric Unit of a level III Pediatric Hospital.

## MATERIAL AND METHODS

A retrospective descriptive study was conducted by reviewing all medical records of pediatric patients with a clinical diagnosis of DS according to Wirrell *et al* (2017) consensus, supported or not by genetic testing, followed at the Neuropediatric Unit of a level III Pediatric Hospital between 2001 and 2019.[10] Demographic, clinical, and neuroimaging data were analyzed. Descriptive analysis was performed with SPSS (*v23*).

## RESULTS

During the 20-year period considered, 22 patients were diagnosed with DS and followed in the study institution, 14 (64%) of whom were female. At the end of follow-up, the median (interquartile range [IQR]) age was 19 (8-23) years, with the oldest patient having 31 years and eleven patients (45%) being under 18 years of age. The median (IQR) follow-up time was 11 (5-18) years, with no reported deaths.

Seven (32%) patients had first or second-degree relatives diagnosed with epilepsy (4; 18%) or febrile seizures (3; 14%). None had developmental delay or other conditions before first seizure onset.

The median (IQR) age at first seizure was 4.5 (4-5.75) months, with all patients presenting the first seizure before the age of nine months. First seizures were described as generalized tonic-clonic, focal, or focal to bilateral tonic-clonic. Thirteen patients (65%, 13/20 - 2 clinical records with missing data) were hospitalized at first seizure, and five (25%, 5/20) evolved to status epilepticus requiring treatment in an Intensive Care Unit. Nineteen patients (95%, 19/20) had febrile

illness at first seizure. Neuroimaging with CT scan and first EEG were normal in all patients. Twelve patients (52%) started an antiepileptic medication after the first seizure.

During the following years, the course of disease was characterized by myoclonic, atonic, focal, and generalized seizures resistant to antiepileptic therapies. All patients had seizures with fever at some point during follow-up, and 19 (86%) also had seizures without fever.

Follow-up neuroimaging with MRI was performed in all patients. Two (9%) showed abnormalities described as supra and infratentorial cortical/subcortical atrophy and hippocampal abnormalities consistent with left hippocampal sclerosis. Twenty patients (91%) had EEG abnormalities at some point, presenting as diffusely slow background and multifocal or generalized interictal discharge, and two patients with one and three years old had normal EEG.

Genetic analysis was performed in all patients, with 21 (95%) presenting SCN1A gene mutations in gene sequencing. Despite the clinical diagnosis, SCN1A mutations were not detected in one patient.

All patients underwent multiple antiepileptic drug (AED) regimens, with combinations of two or more AEDs. All patients were treated with valproic acid, 21 (95%) with topiramate, 15 (68%) with clobazam, and 10 (45%) with stiripentol. Several AED combinations were used, with cannabidiol being used in one patient. Only two (9%) patients were seizure-free by the end of follow-up.

Psychomotor development was delayed in 20 (91%) patients. The two patients without psychomotor delay were one and three years old at the end of follow-up. In six (27%) patients, psychomotor development was severely impaired. Autism spectrum disorder was present in five (23%) patients, and seven (32%) had behavior problems reported by parents. Severe motor deficits were evident throughout the course of disease in most patients, with 13 (59%) presenting ataxia at the end of follow-up.

## DISCUSSION

Infants with DS are usually previously healthy, without significant pathological history, and with normal psychomotor development during their first year of life, as observed in all patients in the present cohort.[1] Most series report a balanced gender proportion or 1:2 female:male ratio, in contrast to the 1.75:1 female:male ratio observed in this series.[10,11]

DS usually starts with fever-induced seizures, mostly related to infectious disease or vaccination in the first year of life, as observed in almost all patients in this study.[10,12] The exception was one patient who did not initially present fever-induced seizures but whose following episodes were triggered by fever, in agreement with other DS series.[1] During follow-up, most (87%) DS patients in this cohort also had seizures without documented fever.

The median age at presentation was around five months, consistent with the typical age of onset described by Charlotte Dravet and other authors.[1,10] Features of the first seizures are relevant for diagnosis. These may be generalized tonic-clonic, hemiclonic, or other focal seizures, and can evolve to status epilepticus, what explains that 65% of patients were hospitalized and 26% required intensive care at onset. DS can later present as pleomorphic epilepsy, exhibiting other seizure types, including myoclonic and atypical absence seizures.[1,2,10,13]

Several studies report a family history of febrile seizures or epilepsy in more than 25% of DS patients, which was also verified in seven (32%) patients in this study.[2,9,10,12]

Wirrell *et al.* (2017) consensus suggests that genetic testing should be performed in children aged less than 12 months with normal development, normal MRI, and no known seizure etiology who present with more than two prolonged (> 15 minutes) generalized febrile seizures.[10] In the present cohort, genetic sequencing revealed SCN1A mutations in 95% of patients. Loss-of-function mutations in the SCN1A gene are reported in most DS patients and, although some (few) patients do not present with SCN1A abnormalities, they may have exon deletions or chromosomal rearrangements involving the same gene.[1,2,8,14] Other genes (not always studied in this cohort) have been identified in patients with DS phenotype, including PCDH19, SCN1B, GABRA1, STXBP1, CHD2, SCN2A, HCN1, KCNA2, and GABRG2.[1,15] SCN1A mutations are also associated with Genetic Epilepsy with Febrile Seizures Plus (GEFS+), and seem to present phenotypic variability.[1] Furthermore, some authors suggest that the nature of a mutation may affect disease phenotype, age at seizure onset, seizure type, severity, and cognitive outcomes.[1,8]

Neuroimaging was performed in all patients, initially by CT scan and later by MRI, and was normal in all patients at presentation. However, during follow-up two patients presented abnormalities consistent with those described in some DS cases, including mild generalized atrophy and hippocampal sclerosis.[10,16] Prolonged seizures appear to cause acute hippocampal injury and may cause the development of sclerosis several months or years later, as reported by Siegler *et al.* (2005).[17] Striano P. *et al.* (2007), on the other hand, reviewed data of 58 DS patients that did not support the association between prolonged febrile seizures and hippocampal sclerosis.[16] Therefore, this subject remains controversial.

Interictal EEG, including wakefulness and sleep, is usually normal or nonspecific at disease onset and during the first year of life, as observed in the present patient population. Over time, 91% of patients presented abnormalities, like diffusely slow background and multifocal or generalized interictal discharges. Typically, and particularly during the second year of life, interictal diffuse background slowing, generalized spikes and waves, and focal or multifocal abnormalities start to emerge and can be more frequent as the disease evolves.[7,12,18,19]

DS patients typically do not respond to classical AEDs. Valproate (VPA) is usually the first AED administered to infants with seizures and was administered to all patients in this cohort at some point. Nevertheless, there is the need to combine other AEDs when further seizures occur.[1,10,18,20] Benzodiazepines like clobazam are often used in

combination with VPA. Like VPA, evidence for the use of clobazam is mostly based on expert opinion.[10,18] Frequently, there is the need to combine other AEDs with those drugs, like topiramate or stiripentol.

Topiramate can lead to good generalized and focal seizure control, with some studies reporting >50% seizure reduction in 35–78% of DS patients.[18,21,22] It has been commonly used since FDA approval in 1996 as an adult AED, namely in children over two years, and was one of the most used AEDs in this study, despite being currently recommended as second-line therapy after stiripentol, a more recent drug.[18,20,23]

Stiripentol, approved in Europe as adjunctive therapy in DS in 2007, acts as an allosteric modulator of the γ-aminobutyric acid (GABA) A receptor and increases clobazam metabolite concentration. It is associated with a significant reduction in the frequency of seizures (50% reduction in around 71% of patients), status epilepticus (50% reduction in 41% of patients), hospitalizations, and use of rescue medication, when used as adjunctive therapy. It is currently one of the first options, as adjunctive therapy to VPA and/or clobazam.[10,18,20] Because stiripentol is a relatively new drug and this is a retrospective study of patients over the last 20 years, this agent has not been widely used in patients included in this cohort.

Cannabidiol was only authorized in Portugal for DS patients at the beginning of 2019 and it was administered in one patient. In a trial of cannabidiol for DS patients, Devinsky O. *et al.* (2017) showed a ≥50% reduction of convulsive seizure frequency in 43% of patients receiving the drug compared to 27% receiving placebo.[24] In an extension of the previous trial (GWPCARE1 Part B), the authors evaluated long-term cannabidiol outcomes and showed a median reduction of 38% to 44% of convulsive seizures and 39% to 51% of total seizures compared to baseline. New therapies, like fenfluramine, also show promising results. In the study by Lagae L. *et al.* (2019), this drug significantly reduced mean monthly convulsive seizure frequency in 32.4−62.3% compared to placebo. Nabbout R. *et al.* (2020) reported a 54.0% reduction in the mean monthly convulsive seizure frequency in DS patients taking stiripentol-containing AED regimens, with patients presenting only mild adverse effects and no cardiovascular events.[23,25,26]

Although not evaluated in this case series, other therapeutic options, like ketogenic diet, have also shown effectiveness in seizure control in 35–70% of patients and could be considered a second-line option, with positive impact on cognition and behavior.[10,18] Surgical therapies, like vagus nerve stimulation, can be offered to patients after failure of first- and second-line therapies, despite low-to-moderate impact on seizure reduction.[10,18,20] Gene therapies, such as ataluren and anti-natural antisense transcripts (AntagoNAT), represent promising new treatment options for DS patients.[18,27]

Cognitive outcomes are typically poor in DS patients, with mild to severe intellectual disability and language impairment. After emerging in apparently normal infants, cognitive impairment gradually becomes more evident after the second year of life and seems to be related to epilepsy severity during the first two years of life.[1,12,28] In this cohort, most patients (91%) presented neurodevelopmental abnormalities, and a significant number (27%) was severely impaired, with significant comorbidities. Behavioral disorders, including autism, were reported in a significant number of patients, similarly to other DS series.[1,2,28,29]

Motor skills often become compromised as the child grows. Hypotonia is the earliest sign, detectable around one year of age, and can be responsible for further orthopedic problems. Ataxia appears when patients start to walk, presenting as walking delay and evolving to unsteady, wide-based stance and poorly coordinated movements. Similar to other series, ataxia was reported at the end of follow-up in 57% of patients in this study. A combination of pyramidal signs, tremors, impaired fine motor skills, and ataxia often become more perceptible through time.[1]

DS children have an increased risk of premature death, with a calculated 15% risk of death within ten years after diagnosis and a median age at death of seven years. The most common death causes are Sudden Unexpected Death in Epilepsy (SUDEP) and status epilepticus.[2,18,29–31] In this study, no patient died until the end of follow-up. Nonetheless, close follow-up and family education are key to preventing premature deaths.

## CONCLUSION

This study described the demographic characteristics, clinical presentation, and evolution of a cohort of DS patients. A different gender proportion was found compared to other DS series, but the sample included was relatively small. Patients had their first seizure during the first year of life and the disease progressed over time, requiring several AED combinations and experiencing significant morbidity. Early diagnosis may help avoid unnecessary investigations, optimize therapeutic strategies, allow genetic counseling, and improve long-term outcomes.

New therapeutics have shown encouraging results and should be offered to DS patients with difficult seizure control.

There is the need for prospective studies with large patient series, investigating disease onset and clinical evolution to clarify DS outcomes.

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# ORIGINAL ARTICLES

## RECURRENT PAROTITIS IN CHILDREN - CASE SERIES AND LITERATURE REVIEW

### PAROTIDITE RECORRENTE EM CRIANÇAS - CASUÍSTICA E REVISÃO DA LITERATURA

Ana Raquel Mendes[1], Liane Moreira[2], Ângela Dias[2], Andreia Lopes[2], Ana Luísa Lobo[2], Teresa São Simão[2]

#### ABSTRACT

**Introduction:** Recurrent parotitis is defined as the occurrence of two or more episodes of the parotid gland. Several etiologies should be addressed in the approach to these patients. The aim of this study was to investigate the clinical, laboratory, and imaging profile of children with recurrent parotitis.

**Material and Methods:** Retrospective review of the medical records of patients referred to a Pediatric Outpatient Clinic between January 2013 and June 2018.

**Results:** The medical records of 24 patients with recurrent parotitis (66.7% male) and a mean age of seven years and five months were reviewed. The median age of onset of episodes was five years and three months. Unilateral and non-febrile episodes prevailed. Non-steroidal anti-inflammatory drugs were universally used to treat symptoms. Non-acute parotid and neck ultrasound predominantly showed the presence of a heterogeneous gland (57.1%). Sialography performed in five patients suggested chronic parotitis in two and Sjögren syndrome/sarcoidosis in one. No significant immunologic defects were found beside a mild C3 reduction in one patient and C4 reduction in another patient, apparently without clinical relevance. A single patient tested positive for antinuclear antibodies. Immunoglobulin A deficit was found in one case. The most common final diagnosis was juvenile recurrent parotitis (37.5%).

**Conclusions:** Most cases of recurrent parotitis in pediatric age have benign etiology. A more judicious request of complementary exams in the acute and non-acute phases could be time- and cost-effective.

**Keywords:** etiology; follow-up; recurrent parotitis

#### RESUMO

**Introdução:** A parotidite recorrente é definida como a ocorrência de dois ou mais episódios de inflamação da glândula parótida. Várias etiologias devem ser consideradas na abordagem a estes doentes. O objetivo deste estudo foi investigar o perfil clínico, laboratorial e imagiológico de crianças com parotidite recorrente.

**Material e Métodos:** Análise retrospetiva dos processos clínicos de doentes referenciados a uma consulta de Pediatria entre janeiro de 2013 e junho de 2018.

**Resultados:** Foram revistos os processos clínicos de 24 doentes com parotidite recorrente (66,7% do sexo masculino), com uma idade média de sete anos e cinco meses. A idade mediana de início dos episódios foi de cinco anos e três meses e predominaram os episódios unilaterais e não-febris. Foram universalmente utilizados anti-inflamatórios não-esteroides no tratamento sintomático. A heterogeneidade

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da glândula foi o padrão predominante na ecografia parotídea da fase não-aguda (57,1%). Foi realizada sialografia em cinco doentes, tendo sido sugestiva de parotidite crónica em dois e de síndrome de Sjögren syndrome/sarcoidose em um. Não foram identificados defeitos imunológicos significativos, exceto uma discreta diminuição do valor de C3 em um doente e de C4 em outro, sem relevância clínica. Foram identificados anticorpos antinucleares positivos num doente e défice de imunoglobulina A noutro. O diagnóstico final mais prevalente foi parotidite recorrente idiopática.

**Conclusão:** A maioria dos casos de parotidite recorrente em idade pediátrica é de etiologia benigna. Uma requisição mais criteriosa de exames complementares na fase aguda e não-aguda pode ser mais eficaz a nível de tempo e custos.

**Palavras-chave:** etiologia, parotidite recorrente, seguimento

## INTRODUCTION

Parotitis is defined as an inflammation of the parotid gland, characterized by swelling with or without pain, which can be accompanied by fever and malaise. It is usually associated with non-obstructive and non-suppurative sialectasis of the parotid gland.[1] The condition is defined as recurrent when two or more episodes occur without a defined time interval. Episodes are usually unilateral, but bilateral episodes can occasionally occur, with more prominent symptoms on one side.[2] Male are usually more affected than females, with a peak incidence between the ages of three and six years. Most patients experience complete and spontaneous resolution in the second decade of life.[1]

Although parotitis etiopathology remains unclear, a multifactorial origin, as suggested by Chirte and Premchandra is the present consensus.[1] The incidence of epidemic parotitis in Portugal has substantially decreased after the universal introduction of a vaccine. Consequently, recurrent idiopathic parotitis is currently considered the most common cause of parotid swelling. However, when approaching a patient with recurrent parotitis, various underlying causes have to be addressed (**Table 1**).

The diagnosis is based on clinical features, but imaging exams can be used to confirm it. Treatment aims at symptomatic relief (analgesics, sialogogues, massage, mouth rinses, oral hydration). In some cases, the use of antibiotics can be considered. A more aggressive approach to parotidectomy is reserved for serious situations that persist into adulthood.[3-4]

The aim of this study was to investigate the clinical, laboratory, and imaging profile of children with recurrent parotitis.

**Table 1-** Recurrent parotitis etiologies[4-5]

| |
|---|
| **Recurrent idiopathic parotitis** |
| **Canalicular malformations** |
| Congenital or acquired |
| **Bacterial infections** |
| *Staphylococcus aureus* |
| **Viral infections** |
| *Parainfluenza 1 and 3, Influenza A, CMV, EBV*, Lymphocytic choriomeningitis virus |
| **Hyposalivation** |
| **Immunodeficiency** |
| HIV, Immunoglobulin A deficiency |
| **Autoimmunity** |
| Sjögren´s syndrome, systemic lupus erythematous, sarcoidosis, connective tissue disease |
| **Stensen´s duct obstruction** |
| Lithiasis |
| **Trauma** |
| Pneumoparotitis, animal bites |
| **Tumor** |
| **Congenital** |
| **Allergic** |

ANA, antinuclear antibodies; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ENA, extractable nuclear antigen antibodies; HIV, human immunodeficiency virus

## MATERIAL AND METHODS

A retrospective review of the medical records of patients referred to the Pediatric Outpatient Clinic of a level II hospital due to recurrent parotitis between January 2013 and June 2018 was conducted. Recurrent parotitis was defined by the presence of at least two parotitis episodes. Retrieved data included sex, age, date of first symptoms and referral, referral origin, and number of episodes. Clinical data regarding the presence of unilateral or bilateral swelling, presence of fever, and patients´ immunization status were also assessed. Data of imaging and analytical studies performed and final diagnosis of patients already discharged were also retrieved from medical records. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean (minimum- maximum) or median (percentile 25-75).

## RESULTS

A total of 24 patients, predominantly male (66.7%), were referred to the Pediatric Outpatient Clinic in the considered time period, with a mean age of seven years and five months (minimum 18 months, maximum 14 years and five months). The Emergency Department was the most common referral origin (70.8%), followed by Primary Care (20.8%) and other hospital external consultations (8.3%). All patients had their immunization status updated according to their age. The median number of episodes per patient during follow-up was two (P25-75: two-four), and the median age of the first episode was five years and three months (P25-75: two years and ten months-seven years and six months). The mean number of episodes per year was two (minimum one, maximum five), and most episodes were unilateral (95.8%).

While all patients presented with parotid swelling and pain, only 58.3% of episodes were associated with fever- none presented with purulent discharge or macroscopically visible alterations in the Stensen´s duct ostium.

Acute- phase parotid and neck ultrasound was requested in 21 patients (87.5%) and mostly showed heterogeneous gland and hypoechoic areas in more than half of patients (**Table 2**).

Non-steroidal anti-inflammatory drugs (NSAIDs) were universally used to treat symptoms. Most cases had no associated complications. The only exception was the first episode of acute parotitis in a previously healthy 18-month-old male child, which was complicated with retropharyngeal edema, prompting hospitalization in the Pediatric Care Unit and treatment with intravenous antibiotics and corticoids.

Non-acute phase parotid and neck ultrasound was requested in the non-acute phase in 87. 5% of patients, with a mean interval of five months after the acute episode. Contrarily to the acute-phase ultrasound, the most prominent features were the presence of a heterogeneous gland and of intraparotid lymph nodes (**Table 3**).

Parotid gland sialography was performed in five patients. The previous ultrasound had shown an enlarged parotid gland in two and calcifications in other two patients. Sialography was requested in the fifth patient due to young age of episode onset and high number of episodes. The exam showed alterations characteristic of chronic parotitis in two patients. In one case, an accessory diversification of the Stensen duct giving the appearance of a “tree in blossom” was described. Further investigation directed at Sjögren syndrome and sarcoidosis was suggested, and the patient was referred to a tertiary hospital. Although fulfilling three criteria for Sjögren syndrome diagnosis, he remains asymptomatic and currently maintains annual follow-up.

Magnetic resonance image (MRI) of the neck was performed in two patients after bilateral hypoechogenic areas potentially related to chronic parotitis or granulomatous disease were identified on ultrasound, showing characteristic features of chronic parotitis in one and no alterations in the other.

Among patients who underwent laboratory study, the one with suspected Sjögren syndrome showed immunoglobulin A deficit (**Table 4**) and tested positive for antinuclear antibodies (ANA). One patient had diminished levels of C3 complement, while another had diminished levels of C4 complement. The latter corresponded to the patient who had been admitted at 18 months due to an episode of acute parotitis with retropharyngeal edema. Because both showed only a discrete decrease in C3 and C4 complement levels, laboratory studies were not repeated during follow-up.

Cellular immunity study was performed in three patients, including in the patient with suspicion of Sjögren syndrome and in one patient with a high total number of episodes. One patient showed a mild decrease in T CD4+ cells, an increase in T CD45RO+ cells, and an increase in T CD4-/CD8- cells, possibly related to the recurrent parotitis episodes. No study indicated cellular immunodeficiency.

The most common final diagnosis in patients already discharged was juvenile recurrent parotitis (**Figure 1**). While a fifth of all patients was still under investigation, about a third maintained regular follow-up in the Pediatric Outpatient Clinic, despite inconclusive study up to that point. The median follow-up time was 22.5 months (P25-75: 5.5 – 31.25 months).

**Table 2 -** Imaging features of acute-phase ultrasound exams

| **Feature** | **n (%)** |
|---|---|
| Heterogeneous aspect | 17 (81) |
| Hipoechogenic areas | 13 (61.9) |
| Cervical lymph nodes | 10 (47,6) |
| Intraparotid lymph nodes | 8 (38.1) |
| Vascularization | 4 (19) |
| Chronicity | 2 (9.5) |
| Calcifications | 1 (4.8) |
| Sialectasis | 1 (4.8) |

**Table 3 - Imaging features of non-acute phase ultrasound exams**

| **Feature** | **n (%)** |
|---|---|
| Heterogeneous aspect | 12 (57.1) |
| Intraparotid lymph nodes | 11 (52.4) |
| Cervical lymph nodes | 6 (28.6) |
| Chronicity | 6 (28.6) |
| Hipoechogenic areas | 4 (19) |
| Parotid gland asymmetry | 3 (14.3) |
| Calcifications | 2 (9.5) |
| Sialectasis | 1 (4.8) |

**Table 4 -** Laboratory studies performed

| **Laboratory studies** | **Performed (n)** | **Altered results (n)** |
|---|---|---|
| Complete blood count | 21 | 0 |
| Sedimentation rate | 14 | 1 |
| HIV serology | 8 | 0 |
| EBV serology | 7 | 0 |
| CMV serology | 7 | 0 |
| Mycoplasma + adenovirus serology | 4 | 0 |
| Immunoglobulin | 20 | 1 |
| Auto-antibodies (ANA, ENA, rheumatoid factor) | 20 | 1 |
| C3 and C4 complement | 16 | 2 |

ANA, antinuclear antibodies; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ENA, extractable nuclear antigen antibodies; HIV, human immunodeficiency virus

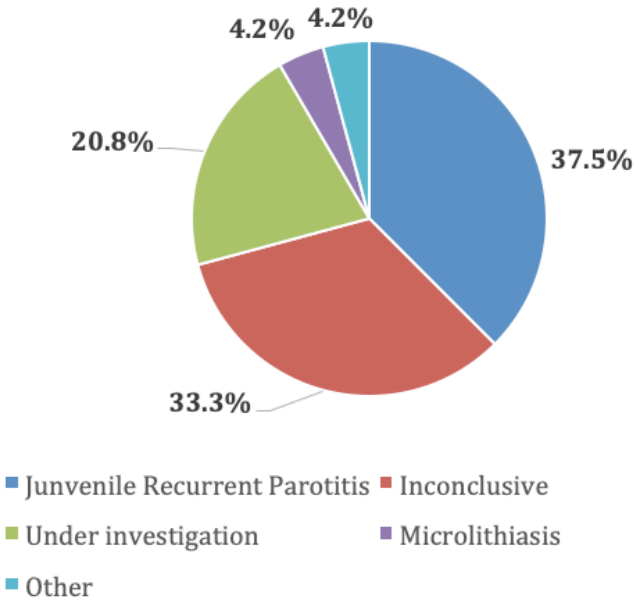


**Figure 1 -** Diagnoses established in the Pediatric Outpatient Clinic (n=24)

## DISCUSSION

Recurrent parotitis onset usually occurs between the ages of three and six years, although cases of earlier or later onset have been described.[6] Ericson *et al*. described a case series with an age of onset between three months and 16 years.[7] In this study, the mean age of onset of episodes was five years and three months, in accordance with the literature, as was the male predominance found.[7]

The frequency of episodes is usually higher in the first school year, with a tendency to decrease until puberty and resolve after puberty.[1] According to Mandel and Kaynar, episodes usually occur one to five times a year, with Henriques *et al*. reporting a medium number of 5.8 episodes/year (mininum one, maximum 18/year).[8,9] The present case series identified a lower incidence of annual episodes.

Symptoms are usually unilateral. When they are bilateral, there is usually a prominent side.[1] Findings of this study agree with this data, as most episodes identified were unilateral.

Painful swelling is frequently associated with fever, as observed in this sample. Most authors report the absence of purulent secretion through the parotid duct ostium, which was also observed in this study. An episode ranging from several days to two weeks was referred to by Henriques et al.[8] The present retrospective analysis did not allow to retrieve data regarding symptom duration.

Parotitis diagnosis is clinical. Ultrasound is the complementary exam of choice to confirm the diagnosis and for regular follow-up of children with recurrent parotitis, as proposed by Shimizu *et al*.[10]

As reported by Rubaltelli *et al*., ultrasounds performed in the non-acute phase usually show an improvement of imaging features, which was observed in the present case series.[11]

If calculi, duct dilatation, cysts, or gland enlargement are identified in ultrasound, sialography is recommended to rule out duct stenosis, obstruction, or other complications.[1] In addition, may play a relevant role in the treatment of patients with obstructive sialadenitis with recurrent infections.[12] However, it should be noted that glandular parenchyma and contralateral gland cannot be evaluated with sialography and that this method is contraindicated during acute episodes. Overall, the use of sialography is discouraged in children with self-limited conditions.[13]

MRI provides a more detailed study of the parenchyma and canalicular system and helps differentiate between acute and chronic inflammatory processes.[4] It is a non-invasive method, but the elevated costs and need to sedate young children pose some limitations.[14] Magnetic resonance sialography is a new non-invasive technique with the purpose of evaluating the ductal system of salivary glands and producing sialographic images without using contrast media or radiation. It may be helpful in atypical cases and cases with bilateral presentation.[13]

Laboratory study should be considered on a case-by-case basis. It is usually indicated in cases of late-onset recurrent parotitis, especially bilateral parotitis, suspicion of underlying chronic disease (Sjögren´s syndrome, systemic lupus erythematous, sarcoidosis) or immunodeficiencies (including acquired immunodeficiency, such as human immunodeficieny virus [HIV]), and in cases of frequent and severe episodes.[1,9] Hence, the initial laboratory workup may include complete blood count, sedimentation rate, immunoglobulins, ANA, extractable nuclear antigen antibodies, and HIV serology.[3,6,9]

Due to uncertainty regarding etiology, there are no universally accepted strategies or treatment guidelines for recurrent parotitis.

Treatment of acute episodes aims at delivering symptomatic relief and preventing damage to the gland.[1] Analgesics and/or antipyretics, adequate oral hygiene, parotid gland massage, warmth, and use of chewing gum and sialogogue agents seem to be helpful in the acute phase.[15] Most authors agree on the use of antibiotics in cases of conservative treatment failure or severe symptoms. In a series of 50 patients, Landaeta *et al*. found out that the most common bacterial pathogens in salivary samples were *Streptococcus pneumoniae, Haemophilus influenzae,* and *Streptococcus viridans.*[16] Consequently, in the absence of evidence of staphylococci, penicillins, cephalosporins, or macrolide may be prescribed, with the first choice usually being aminopenicillin in combination with beta-lactamase inhibitors, as amoxicillin/clavulanic acid.[16]

Surgical treatment includes parotidectomy, which is a relatively invasive procedure and carries the risk of facial nerve paralysis, and thus regarded as a last resort. Parotid duct ligation leading to gland atrophy represents another option and an alternative to parotidectomy in refractory cases. However, the success rate of this procedure is no greater than 50%.[14]

Recent studies suggest that sialendoscopy with steroids instillation may be successful in treating juvenile recurrent parotitis and autoimmune parotitis. According to Canzi *et al*., complete symptom resolution after sialendoscopic treatment was observed in 78% and partial regression in 22% of patients. This type of treatment is generally recommended in cases of frequent recurrence or pronounced symptoms. However, the true value of sialendoscopy in the diagnosis and therapeutic intervention in pediatric recurrent parotitis requires further studies.[17]

In accordance with the literature, juvenile recurrent idiopathic parotitis was the most common diagnosis in this case series. Microlithiasis was the second most common finding. However, compared to the adult population, sialolithiasis or autoimmune disorders are less likely to be the pathologic condition for pediatric recurrent parotitis.[4,5,18]

Recurrent parotitis prognosis depends on the underlying cause. Idiopathic parotitis has a favorable prognosis, with remission after puberty, although according to Cohen *et al*., 10-20% of cases may persist into adulthood.[19]

## CONCLUSIONS

Most recurrent parotitis etiologies in pediatric age are benign, and the most common diagnosis is juvenile recurrent idiopathic parotitis, which is usually a self-limited condition. In this report, the authors intend to remind that a more judicious request of complementary exams in the acute and non-acute phase can be time- and cost-effective. Laboratory and imaging studies should be requested in cases of suspicion of an underlying disease and not as routine studies. Implementation of a standardized approach could be the first step in that direction.

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# REVIEW ARTICLES

## NEEDS AND CONCERNS OF SIBLINGS IN PEDIATRIC PALLIATIVE CARE: SCOPING REVIEW

### NECESSIDADES E PREOCUPAÇÕES DOS IRMÃOS EM CUIDADOS PALIATIVOS PEDIÁTRICOS: *SCOPING REVIEW*

Filipa Martins Silva[1,2]

## ABSTRACT

**Introduction**: Understanding the needs of each family member in the setting of Pediatric Palliative Care is crucial. Sibling support is still an emerging area, with recommendations based on clinical experience and adaptation from other contexts. The aim of this study was to assess and describe the needs and concerns of siblings of children in Pediatric Palliative Care.

**Methods**: A literature search was conducted in Medline database. Only research articles with reports of siblings of children in Palliative Care were included. The main characteristics and results of studies included were summarized, and a narrative synthesis was performed.

**Results:** Nine studies were included showing that, although siblings' needs vary over the course of the disease, these generally include the need for self-support, access to information, and engagement in brother/sister care. Bereaved siblings are usually resilient, but poor-quality support can have a negative psychosocial impact.

**Discussion and Conclusion:** Siblings need informational, instrumental, appraisal, and emotional support. Quantitative prospective studies are needed, as well as accurate clinical practice recommendations taking into account the specificities of each child, family, and sibling.

**Keywords:** adolescent; child; emotional adjustment; palliative care; sibling

## RESUMO

**Introdução:** Compreender as necessidades de cada membro da família em contexto de Cuidados Paliativos Pediátricos é crucial. O suporte aos irmãos ainda é uma área emergente, com recomendações baseadas sobretudo na experiência clínica e adaptadas de outros contextos. O objetivo deste estudo foi analisar e descrever as necessidades e preocupações de irmãos de crianças em Cuidados Paliativos Pediátricos.

**Métodos:** Foi efetuada uma pesquisa bibliográfica na base de dados Medline. Apenas artigos originais com relatos de irmãos de crianças em Cuidados Paliativos foram incluídos. As principais características e resultados dos estudos foram sintetizados, procedendo-se à sua descrição narrativa.

**Resultados**: Foram incluídos nove artigos, cuja análise demonstrou que, embora as necessidades dos irmãos variem ao longo do curso da doença, geralmente incluem a necessidade de suporte para o próprio, acesso a informação e envolvimento no cuidado ao irmão. Os irmãos enlutados são geralmente resilientes, mas um suporte de baixa qualidade pode ter um impacto psicossocial negativo.

**Discussão e Conclusão:** Os irmãos necessitam de suporte informacional, instrumental, de aprovação e emocional. São necessários estudos prospetivos quantitativos, bem como recomendações precisas para a prática clínica que considerem as especificidades de cada criança, família e irmão.

**Palavras-chave:** adolescente; ajustamento emocional; criança; cuidados paliativos; irmão

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## INTRODUCTION

Pediatric Palliative Care (PPC) encompasses an active and global approach to the care of children and young people with life-limiting or life-threatening conditions (LLC or LTC), from the moment of diagnosis or recognition and throughout the child's life until potential death and beyond. It embraces physical, emotional, social, and spiritual elements and focuses on enhancing the quality of life of the child/young person and supporting the family.[1] Conditions in PPC can be grouped in four broad categories: (i) LTC for which there is curative treatment, but it can fail (e.g., cancer, irreversible organ failure of the heart); (ii) LLC with inevitable premature death (e.g., cystic fibrosis, muscular dystrophy); (iii) progressive LLC without curative treatment options (e.g., Batten disease); and (iv) non-progressive, irreversible LLC associated with severe disability, health complications, and premature death (e.g., cerebral palsy).[1] Pediatric conditions requiring palliative care are known to impact the family network.[2,3] Coupled with the threat of premature death, the emotional impact on the family of a lifetime diagnosis in a child is profound.[4] Furthermore, the demands of treatment may be highly disruptive, not only to parents but also to siblings at home.[5] As a result, the family-centered approach in PPC should seek to maintain the integrity of each individual and family as a whole, providing guidance and support through the entirety of child medical care, from diagnosis to end of life and bereavement, and allowing time to prepare for impending challenges. For that purpose, understanding the needs of each family member, including siblings, is fundamental.[3,6]

According to previous studies, siblings of children with cancer do not consistently show elevated rates of psychopathology, but they do have psychosocial needs that should be recognized and addressed, such as loss of needed attention and threatened sense of security within the family.[7,8] The demands of caring for a child with cancer often limit «parents' physical and emotional availability to fully attend the needs of other children». Consequently, recommendations indicate that the extended family, health care professionals, siblings' school staff, and relevant community members should consider the unique needs of siblings, in addition to the needs of the family in general and the health of the child with cancer.[7] Moreover, studies investigating the psychological functioning of siblings of children with chronic illnesses also show a risk of negative psychological effects, demanding intervention programs.[8]

Accordingly, support for siblings in PPC setting is widely recommended.[1] This support should include the identification of increased needs and access to more specialized support when required, assuming that most siblings will cope with upcoming challenges if the appropriate support is given. Bereavement support should also be provided to all children and young people experiencing the death of a sibling.[1] However, sibling support is still an emerging area, and proposed recommendations are based on clinical experience and adaptation from specific settings, as Pediatric Oncology or chronic diseases.[7,8] In fact, although a variety of tools have been developed to assess the needs of caregivers of adult palliative patients, few are in place for siblings of patients in PPC.[6] Overall, there is a lack of primary research on the needs and concerns of siblings of children in PPC. Additionally, no reviews on the topic have been found in a preliminary search in Medline.

The aim of this scoping review was to assess and describe the needs and concerns of siblings of children in PPC, as a greater understanding of this subject may lead to improved sibling support and, eventually, more specific clinical recommendations.

## METHODS

A scoping review was performed based on the methodological frameworks proposed by Arksey and O'Malley[9] and Joanna Briggs Institute.[10] First, the research question was defined: "What should a young researcher in Pediatric Palliative Care know about the needs and concerns of siblings?", pinpointing participants (siblings), concept (needs and concerns), and setting (PPC).

The literature search was conducted in Medline database until December 31, 2020, using the following queries: 1) *("Siblings"[Mesh]) AND ("Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Medicine"[Mesh] OR "Palliative Care"[Mesh] OR "Hospice Care"[Mesh] OR "Terminal Care"[Mesh] OR "Hospices"[Mesh])*; 2) *children palliative care siblings.* The search strategy was limited by publication date (*2000-2020*) and language (*English or Portuguese*).

The following inclusion criteria were used: 1) research articles; 2) studies related to PPC; 3) studies having siblings themselves as study participants (as the evidence shows that children's perspective on their experiences offers useful augmentation to parental proxy reports, which may obfuscate some of the more sensitive issues and opinions);[2] 4) studies with siblings in the pediatric age range at the time of diagnosis. Exclusion criteria applied comprised: 1) studies related to adult Palliative Care; 2) studies whose participants were not siblings themselves (but instead parents, health professionals, etc.); 3) studies not exploring the needs and concerns of siblings in PPC; 4) studies with no abstract available; 5) review articles.

Data about place and date, aim, participants, design/measurements, and main results were retrieved from studies included in the analysis and narratively described.

## RESULTS

The literature search retrieved 151 citations. After exclusion of duplicates, 131 articles were screened for eligibility, resulting in the further exclusion of 122 articles. In the end, nine articles were fully assessed and included in the analysis.

Data are summarized in **Table 1**. Studies included show that perceptions of the condition of the ill child and his/her symptoms, impact on daily life, emotional consequences, and way of coping

seem to be key issues for siblings of children in PPC.[2] Particularly, siblings report the need for their own support,[11] referring engagement in the exchange of information and in care of the brother/sister as relevant to them.[6,11,12] Siblings also report insufficient or poor information regarding the ill child's prognosis and psychological health outcomes, but also where to seek support for themselves.[13] Siblings' needs vary across the course of the disease: the most common problems are initially centered in deriving information to understand what is happening and why, in trying to keep up with self responsibilities (schoolwork) afterward, and in learning to cope with changes in the ill brother/sister in later stages. Regarding end-of-life, relevant concerns experienced by siblings include pain palliation, the ability to provide comfort to the brother/sister, the need to obtain information about death, preparing for death, and obtaining social support and family harmony.[4] Bereaved siblings of cancer patients are generally resilient and, although risky behaviors and psychological distress increase during the year after the brother/sister's death, most return to baseline over time. Siblings who report dissatisfaction with communication, poor preparation for death, missed opportunities to say goodbye, and/or perceived negative impact of the cancer experience on relationships tend to have higher distress and lower social support scores.[5] Furthermore, siblings' perception of a nonpeaceful death and avoidance of physicians, poor medical information, and poor communication about the brother/sister's death with family and friends predicted unresolved grief two to nine years post-loss.[14] On the other hand, supporting the siblings of children with cancer throughout the cancer journey and afterward into bereavement has shown to have a positive buffering effect on their own endurance and personal growth, family cohesion, and social support.[15]

**Table 1 -** Characteristics and main results of studies included in the analysis

| ***Place and Date*** | ***Aim*** | ***Participants*** | ***Design / Measurements*** | ***Main Results*** |
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| *Freeman et al, 2003* | | | | |
| USA<br><br>1999-2000 | Identify the main concerns of children with brain or spinal cord tumors and siblings during different phases of illness.<br><br>*Note: in this review, only results concerning siblings were considered.* | 25 children with brain or spinal cord tumors and 32 siblings (mean age of siblings: 17 years [Standard Deviation (SD) 5.5]; average time from diagnosis to survey: 4.5 years [SD 3.0]; no information on gender). | Participants responded to a survey about health care provider interactions, medical information, health care utilization, and psychosocial aspects, rating individual items as helpful, a problem, and for importance. | The following problems (>30% of siblings) and helpful resources were reported: 1) at diagnosis: lack of information about etiology and prognosis and the manner physician and parents provided information; family and social support, as well as family harmony, were the two most commonly reported helpful resources; 2) during hospitalization/surgery: lack of information about prognosis, lack of help with schoolwork; in addition to family and social support, liberal visitation policies were reported as helpful and very important; 3) after hospital discharge: lack of help with schoolwork; support from friends, family, and religion were helpful and important; 4) during adjuvant treatment: lack of help with changes in sister or brother's appearance, physical activity, mood, and information about the treatment; 5) at end of life: treatment of sister/brother's pain, lack of information about dying, family harmony (although family and social support were reported as the leading helpful resource), support from friends, help with schoolwork, and preparation for the death; their ability to comfort their brother or sister was helpful and important. |
| *Malcom et al, 2013* | | | | |
| UK<br><br>2009-2010 | Report sibling experiences related to two rare degenerative and progressive conditions (Mucopoly-saccharidoses (MPS) and Batten Disease). | 8 siblings of children with MPS (n=7) and Batten Disease (n=1) (mean age: 10.5 years, range 7–12 years; 5 males and 3 females). | Semi-structured qualitative interviews were administered to participants and analysis was informed by grounded theory. | Four key themes demonstrated impact on siblings: 1) perceptions of the condition and its symptoms (siblings often had considerable knowledge of the condition, yet they protected parents from an awareness of how much they knew); 2) impact on daily life (while many spoke affectionately about their caregiving roles – supporting others to care, rather than taking full responsibility-, they also experienced limitations in social activities as a result of their sibling's condition; this was described with acceptance and sadness); 3) emotional consequences (concern often dominated their thoughts, leading to difficulties in concentrating at school and also impacting on their social time with friends; they were also very aware of how worries could reverberate around the family system; siblings were affected by negative social attitudes towards disabilities, namely by peers); and 4) ways of coping (organised sibling support groups were mentioned as important; several siblings described their main sources of support as being family members and friends). |

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| *Gaab et al, 2014* | | | | |
| New Zealand<br><br>2010-2011 | Identify the concerns of siblings of PPC patients. | 18 siblings of PPC patients (aged 9 to 22 years, including bereaved (six months to two years after their sibling's death) and nonbereaved children; no information on gender). | Semi-structured interviews were administered to participants and analysed using qualitative inductive thematic analysis. | Participants held two main concerns: 1) Most siblings felt it was important to discuss the impending death, because it increased their understanding of the situation (this knowledge gave them a greater appreciation of their sibling; a few mentioned anger at being 'left in the dark' or expressed confusion and fear of siblngs' symptoms without having them explained; siblings generally wanted to be informed of their ill siblings' health statuses but did not want death/mortality to be the topic of every conversation); 2) Most siblings expressed the importance of helping the ill child (with practical support such as transporting wheelchairs or fetching medications, but also with games, schoolwork, etc; they helped in order to worry less, provide comfort, keep things positive and normal; they recognized the ill children's needs were greater than their own and most expressed gratitude that the ill children received extra attention). |
| *Rosenberg et al, 2015* | | | | |
| USA<br><br>2008-2009 | Describe the prevalence of risky health behaviours, psychological distress, and social support among bereaved siblings and potentially modifiable factors associated with poor outcomes. | 58 bereaved siblings (mean age at survey: 25.6 years [SD 7.8]; mean age at sibling's diagnosis of cancer: 10.9 [SD 6.2]; mean age at sibling's death: 13.8 [SD 7.3]; on average 11.8 years had passed since their sibling's death [SD 3.2]; 40 females and 18 males). | Survey-based study; linear regression models identified associations between personal perspectives before, during, and after the family's cancer experience and outcomes (health behaviours, psychological distress, and social support). | Anxiety, depression, and illicit substance use increased during the year after the brother/sister's death but then returned to baseline. Siblings who reported dissatisfaction with communication, poor preparation for death, missed opportunities to say goodbye, and/or a perceived negative impact of the cancer experience on relationships tended to have higher distress and lower social support scores.<br><br>Almost all siblings (88%) reported that their loss still affected them; half stated that the experience impacted current educational and career goals (for example, 12% reported that their experience had negatively impacted their work or career, whereas 45% reported a positive impact on work or career). Personal growth was reported in subsets of cases (36% reported that they were better communicators, 43% more mature, 45% more kind-hearted, and 17% more confident than others their age). None of these responses (personal growth, impact on education/career) were related to current distress or social support. |
| *Lövgren et al, 2016* | | | | |
| Sweden<br><br>2009 | Explore bereaved siblings' advice to healthcare professionals (HCP) working with children with cancer and their families. | 108 bereaved siblings (mean age at time of death: 18 years [SD 3.7]; mean age at data collection: 24 years [SD 3.7]; mean time since loss 6.3 years [SD 2.2]; 69 females and 39 males). | Participants answered an open-ended question about what advice they would give to HCP working with children with cancer and their families; responses to this single question were analysed using content analysis. | Six categories of advice were constructed: *1) Siblings' Wish for Own Support* (56%; included support from someone to talk to, support groups, or other kinds of activities for siblings; support in daily life, for example, with homework, school activities, and hobbies); 2) *Siblings' Wish for Information About Their Brother's or Sister's Disease and Care* (31%; siblings felt that information should be given continuously during all the different phases; explanations given in a playful way, such as with illustrations using cartoons and *emojis*, were appreciated more than those given in a more formal way); 3) *Siblings' Wish to Participate in the Care of Their Brother or Sister (*7%; these siblings whished HCP involved them more); 4) *Support and Information to Parents (*3% of siblings suggested that parents should receive information from HCP about how to talk to, help, and involve siblings in their brother's or sister's care); 5) *Advice About the Brother's or Sister's Care* (12%; siblings emphasized the importance of letting the ill brother or sister have a normal life, and of asking them how they wanted to be cared for); 6) *Psychosocial Aspects to Consider in Relation to the Affected Family* (44%; common suggestions were related to positivity, hope, and happiness, but also to realism and honesty). No differences between sexes or age groups in relation to the type of advice were found, except that significantly more women reported advice associated with the wish for own support. |

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| *Eilertsen et al, 2018* | | | | |
| Sweden<br><br>2009 | Explore cancer-bereaved siblings' positive and negative memories and experiences of their brother's or sister's illness and death. | 123 bereaved siblings (between 12 and 25 years old when their brother or sister died and between 19 and 33 at the time of data collection; no further age or gender data). | Participants responded to two open-ended statements, which focused on siblings' positive and negative memories and experiences of illness and death. The data was analyzed using systematic text condensation. | Bereaved siblings have many positive memories and experiences, even though the death of a brother or sister is a distressing and grievous situation; sick siblings, as well as parents, seem to play play important roles in the shaping of their healthy siblings' experiences. The bereaved siblings' responses were categorized into four different themes: 1) *endurance versus vulnerability* (endurance was expressed as the influence that the ill siblings' strong willpower, good mood, and stamina in their difficult situation had on healthy siblings, whereas vulnerability was expressed as the feeling of emptiness and loneliness involved with having an ill and dying sibling); 2) *family cohesion versus family conflicts* (family cohesion was expressed as the bonds being strengthened between family members, whereas family conflicts often led siblings to feel invisible and unacknowledged); 3) *growth versus stagnation* (most siblings expressed the feeling that they grew as individuals in the process of their brother's or sister's illness and death, whereas others experienced stagnation because of the physical and mental distress they bore throughout this time, often feeling forgotten); 4) *professional support versus lack of professional support* (most siblings perceived physicians and staff at the hospital as being warm, kind, and honest, while some siblings had negative experiences). |
| *Lövgren et al, 2018* | | | | |
| Sweden<br><br>2009 | Identify modifiable or avoidable family and care-related factors associated with unresolved grief among cancer-bereaved siblings two to nine years post loss. | 174 cancer-bereaved siblings (mean age at time of death: 18 years [SD 3.7]; mean age at data collection: 24 years [SD 3.8]; 101 females and 73 males). | Participants answered 29 close-ended questions on grief, family and care-related factors, as well as the Hospital Anxiety and Depression Scale. A multivariable prediction model was built. | Several predictors for unresolved grief were identified: siblings' perception that it was not a peaceful death [odds ratio (OR): 9.86, 95% confidence interval (CI): 2.39–40.65], limited information given to siblings the last month of life (OR: 5.96, 95% CI: 1.87–13.68), information about the impending death communicated the day before it occurred (OR: 2.73, 95% CI: 1.02–7.33), siblings' avoidance of the doctors (OR: 3.22, 95% CI: 0.75–13.76), and lack of communication with family (OR: 2.86, 95% CI: 1.01–8.04) and people outside the family about death (OR: 5.07, 95% CI: 1.64–15.70). Depressive symptoms (OR: 1.27, 95% CI: 1.12–1.45) and time since loss (two to four years: OR: 10.36, 95% CI: 2.87–37.48 and five to seven years: OR: 8.36, 95% CI: 2.36–29.57) also predicted unresolved grief. Together, these predictors explained 54% of the variance of unresolved grief. |
| *Wallin et al, 2020* | | | | |
| Sweden<br><br>2009 | Explore cancer-bereaved siblings' advice to peers with a brother or sister with cancer. | 125 cancer-bereaved siblings (mean age at time of brother's / sister's death: 17.9 years [SD 3.6]; mean age at data collection: 24 years [SD 3.8]; 74 females, 51 males). | Participants answered an open-ended question about what advice they would give to peers with a brother or sister with cancer; responses to this single question were analysed using content analysis. | Siblings gave 257 pieces of advice, presented in four categories: 1) *Be together* (n=131; a majority of the advice from cancer-bereaved siblings to peers related to being with the ill brother or sister, participating in his/her care, cherishing the time together, staying friends, doing fun things together, saying how much the brother or sister means, saying goodbye, and letting him/her know that he/she will never be forgotten); 2) *Communicate openly* (n=81; communicate opnely with the ill brother or sister, but also with parents, peers, in school and with HCPs, asking for help and information); 3) *Let go of guilt* (n=27; siblings also advised peers not to blame themselves, stressing the importance of making themselves heard and showing their feelings in order to avoid loneliness); 4) *Live life as usual* (n=18; keep taking part in everyday activities like going to school, after-school programs and other things that would make life go on as before; the siblings advised peers to occasionally take a break from illness and death, as a way of taking care of themselves). |

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| *Lövgren et al, 2020* | | | | |
| Sweden<br><br>2018-2019 | Explore how families in pediatric oncology experienced illness-related information and communication with HCP and within the family.<br><br>*Note: in this review, only results concerning siblings were considered.* | 118 family members, representing 27 families.<br><br>38 siblings participated (20 females, 18 males; mean age 12 yeas [SD 5.2]). | Participants responded to open and closed questions; those aged ≥13 years also filled the Family Adaptability and Cohesion Scale IV (FACES IV) Family Communication. Descriptive statistics and content analysis were applied. | All siblings reported that someone had told them about the cancer illness, but 45% of the siblings wanted to know more about the Illness. A vast majority of the siblings aged 13 years and older (n=14) reported that they had not received information or that they wanted more information regarding several areas: prognosis (64%), how the cancer and its treatment could affect the child's physical (64%) and psychological health (71%), where or whom they could turn to if they have questions about the ill child's care (57%), and where or whom they could turn to for own support (50%). The siblings described that they did not dare talk to HCP because "they talk around things," which resulted in even more uncertainty. Moreover, the siblings reported that HCP interpreted everything as negative criticism, which led the siblings to keep silent. 52% of siblings reported that they had feelings or thoughts that they did not want to share with their family, related to their school situation, sadness at night, feeling neglected, and anger/disappointment at the parents. Conversely, 24% siblings reported that they wanted to reveal more about how they felt to someone in the family. |

HCP, health care professionals; MPS, mucopolysaccharidoses; PPC, Pediatric Palliative Care; SD, standard deviation

## DISCUSSION

Results of this study indicate that there is room for improvement in the support to siblings of children in PPC[11,13,15] in various dimensions (informational, instrumental, appraisal, and emotional) and throughout the course of the disease.[4] Informational support should be tailored to siblings in a developmentally targeted manner[5] and include the description of the disease and possible side effects of treatment that may involve changes in the appearance and level of activity of the affected child. Most importantly, health care providers should emphasize that siblings had no role in causing the disease.[4] Additionally, siblings may benefit from being prepared for the death of the brother/sister and from having the opportunity to say goodbye.[5] In fact, the International Society for Paediatric Oncology guidelines for the support of siblings of children with cancer[16] advise health care professionals and parents to involve siblings from the time of diagnosis, keeping them informed.[4,11,16] As shown by Roseberg *et al.*, a period of great vulnerability seems to exist during and immediately after the illness (or death) experience. Sharing information during this time may be challenging for parents, with most seeking to protect their children from difficult information.[5] Additionally, staff overidentification with parents' needs to protect the sibling often leads to a lack of information. Consequently, these siblings often have mistaken ideas regarding the disease,[4] which may ultimately hamper the bereavement process,[5] leading to unresolved grief.[14] Actually, the consequences of talking to siblings about sensitive issues are likely to outweigh the costs of remaining silent.[6] Caregivers who are apprehensive about involving siblings should be explained that being involved in the care of the ill child and having conversations about his/her general health status are generally viewed as important by the siblings themselves.[6] In the study by Freeman *et al.*, one of the most helpful resources identified by siblings was the ability to visit the hospitalized child when desired. According to the authors, visiting allows the sibling to directly observe how the ill brother or sister is doing medically and the type of treatment and care provided, promoting the reality of the situation and positioning the sibling to interact with health care providers for the acquisition of information. Additionally, visiting likely involves other family members, which may foster feelings of family cohesion.[4] It is also important to be aware of how siblings engage in protective buffering. Consequently, professionals need to assess siblings' level of knowledge of the condition and its impact directly from the child, rather than from parental proxy reports, which may underestimate the impact on siblings.[2] Siblings also need instrumental support, especially as the disease progresses and they tend to return to their own concerns, requiring parental attention.[4] In the study by Lövgren *et al.* (2016), more than half of siblings suggested advice related to their own need for day-to-day support from diagnosis to several years after bereavement.[11] Also, in the study by Wallin *et al.,* siblings advised peers to occasionally take a break from illness and death as a way of taking care of themselves.[12] Accordingly, studies in pediatric cancer setting show that minimal gestures, such as asking healthy siblings how they are doing (instead of asking about the child with cancer) or providing them with individual attention concerning their interests, may be beneficial and appreciated.[7] It may be important to increase support for siblings from their extended family, school, and community members, by raising awareness of the situation of the healthy sibling in these groups.[7,11] Siblings may also benefit from appraisal support, including instruction in coping strategies to deal with changes of the affected child and engagement in his/her actual care and comfort.[4,15] With open, transparent, directive instructions on how to care for their brothers/sisters and family in general, siblings may engage in helping behavior, fulfilling their cognitive and

active coping styles.[6] Additionally, this may in turn promote strong family cohesion, thus contributing by helping bereaved siblings to create more positive experiences with and memories of the sick sibling.[15] This has been previously recommended for siblings of children with cancer, with advice for the Oncology team to include siblings in treatment, as appropriate (e.g. giving tours of the hospital ward; explaining tests, procedures, and treatments), as this may help siblings feel more included and less isolated.[7] The need for emotional support can be addressed with support groups during hospitalization, throughout treatment[4] and, importantly, after the child's death.[5] Health professionals have an active role in this domain, since they must mediate hope in a realistic and honest way.[11] It is important to adopt a systemic approach to better understand the mutually reinforcing relationship between the family and wider environment on sibling adjustment.[2] This review parallels previous findings in siblings of children with cancer, where higher levels of distress were more common within two years after diagnosis, with most siblings responding well with minimal support. As in Oncology setting,[7] it seems reasonable to recommend that those who display significant distress should be referred to evaluation and treatment by mental health care specialists.

Although seven studies included in this review refer to the Oncology setting, siblings' needs may vary substantially,[6] as PPC patients have a great diversity of medical conditions, with very different trajectories and prognosis, making generalizations from disease-specific studies inappropriate. For example, for siblings of children with progressive LLCs, the ongoing deterioration of the child's condition requires that support be flexible enough to respond to changes, symptoms, and relationships, to provide the best care to siblings.[2] In fact, previous studies show that chronic illnesses with daily treatment regimens are associated with negative effects compared to chronic illnesses that do not affect daily functioning.[8]

Five of the nine studies included in this review focused on the bereavement stage. However, as previously described, PPC encompasses a far broader and earlier approach than solely bereavement support.[1] Therefore, future research should focus on the needs and concerns of siblings in PPC using an earlier and longitudinal assessment. It should also be noted that the exclusion of studies in which participants were not the siblings themselves, although informed by evidence showing that siblings' own perspectives provide beneficial augmentation to proxy reports,[2] may have omitted research articles concerning younger siblings - a population that requires special attention and care.

## CONCLUSION

Siblings of children in palliative care have the need for information, engagement in brother/sister's care, and psychosocial support. In the future, quantitative studies of siblings' wishes may enable a more effective assessment.[6] Prospective studies in which siblings are interviewed as they go through the different stages of disease should be performed in order to evaluate their perspectives, experiences, and outcomes.[4,5] Clinical practice recommendations should also be developed, taking into account the general principles of palliative care but also leaving room to include the specificities of each disease course and, most importantly, the uniqueness of each child, family, and sibling.

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# CASE REPORTS

## NASOLABIAL CYST IN PEDIATRIC AGE

### CISTO NASOLABIAL EM IDADE PEDIÁTRICA

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## ABSTRACT

Herein is described the case of a 26-month-old male observed in the Emergency Department for edema of the upper lip and left malar region with less than 24 hours of evolution and progressive worsening. No other associated complaints, previous history of trauma, or insect sting were reported. Computed tomography revealed a "left premaxillary abscess associated with ipsilateral nasogenian phlegm". Intravenous antibiotic therapy with clarithromycin and clindamycin and systemic corticosteroid therapy with dexamethasone were started, and the boy was admitted to the Pediatric Department. He presented favorable clinical evolution, with complete resolution of inflammatory signs. At discharge, the patient remained asymptomatic and was referred to Otorhinolaryngology consultation for follow-up.

Although nasolabial cysts are rare in pediatric age, this case intends to raise awareness of the condition, enabling its recognition by clinicians, and increase knowledge about its course and treatment.

**Keywords:** infection; nasolabial cyst; non-odontogenic cyst

## RESUMO

É apresentado o caso de uma criança do sexo masculino com 26 meses de idade, que recorreu ao Serviço de Urgência por edema do lábio superior e região malar esquerda com menos de 24 horas de evolução e agravamento progressivo. Não foram reportadas outras queixas associadas, história prévia de traumatismo ou picada de inseto. Foi efetuada tomografia computorizada maxilofacial com contraste, que revelou "abcesso pré-maxilar esquerdo associado a fleimão nasogeniano ipsilateral". O doente iniciou antibioterapia endovenosa com claritromicina e clindamicina e corticoterapia sistémica com dexametasona e foi internado no Serviço de Pediatria, apresentando evolução clínica favorável, com resolução total dos sinais inflamatórios. À data da alta, mantinha-se assintomático e foi orientado para consulta de Otorrinolaringologia para seguimento.

Apesar de o cisto nasolabial ser uma entidade rara em idade pediátrica, este caso clínico pretende alertar para a sua existência e reforçar a importância do seu reconhecimento pelos clínicos, bem como aumentar o conhecimento da sua evolução e tratamento.

**Palavras-chave**: cisto nasolabial; cisto não-odontogénico; infeção

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## INTRODUCTION

Non-odontogenic cysts within the jaws are not a common finding, especially in pediatric age. It is well documented that cysts in the pediatric population tend to be developmental and odontogenic.[1] Nasolabial cyst is a rare development cyst, comprising only 0.7% of all jaw cysts. It occurs in the upper lip, laterally of the midline, or near the lateral and canine tooth junction.[1,2] The pathogenesis of nasolabial cysts remains uncertain. Currently, the most widely accepted theory is that it originates from the inferior and anterior portion of the nasolacrimal duct. This theory is supported by the fact that the nasolacrimal duct is lined with pseudostratified columnar epithelium, also found in nasolabial cyst cavities.[3,4] Clinically, nasolabial cysts are characterized by unilateral volume increase in the nasolabial region, causing an elevation of the nose wing, projection of the upper lip, and sometimes nasal obstruction. They present slow and asymptomatic growth.[2] Local pain and abrupt lesion enlargement may occur when associated with infection, which may be present in up to 50% of cases.[3,4] The diagnosis is usually based on clinical course, with imaging tests valuable in assisting it. For being soft tissue lesions, nasolabial cysts are not visualized with traditional plain film radiographs. Traditional computed tomography (CT) or magnetic resonance imaging (MRI) show a soft tissue mass of varying size usually well demarcated.[1,2]

Treatment of nasolabial cysts can be accomplished through fine-needle aspiration, incision and drainage, cystic enucleation by intraoral access, endoscopic dorsal marsupialization, and intralesional injection of sclerosing agents.[1,2,4]

## CASE REPORT

A 26-month-old male with a personal history of allergy to penicillin resorted to the Emergency Department for edema of the upper lip and left malar region with less than 24 hours of evolution and perception of progressive worsening, according to the mother. No other associated complaints or previous history of trauma or insect bite were reported. The patient had good general condition and no fever. Extraoral examination revealed facial asymmetry with rubor and edema of the upper lip, slight elevation of nasal ala, and deformity of the left nasolabial sulcus (**Figures 1 and 2**). A small and circumscribed fluctuant area in the maxillary region was detected on palpation. Observation by an otolaryngologist (ENT) revealed intraoral edema of the left oral vestibule and no intranasal alterations.

CT scan with intravenous contrast was performed, revealing a premaxillary left abscess with ipsilateral nasolabial phlegm (**Figure 3**). Based on clinical history and imagiological findings, diagnosis of infected nasolabial cyst was proposed.

Treatment with endovenous clarithromycin and clindamycin and systemic corticosteroid therapy with dexamethasone was initiated, and the patient was admitted to the Pediatric Department with progressive improvement of inflammatory signs. During hospitalization, stomatological observation discarded associated dental pathologies.

At discharge, the patient was completely asymptomatic and was referred to ENT consultation for follow-up. He remained asymptomatic, with no additional infectious episodes.

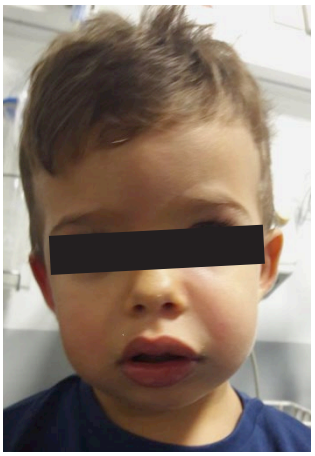

**Figure 1 -** Facial asymmetry with rubor and edema of the upper lip

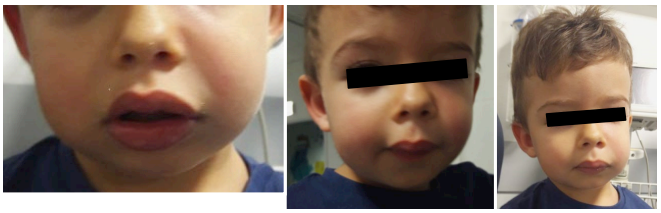

**Figure 2 -** Elevation of left ala nasi and deformity of the nasolabial sulcus

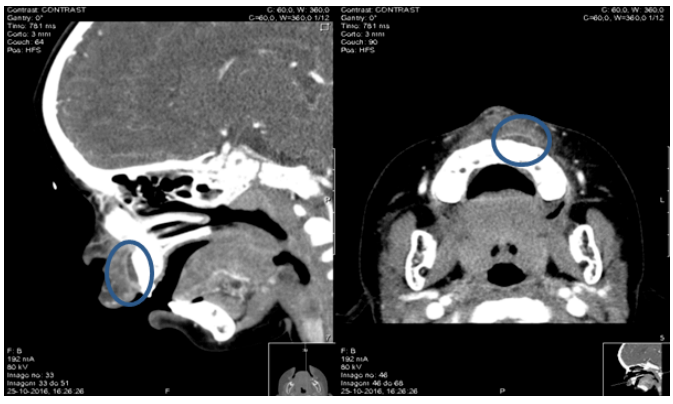

**Figure 3 -** CT images showing the lesion marked with a blue circle

## DISCUSSION

Although nasolabial cyst is a rare diagnosis in children, this case illustrates the most common features in patients with this condition. Although the case refers to a male patient, nasolabial cysts are more frequent in females, according to the literature.[1-5] The differential diagnosis may include other lesions affecting the anterior maxillary region, such as odontogenic cysts and periapical abscesses and granulomas.[3-5] Pulp vitality testing of adjacent teeth is essential to confirm the diagnosis since coincidental dental lesions are a frequent cause of abscesses and require exclusion as a possible etiological factor.[3] In the present case, this differential diagnosis was excluded by stomatological observation. Other possible diagnoses, such as dermoid and epidermoid cysts, are usually associated with yellow discoloration of the overlying mucosa, whereas in nasolabial cysts, the mucosa preserves its normal pink hue or appears blue-tinged.[4]

The traditional approach to this lesion in the adult population is surgical excision via intraoral/sublabial approach.[1] However, data regarding the best approach in pediatric age is scarce. Additionally, as nasolabial cysts are usually located near the nasal cavity floor, complications as nasal mucosa perforation during surgical excision are not uncommon.[3] In this case, given the patient's age and favorable clinical evolution after resolution of the acute infectious process, a wait-and-watch attitude with regular follow-up was chosen as the preferential approach. In the future, surgical removal may be considered if the patient presents complaints or new infectious events.

## CONCLUSION

Data in the literature and from the present case report suggest that, although nasolabial cysts are a rare finding in pediatric age, pediatricians, ENT, and dental practitioners should be aware of its key features and be able to distinguish it from other odontogenic lesions. More studies are required to determine the best approach for treating this condition in pediatric populations.

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# CASE REPORTS

## INFANTILE HEPATIC HEMANGIOENDOTHELIOMA IN A NEWBORN

### HEMANGIOENDOTELIOMA HEPÁTICO INFANTIL NUM RECÉM-NASCIDO

Joana Silva[1], Liliana Quaresma[1], Fátima Ribeiro[1], Inês Ferreira[1], Eunice Trindade[2], Teresa Caldeira[1], Teresa Andrade[1]

## ABSTRACT

Infantile hepatic hemangioendothelioma is the most common benign hepatic vascular tumor in infants younger than six months and may undergo spontaneous regression during the first years of life.

Diagnosis of these lesions in preterm newborns can be challenging, with its timing and accuracy relevant to avoid inappropriate therapeutic measures.

**Keywords**: hemangioendothelioma; liver tumor; newborn

## RESUMO

O hemangioendotelioma hepático infantil é o tumor benigno hepático vascular mais comum em lactentes com menos de seis meses, podendo regredir espontaneamente nos primeiros anos de vida.

O diagnóstico destas lesões em recém-nascidos prematuros pode ser um desafio, sendo a sua realização atempada e correta importante para evitar medidas terapêuticas desadequadas.

**Palavras-chave:** hemangioendotelioma; recém-nascido; tumor hepático

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## INTRODUCTION

Primary liver tumors are rare in the neonatal period, with vascular lesions as the most frequent.[1] Infantile hepatic hemangioendothelioma (IHH) is a benign vascular liver tumor commonly diagnosed within the first six months of life.[2-4] It is usually asymptomatic and may regress spontaneously within 12 to 18 months.[2,5] Rarely, it can cause severe symptoms, such as liver dysfunction, congestive cardiac failure, and coagulopathy, requiring aggressive treatment.[2,6] The diagnosis is established based on the child's age, clinical features, serum α-fetoprotein level, and imaging findings.[4,7]

Herein the authors report the case of a preterm newborn with hepatic hemangioendothelioma incidentally diagnosed during echocardiographic evaluation in the context of sepsis.

## CASE REPORT

Herein is reported the case of a male Caucasian newborn, born at 27 weeks of gestational age by spontaneous vaginal delivery after preterm premature rupture of membranes, weighing 1000 g. Physical examination was normal for age.

Eighteen days after admission, the boy developed a clinical-analytical condition compatible with sepsis, being prescribed cefotaxime and vancomycin.

Two intrahepatic cystic lesions were incidentally identified at subcostal view during functional echocardiography. Abdominal ultrasound confirmed the presence of two adjacent cystic hepatic formations in segment VIII, with 13 and 17 mm, both without detectable vascularization (**Figure 1**). Considering the hypothesis of fungal liver abscesses, amphotericin B was added to antibiotic therapy and maintained for five weeks. In the absence of positive cultures and normal complete blood count, liver function tests, and serum alpha-fetoprotein (AFP) for age (16,692 ng/mL; normal range for age, 134,734 ± 41,444 ng/mL), the hypothesis of hepatic hemangioendothelioma was raised.

Abdominal magnetic resonance imaging (MRI) performed on the 66$^{th}$ day of life confirmed the presence of two hepatic hemangioendotheliomas in segments IV and VIII, with 14 and 12 mm, hypointense on T1- and hyperintense on T2-weighted images (**Figure 2**).

The boy was discharged home on the 75$^{th}$ postnatal day, clinically asymptomatic. Ultrasound control performed five weeks later showed stable liver lesions. At six-month follow-up, abdominal ultrasonography showed total regression of the previously described masses, and analytical control was normal.

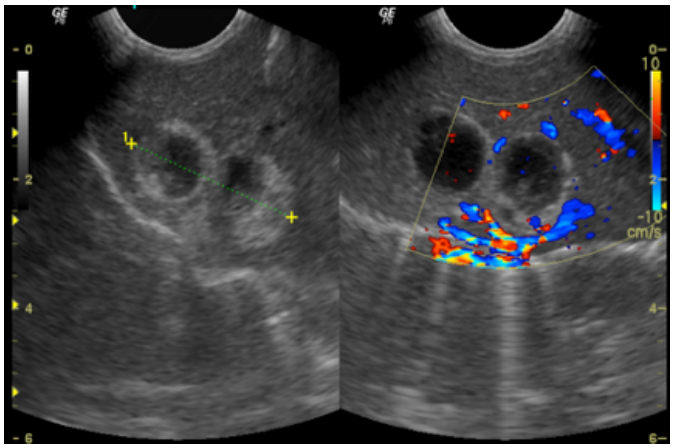

**Figure 1 -** Abdominal ultrasound showing two adjacent cystic formations in segment VIII, with 13 and 17 mm, the largest with some peripheral hyperechogenic areas and the smallest more liquefied, and both without detectable vascularization.

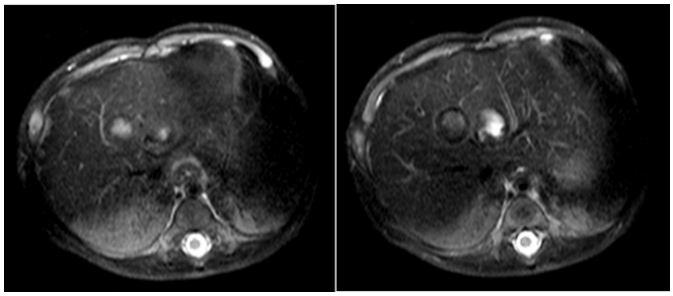

**Figure 2 -** MRI showing two nodules in segments IV and VIII with 14 and 12 mm, respectively, hypointense on T1- and hyperintense on T2-weighted images, with filling-in in the arteriovenous phase.

## DISCUSSION

Functional echocardiography has become an invaluable tool in the Neonatal Intensive Care Unit and was crucial for the incidental diagnosis of the hepatic masses observed in the present case.[8]

The differential diagnosis of hepatic masses in neonates can be categorized into congenital, neoplastic, or infectious. In this case, and given the clinical-analytical sepsis condition, the hypothesis of liver abscess was raised. The incidence of liver abscesses in preterm increased over the past two decades, probably due to their increased survival and use of invasive procedures (as umbilical catheterization and central catheters) and total parenteral nutrition.[9] In the present case, the absence of therapeutic response despite escalating therapy required an additional imaging modality to establish the diagnosis. As mass differentiation is complex, only MRI allowed a definitive IHH diagnosis in this case.

Benign liver tumors account for one-third of all hepatic lesions in

children. IHH represents the most common benign vascular tumor of the liver, with female predominance and mostly apparent in the first six months of life.[3,4,10,11] It is usually multifocal or diffuse, but single lesions may also be found.[3,12]

In most cases, IHH continues to grow during the first year of life, remaining asymptomatic and only incidentally detected in imaging assessment. During its natural course, spontaneous involution occurs within a few years.[2,3] In the present patient, total regression occurred within the first year of life, without symptoms.

Despite its benign nature, multiple and diffuse lesions can present with life-threatening complications, including severe hypothyroidism, cardiac failure, fulminant hepatic failure, consumption coagulopathy, or intraabdominal hemorrhage, requiring aggressive treatment.[6,11]

Clinical manifestations – as abdominal distension, hepatomegaly, skin hemangioma, anemia, thrombocytopenia (Kasabach-Merritt syndrome), and rarely biliary and gastric outlet obstruction – can also occur.[3]

The initial diagnostic approach consists of ultrasonography, but contrast-enhanced CT or MRI can provide a more definitive diagnosis.[3] MRI may identify IHH as hypointense on T1- and hyperintense on T2-weighted images and with centripetal or homogeneous enhancement.[13,14]

Some evidence suggests an increased risk of hepatoblastoma in preterm, with early exposure to oxidative stress potentially representing the main etiological factor. Consequently, a high index of suspicion for malignant liver lesions is essential.[15]

Serum AFP has been used as an important tumor marker for hepatoblastoma, hepatocellular carcinoma, and germ cell tumors and should be tested in all cases. Although AFP levels may be elevated in IHH, they are never as high as seen in malignant lesions.[2,4]

Symptom severity and tumor size affect treatment decisions, which remain controversial.[6] While asymptomatic lesions may experience spontaneous regression and expectant management can be safely adopted, symptomatic lesions may require aggressive management to avoid severe complications. Several therapeutic options are available, including radiotherapy, hepatic artery ligation, and embolization, but systemic corticosteroids remain the mainstay of treatment.[2,3]

In the present case, nosocomial sepsis led to the diagnosis of hepatic masses, incidentally detected on functional echocardiography and initially interpreted as hepatic abscesses. However, lesion non-regression despite instituted therapy suggested other diagnostic hypotheses.

This case is an example of the diagnostic challenge that hemangioendothelioma represents in the neonatal period, particularly in extremely low birth weight preterm, and of successful conservative management with periodic radiological surveillance.

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# CASE REPORTS

## RHINO-ORBITAL-CEREBRAL MUCORMYCOSIS IN A PEDIATRIC CANCER PATIENT

### MUCORMICOSE RINO-ORBITO-CEREBRAL NUM DOENTE ONCOLÓGICO PEDIÁTRICO

Maria Eduarda Couto[1], Tereza Oliva[2], Pedro Alberto[3], Ana Lebre[4], Armando Pinto[2], Ana Maia Ferreira[2]

## ABSTRACT

**Aim:** Mucormycosis infections are highly lethal in immunosuppressed patients. The authors present a rare case of successful treatment of the condition.

**Case description:** A 14-year-old male with acute lymphoblastic lymphoma in remission was diagnosed with pansinusitis, cerebral osteomyelitis, and encephalitis with an abscess caused by Rhizopus sp. Neurosurgical drainage, endoscopic sinus surgery, and left eye enucleation were performed, and the patient was simultaneously treated with lipossomal-amphotericin B and posaconazol (later replaced by isavuconazol). However, complications (left frontal lobe herniation and cerebrospinal fluid fistula) ensued, requiring surgical reoperation. Chemotherapy was restarted four months later.

**Comments:** This is a rare case report, in which early and aggressive surgery, antifungal treatment, and multidisciplinary team work were crucial for the successful outcome.

**Keywords:** antifungal; encephalitis; mucormycosis; osteomyelitis; Rhizopus sp

## RESUMO

**Objetivo:** As infeções por mucormicose associam-se a elevada mortalidade em doentes imunocomprometidos. Os autores descrevem um raro caso clínico de tratamento com sucesso da condição.

**Descrição do caso:** Um rapaz de 14 anos de idade com linfoma linfoblástico agudo em remissão foi diagnosticado com pansinusite, osteomielite cerebral e encefalite com abcesso causada por Rhizopus sp. Foi realizada drenagem neurocirúrgica, cirurgia endoscópica naso-sinusal e enucleação do olho esquerdo. O doente iniciou tratamento com anfotericina B lipossómica e posaconazol (posteriormente substituído por isavuconazol). No entanto, o desenvolvimento de complicações (herniação do lobo frontal esquerdo e fístula de líquido cefalorraquídeano) exigiu reintervenção cirúrgica. Quatro meses depois, foi reiniciada quimioterapia.

**Comentários:** Este é um caso clínico raro, no qual cirurgia precoce e agressiva, antifúngicos adequados e abordagem por uma equipa multidisciplinar foram determinantes para o sucesso alcançado.

**Palavras-chave:** antifúngico; encefalite; mucormicose; osteomielite; Rhizopus sp

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## INTRODUCTION

Acute invasive fungal infection (AIFI) is a life-threatening condition with an annual incidence of 1.7/1 million inhabitants in the United States of America.[1-4] The most common etiological agents are Aspergillus, Rhizopus, and Mucor species, which are often present in the natural environment and transmitted through inhalation or ingestion of spores, causing illness in immunosuppressed patients.[4] Their fungal hyphae are highly destructive for the mucosae, invade blood vessels and bones, and cause neutrophilic infiltration and tissue necrosis.[1-4]

Mucormycosis is a rare AIFI infection caused by a group of fungi called Mucormycotina. Nineteen mucormycosis cases were identified in Portugal between 2001 and 2015, both in adults and children. Relevant risk factors associated with the disease include hematological disorders, HIV infection, transplant history, chemotherapy or corticosteroids exposure, prolonged antibiotic therapy, diabetic ketoacidosis, renal failure, and intravenous drug use.[3-7]

The most common mucormycosis locations are rhino-orbital-cerebral sites (33-44%), skin (10-16%), and lung (10-11%). The most common agent is Rhizopus sp (37% of cases), followed by Mucor sp. and Rhizopus spp. Fungi are ubiquitous in the environment and a rare but substantial cause of infection in immunosuppressed persons and surgery patients. Frequent clinical signs of rhino-orbital-cerebral mucormycosis include fever, face swelling, diplopia, decreased vision, nasal discharge, facial pain, headache, decreased mental function, black nasal discharge crusts, turbine necrosis, ulceration, and palatal perforation. Cerebral infarction with neutrophilic infiltration and angioinvasion can also occur.[1-4]

The diagnosis is established based on clinical symptoms combined with risk factors and imaging assessment, as well as tissue biopsy for culture (positive in 33-61%) and histopathology.[1-4,8,9]

Regarding treatment options, lipossomal amphotericin B (L-Amb B) and posaconazol/isavuconazol are first- and second-line antifungal options that should be used in addition to aggressive surgical treatment. The choice of the agent for central nervous system (CNS) infection depends on CSF penetration and activity spectrum. L-Amb B has relatively limited distribution in CSF but achieves detectable therapeutic levels in CNS. Posaconazol achieves negligible concentrations in CSF, but isavuconazol has considerable efficacy in CNS infections.[3] Successful use of isavuconazol has been mostly reported in adults, but also in children.[3]

Despite aggressive surgical debridement, immune restoration therapy, and long-term high-dose antifungal treatment, the risk of recurrence is high.[1-4,8,9] In the course of rhino-orbital-cerebral mucormycosis, morbidity varies between 30-97%, and mortality between 70-80%.[3,9-12]

## CASE REPORT

A 14-year-old male was diagnosed with acute T-lymphoblastic lymphoma (mediastinal mass, testicular and cutaneous disease at presentation; no CNS involvement). Chemotherapy was prescribed according to CLG-EORTC arm AR2 protocol (high average risk), with complete response after one month.

While in the seventh month of reinduction chemotherapy, the patient was admitted to the Emergency Department with discrete left facial paresthesia. No neurologic deficits were found, as well as no neutropenia in blood work. Cerebral computerized tomography (CT) scan disclosed no abnormalities, and the boy was discharged home with a reevaluation appointment scheduled for less than one week.

On the following day, the boy returned to the hospital with left peripheral facial paresis and neutropenia. Cerebral CT scan was repeated, showing rapidly progressive pansinusitis, and the patient was admitted for intravenous therapy with meropenem, vancomycin, and L-Amb B 3 mg/kg. On the next day, he developed diplopia, opthalmoplegia, and left ptosis, requiring neurological evaluation. CT scan showed a completely different image from the previous day, suggestive of mucormycosis with extension to the left orbit and nasal region. On day four, the patient developed fever, together with right deviation of the labial commissure and amaurosis. On day five, magnetic resonance imaging (MRI) of the brain confirmed pansinusitis with extension to pterygoids muscles and posterior part of the nasopharynx and orbit, facial cellulitis, thrombosis of the left cavernous sinus, venous congestion of the left orbit and proptosis, left carotid artery stenosis, and encephalitis of the left temporal lobe and orbital portion of the left frontal lobe. L-Amb B was increased to 5 mg/kg and prophylactic enoxaparin was started. On day six, microbiological analysis of a sample aspirate confirmed Rhizopus sp infection. Sequential blood cultures collected since admission were all negative, and CSF cytological and microbiological analysis was negative for other infections and malignant disease.

On day 12, control MRI (**Figures 1 and 2**) showed pansinusitis worsening and extension of the infection through muscular and adipose tissues, optic nerve, and optical chiasma; invasion of the II, III, IV, V, and VI nerves; and irregular fronto-temporo-insular cerebral abscess, with 51 x 42 x 46 mm, causing a mass effect. At this time, L-Amb B was increased to 10 mg/kg and posaconazol was added.

On day 13, successful multidisciplinary surgery involving Neurosurgery, Ophthalmology, and Otorhinolaryngology was conducted. The procedure included removal of the affected area of the brain and surroundings, lateral and upper orbitotomy, optical nerve section, enucleation of the left orbit, and endoscopic sinus surgery.

One week later, posaconazol was replaced by intravenous isavuconazol 200 mg twice daily, and fever decreased. Hyperbaric

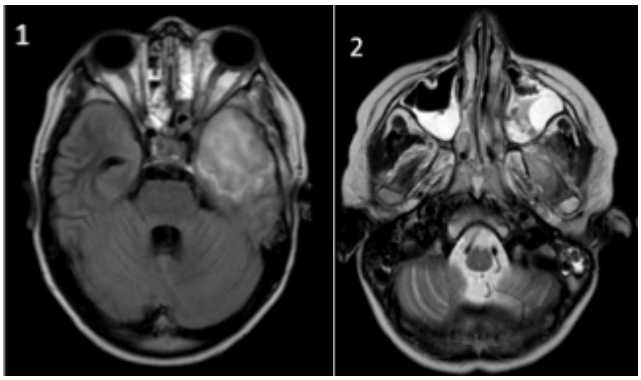
chamber treatment was also attempted to improve local tissue vascularization but was poorly tolerated, with nausea and vomiting, and suspended after four sessions. The patient developed severe hypokalemia, decreased renal clearance, nausea, vomiting (assumed as an adverse event of the antifungal agents), and stable thrombocytopenia (≈ 90.000x109/L platelets; no bleeding).

The need to remove the invaded orbital walls, together with orbital enucleation, left the patient with no anatomical support for the surrounding structures. Progressive left frontal herniation through the bony defect occurred, leading to a CSF fistula. Brain MRI performed two weeks later (**Figures 3 and 4**) confirmed cerebral herniation of the frontal lobe, with no ischemic tissue and slight improvement of fungal encephalitis. Persistence of osteomyelitis and infection of muscles and cerebral parenchyma were evident, besides multiple newly diagnosed mycotic aneurisms in the left internal carotid and middle cerebral arteries, and severe reduction of the left internal carotid artery flow.

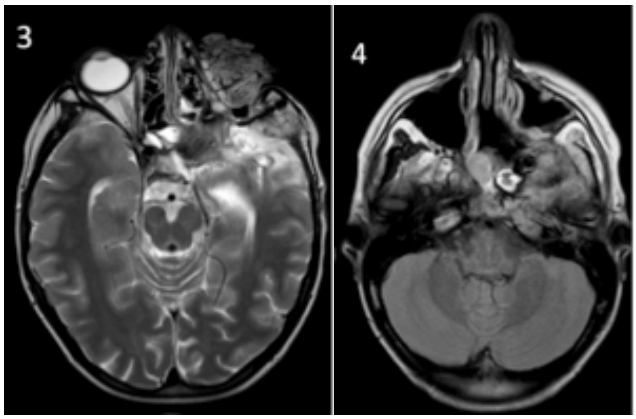
The day before scheduled angiography, the patient had a spontaneous severe mouth and nose bleeding that coursed with self-limited hypovolemic shock. He was transfused, intubated, and admitted to the Intensive Care Unit (ICU) for surveillance. Brain CT and angiography suggested post-hemorrhage spontaneous thrombosis of mycotic aneurysms, subsequently confirmed by MRI. This warranted neurosurgical reintervention through orbital reconstruction (with a titanium plate and patient's abdominal fat) and correction of the CSF fistula and frontal lobe herniation, with extraction of devitalized tissues (**Figures 5 and 6**). After this surgery, the patient developed acute pancreatitis with small-volume bilateral pleural effusions, small-volume ascites, and decreased renal clearance with metabolic acidosis. He was discharged from the ICU one week later.

Overall, the boy remained in the hospital for four months since diagnosis, under L-Amb B and isavuconazol treatment, ionic supplementation, and physical rehabilitation. Subsequently, the same dosage of intravenous antifungal therapy was administered in outpatient setting. He is currently completely autonomous and cognitively able to have a normal social life, with initial concerns about cognitive frontal lobe impairment shown to be unfounded.

Chemotherapy was restarted four months after infection diagnosis, and the patient is currently in the maintenance phase (oral 6-mercaptopurine and methotrexate). L-Amb B was deescalated to 5 mg/kg six months after the infection (MRI showed a more limited infectious region), being stopped after 15 months. Intravenous isavuconazol was replaced by an oral formulation after 15 months, being still in use. The patient was reoperated two more times due to relapse of the frontal hernia and CSF fistula, with progressive fistula resolution.




**Figures 1 and 2 -** Different sections of the first brain MRI at diagnosis




**Figures 3 and 4 -** Brain MRI after the first surgery

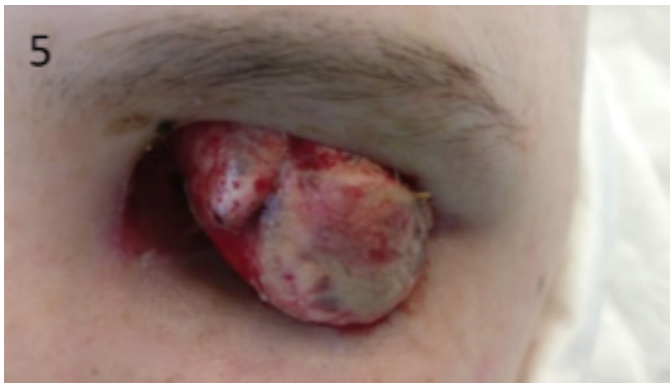



**Figure 5 -** Frontal lobe herniation

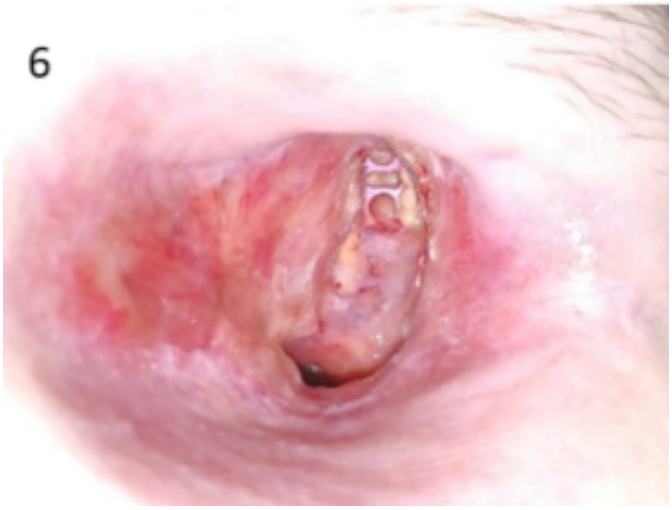



**Figure 6 -** Empty left orbit after correction of frontal lobe herniation

## DISCUSSION

Case reports of mucormycosis infections in immunosuppressed patients are scarce, challenging the definition of the best approach.[13-21] This case highlights that immunosuppressive treatment is a relevant risk factor for fungal infection. With the availability of new and more potent drugs, the ideal prophylactic antifungal agent is yet to be defined.

Mucormycosis diagnosis demands a high index of suspicion and involvement of a multidisciplinary team to manage the accelerated destruction of infected structures, organ dysfunction, and mortality. Chemotherapy must be immediately stopped after diagnosis. Early and aggressive surgery seems to be the most relevant indicator of success, by controlling the infectious focus. Additionally, medical treatment must be optimized by selecting the most suitable agents against Mucorales – in the present case, L-Amb B in high dose (10 mg/kg/daily) and isavuconazol. The use of adjuvant therapies (such as hyperbaric chamber treatment) should be considered, if appropriate.

To the authors' knowledge, this is the first report of (off-label) use of isavuconazol in the pediatric setting in Portugal. The drug is associated with less resistance compared to posaconazol and better CNS penetration.[22-25] Side effects likely attributed to this agent have been reported, and include nausea, vomiting, hypokalemia, and renal impairment. In the present case, fever subsided as soon as the drug was started. A double antifungal strategy, previously described in similar case reports, was justified given the high disease severity in an immunosuppressed patient.[26-27] The combination of a new and highly effective option with limited use in pediatric patients (isavuconazol) and an old and well-known drug (L-Amb B) provided the rational for improved CNS penetration and patient outcomes, by using the most suitable antifungals available for this type of infection with no known interactions. The patient currently remains on oral isavuconazol and maintenance chemotherapy. L-Amb B proved to be a suitable first-line option for mucormycosis and an adequate agent to combine with isavuconazol. Although there are no guidelines stating for how long antifungal treatments should be maintained, waiting for chemotherapy completion and imaging resolution seems advisable.

After a long inpatient period, the boy's functional status started improving with daily physical rehabilitation. He is currently accompanied by a multidisciplinary team including Pediatric Oncology, Neurosurgery, Otorhinolaryngology, and Ophthalmology. Chemotherapy was continued, with no other relevant adverse events. Psychological, psychiatric, social, and nutritional support were also provided. Close communication with the patient an family facilitated understanding and acceptance of medical team decisions, an important step to achieve success.

## ABBREVIATIONS

| | |
|---|---|
| *AIFI* | *acute invasive fungal infection* |
| *L-Amb B* | *liposomal amphotericin B* |
| *CNS* | *central nervous system* |
| *CT* | *computerized tomography* |
| *MRI* | *Magnetic resonance imaging* |
| *CSF* | *cerebrospinal fluid* |
| *ICU* | *intensive care unit* |

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# CASE REPORTS

## NASAL OBSTRUCTION IN A NEWBORN

### OBSTRUÇÃO NASAL NUM RECÉM-NASCIDO

Tiago Lourenço Coelho[1], João Fonseca Neves[1], Ricardo Caiado[1], Luís Filipe Silva[1]

### ABSTRACT

Dacryocystocele is an uncommon congenital disease affecting less than 1% of newborns.

Herein is presented the case of a female newborn with respiratory distress with onset in the first hours of life and worsening during breastfeeding.

Resistance to endoscope progression due to narrowing of both patent nasal cavities was noticed during flexible nasal endoscopy, and computed tomography revealed an extremely rare case of bilateral dacryocystocele.

A conservative approach was chosen, with surveillance in the Intensive Care Unit.

Although most dacryocystocele cases resolve spontaneously in the first year of life, recognition of this rare condition (particularly in Otolaryngology and Ophthalmology clinical practice) is crucial to prevent complications.

**Keywords:** bilateral congenital dacryocystocele; neonatal respiratory obstruction

### RESUMO

Dacriocistocelo é uma patologia congénita rara que afeta menos de 1% dos recém-nascidos.

É apresentado o caso de um recém-nascido do sexo feminino com 24 horas de vida que manifestou um quadro de dificuldade respiratória nas primeiras horas, com agravamento durante a amamentação.

Durante a realização de nasofibrolaringoscopia flexível, foi detetado o estreitamento de ambas as fossas nasais devido a resistência na progressão do endoscópio, sem alterações de permeabilidade, e a tomografia computorizada revelou um caso extremamente raro de dacriocistocelo congénito bilateral.

Do ponto de vista terapêutico, optou-se por uma abordagem conservadora, com vigilância em Unidade de Cuidados Intensivos neonatais.

Apesar da evolução favorável com resolução espontânea no primeiro ano de vida, o reconhecimento desta patologia rara (sobretudo na prática clínica de Otorrinolaringologia e Oftalmologia) é fundamental para a prevenção de complicações.

**Palavras-chave:** dacriocistocelo congénito bilateral; obstrução respiratória neonatal

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## INTRODUCTION

Congenital dacryocystocele is a very rare condition, affecting 0.1–0.3% of newborns with nasolacrimal duct blockage. It is more prevalent in females and the mean age at presentation is seven days.[1-3]

Although most cases spontaneously resolve in the first year of life, the condition can be associated with local complications, such as acute dacryocystitis, lacrimal abscess, fistula formation, or sepsis, making its early recognition crucial.[1]

## CASE REPORT

A female newborn with 24 hours of life and unremarkable family history was transferred to a tertiary pediatric hospital due to respiratory distress with onset in the first hours of life and worsening during breastfeeding. The girl remained calm and eupneic between meals and after aspiration of nasal secretions.

Pregnancy was uneventful, with no changes on ultrasound scans or evidence of congenital malformations.

On admission, the patient presented superior transmission noises at pulmonary auscultation, with peripheral oxygen saturation of 94% in room air. No other signs or symptoms were evident.

During flexible nasal endoscopy, some resistance was noticed in both nasal cavities after the nasal vestibule, but a patent nasal cavity without atresia was confirmed. Due to persistence of periodic respiratory distress episodes, computed tomography (CT) of the perinasal sinuses was performed, showing bilateral enlargement of lacrimal fossae creating a bulging in the inferior third of the lateral wall of both nasal cavities, suggesting dilation of the lacrimal sacs resulting in bilateral narrowing of nasal cavities (**Figures 1 and 2**). CT scan also confirmed the absence of bone or membranous atresia in choanae.

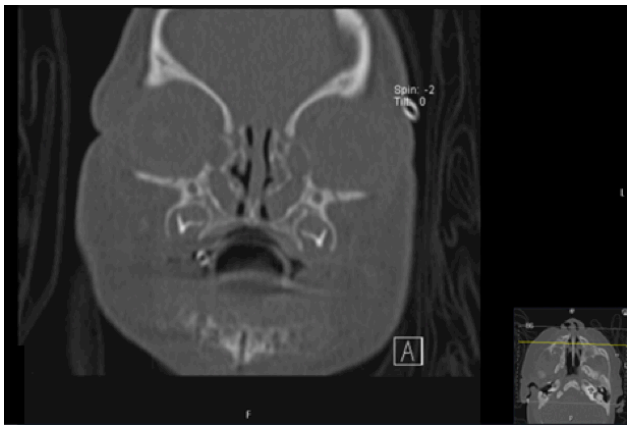


**Figure 1** - Coronal image of computed tomography of the sinuses showing mucus accumulation in the nasolacrimal system and distention of the lacrimal sac to the Rosenmüller valve level

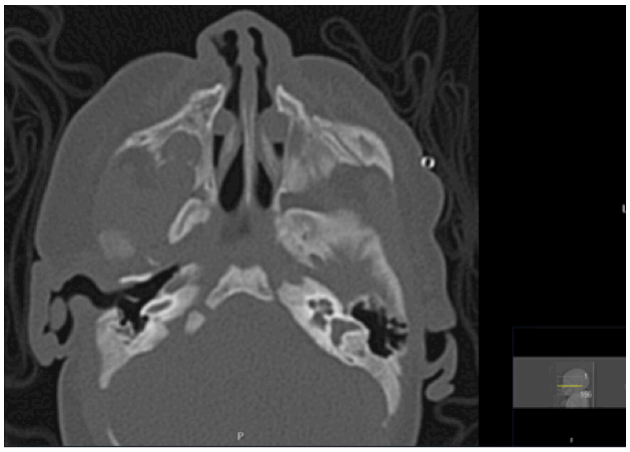

**Figure 2** - Axial image of computed tomography of the sinuses showing enlargement of the nasolacrimal channels, resulting in bilateral reduction of nasal cavity permeability

After evaluation by a multidisciplinary team including pediatricians, otolaryngologists, and ophthalmologists, the patient was kept under surveillance in the Intensive Care Unit (ICU).

A conservative approach was decided, consisting of lacrimal sac massage (Crigler massage), regular nasal wash followed by aspiration, and regular peripheral oxygen saturation measurements.

After five days of uneventful admission, the patient was discharged.

She is currently periodically followed at Ophthalmology and Otolaryngology consultations, remaining asymptomatic and with no ophthalmic, respiratory, or eating distress.

## DISCUSSION

Since newborns are mandatory nasal breathers, any nasal cavity permeability reduction can lead to respiratory distress.[4,5] In the present case, symptoms presented led to high clinical suspicion of obstructive pathology.

Dacryocystocele results from a persisting distal membrane of the nasolacrimal canal due to imperforation of the Hasner valve, leading to mucus retention in the nasolacrimal system and distention of the lacrimal sac to the level of Rosenmüller valve. [1,2,4,5]

The classic dacryocystocele presentation consists of a blue, cystic, firm mass below the medial canthus observed after birth. Other common symptoms include persistent tearing and ocular discharge.[2] None of these typical symptoms was observed in the present case.

Most cases are not associated with other syndromes or congenital anomalies.[1]

Although the diagnosis is clinical, imaging tests can exclude other causes of nasal obstruction, such as choanal atresia or meningocele/meningoencephalocele [2,4,6] CT and MRI have similar sensitivity for identifying dacryocystocele. [4-6,8] Nasal endoscopy also plays a relevant

role, showing a bilateral polypoid lesion occupying the inferior nasal meatus in most cases. [4,8]

In the present case, a conservative approach was chosen after evaluation by a multidisciplinary team including pediatricians, ophthalmologists, and otorhinolaryngologists. Given the respiratory distress presented on admission, the newborn was admitted to the ICU for close surveillance.

Most dacryocystocele cases resolve spontaneously or with conservative treatment within the first year.[1,2] When infected, treatment with systemic antibiotic may be necessary.[1,5-8]

Periodic surveillance and expectant attitude represent the best management option in cases with no evidence of complications.

Few patients may require endoscopy-assisted probing of the lacrimal pathway. However, surgical intervention, either as first-line or end-of-line approach, is still a matter of debate in congenital dacryocystocele, with no conclusive evidence supporting its value.[1,2]

## CONCLUSION

Although dacryocystocele is a rare congenital disorder, this case report emphasizes the importance of its early recognition and multidisciplinary approach, enabling to start appropriate targeted therapy and avoiding complications and potential morbidity.

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# IMAGING CASES

## BIOCHEMICAL CLINICAL CASE

### CASO CLÍNICO BIOQUÍMICO

Joana Silva[1], Joana Ferreira[2], Mariana Silva[2], Miguel Costa[1]

A nine-month-old infant girl, previously healthy and with unremarkable family history, was referred to the Pediatric consultation due to elevated aminotransferase identified while investigating failure to thrive.

In the first assessment, although the patient achieved the original birth weight percentile, she kept hypertransaminasemia. Physical examination was normal. Complementary study found a bicuspid pattern in albumin fraction on serum electrophoresis (**Figure 1**). Total albumin variation was within the normal range.

**What is your diagnosis?**

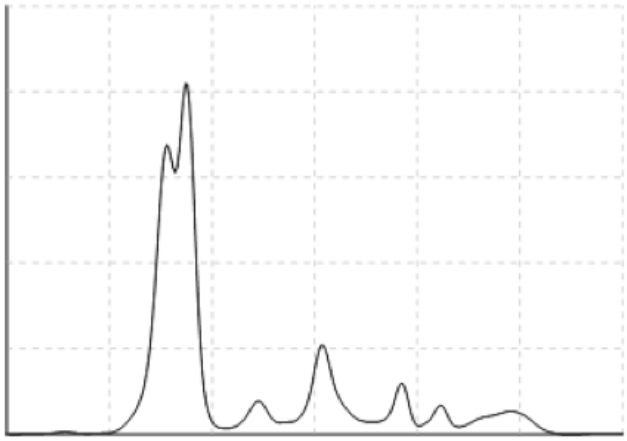

**Figure 1 -** Serum protein electrophoresis showing two peaks in the albumin region

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## DIAGNOSIS

Bisalbuminemia

## DISCUSSION

Assessment of renal function, total proteins, immunoglobulins, pancreatic enzymes, and thyroid function and abdominal ultrasonography were requested to exclude secondary causes of bisalbuminemia. Complementary studies showed no changes, and no therapy was instituted.

Given suspicion of a hereditary disorder, other family members were tested through serum protein electrophoresis, with the condition only confirmed in the mother.

During follow-up, the patient remained clinically asymptomatic and liver enzymes returned to the normal range, but no overt cause of hypertransaminasemia was identified.

This case describes bisalbuminemia findings in two family members, confirming its inherited nature. Genetic study has not yet been performed, as it has no implications in clinical management.

Bisalbuminemia represents a qualitative albumin variation, relatively rare and defined by a bicuspid pattern in the albumin fraction of serum protein electrophoresis. The modified albumin form may present increased (fast type) or decreased (slow type) electrophoretic mobility.[1-3]

Bisalbuminemia may be inherited (or permanent) or acquired (or transient). Inherited bisalbuminemia has a frequency between 1:1000 and 1:10000[5] and may have an autosomal dominant form, being frequently found in several members of the same family.[1,2,4] The causative genetic lesion is a point mutation of human serum albumin gene, and more than 100 variants have been identified. Slow-type variants predominate in Europe.[3,4]

The modified albumin form generally has no pathological significance, but some albumin variants may have altered affinity for some hormones, metal ions, fatty acids, and drugs, with clinical implication in some cases.[4,6] That is the case of familial dysalbuminemic hyperthyroxinemia and familial dysalbuminemic hypertriiodothyroninemia, which have been linked to inherited bisalbuminemia.[7-9] Mutations involved form a protein with preferential L-thyroxine or triiodothyronine affinity, resulting in increased total serum levels.[10]

Bisalbuminemia diagnosis is established by first eliminating the main acquired etiologies: drug interference (mostly high doses of beta lactam antibiotics), acute pancreatitis, and binding of monoclonal immunoglobulins.[4]

The present report described a rare case of hereditary bisalbuminemia in an infant after excluding other causes and investigating family members. Although this condition seems to have no clinical implications, it should be acknowledged to ensure the best management of these patients.

## ABSTRACT

Bisalbuminemia is a qualitative albumin variation defined by coexistence of two types of serum albumin with different electrophoretic mobilities in the same individual. It can be of two different types: hereditary (or permanent) and acquired (or transient).

Herein is described a rare case of hereditary bisalbuminemia in a healthy infant, incidentally found during elevated aminotransferase study.

Despite not having pathological significance, acknowledgement of this analytical alteration is key for adequate management of these patients.

**Keywords:** blood protein disorder; electrophoresis; serum albumin

## RESUMO

A bisalbuminémia é uma alteração qualitativa da albumina, definida pela coexistência de dois tipos de albumina sérica com mobilidade eletroforética diferente no mesmo indivíduo. Existem duas formas: hereditária (ou permanente) e adquirida (ou transitória).

É descrito um caso raro de bisalbuminémia hereditária num lactente saudável, acidentalmente detetada durante a investigação de aminotransferase elevada.

Apesar de não ter significado patológico, o reconhecimento desta alteração analítica é essencial para a adequada orientação destes casos.

**Palavras-chave:** albumina sérica; distúrbio de proteínas sanguíneas; eletroforese

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Nascer e Crescer - Birth and Growth Medical Journal congrats the Editorial & Scientific board members, as also the reviewers listed below, responsible for reviewing the works submitted in 2021, which enabled the publication of articles with high scientific level.

Alexandra Chaveiro
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Victoria Guiote Dominguez

# AUTHOR GUIDELINES

## AIMS AND SCOPE

Nascer e Crescer – Birth and Growth Medical Journal is a scientific, peer-reviewed journal, published in English language, property of Centro Hospitalar Universitário do Porto.

It is quarterly published since 1992 and indexed in SciELO.

The journal's main purpose is to convey accurate and up-to-date scientific information, promoting research in the areas of Maternal-Fetal, Neonatal, and Pediatric Health.

The journal publishes editorials, original articles, review articles, clinical cases, imaging cases, letters to the editor, and current perspectives.

The journal follows an open access policy, with all manuscripts fully available through the website https://revistas.rcaap.pt/nascercrescer, licensed under Creative Commons: Attribution–Noncommercial 4.0 International (CC BY-NC 4.0).

Nascer e Crescer – Birth and Growth Medical Journal does not charge fees to authors or readers.

All scientific contents are handled by the editorial board.

## AUTHORSHIP AND RESPONSIBILITY CRITERIA

NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL is a signatory journal to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, issued by the International Committee of Medical Journal Editors (ICMJE Recommendations), and to the Committee on Publication Ethics (COPE) code of conduct for editors.

Designated authors should meet authorship criteria in the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" of ICMJE Recommendations. Authorship or co-authorship cumulatively require:

1. Contribution in study planning or design; participation in data collection, analysis, and interpretation;
2. Participation in manuscript writing and in critical content review;
3. Approval of the final version for publication;
4. Agreement in responsibility for work accuracy and integrity.

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

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

### Ethics

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

When relevant, authors should mention that participants signed an informed consent form and that the study protocol was approved by the Ethics Committee of involved institutions.

A conflict of interest or funding statement is required.

# PUBLICATION RULES

## SUBMISSION

Manuscripts should be submitted online through the journal's interface at https://revistas.rcaap.pt/nascercrescer.

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

Manuscripts undergo a double-blind peer-review process, after which they can be:

a) Accepted without modifications;
b) Accepted after modifications suggested by reviewers;
c) Rejected.

Manuscripts should be written in English language and have the following structure: 1 – Title in English and Portuguese; 2 – Name of the authors; 3 – Abstract in English and Portuguese. Keywords in both languages; 4 – Text; 5 – References; 6 – Figures; 7 – Tables; 8 – Legends; 9 – Acknowledgements and clarifications.

Pages should be consecutively numbered according to the above mentioned structure.

### First page

a) Explicit and concise title, in English and Portuguese, not identifying the institution where the study took place.
b) Author names (first and last or clinical name) followed by their affiliations (Unit, Department, Institution) and email contacts.
c) Identification of the Corresponding Author, indicating postal address, email, and telephone number.

### Second page

a) Abstract in Portuguese and in English, avoiding the use of abbreviations.
b) Abstracts must follow the specific structure of the type of article in question.
c) After the abstract, keywords written in English and Portuguese must be provided, in alphabetical order, which will be used for indexing purposes. Keywords must be in accordance with the recommended nomenclature in Medical Subject Headings (MeSH).

## TEXT

### Editorials

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

### Original Articles

Text should be divided in Introduction, Material and Methods, Results, Discussion, and Conclusions. It must not exceed 5000 words, eight tables or figures, and 40 references. The abstract follows the same structure of the text and should not exceed 250 words. A maximum of seven keywords are allowed.

### Review Articles

Review articles should be structured in Introduction, Objectives,

Text, and Conclusions, and not exceed 5000 words, five tables or figures, and 80 references. The abstract must not exceed 250 words and should be structured according to the main text. A maximum of seven keywords are allowed.

**Clinical Cases**

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

**Imaging Cases**

This modality is appropriate for clinical cases in which image proves fundamental for diagnosis. Suitable images (two or three) include clinical images of patients or complementary exams. Text should be no longer than 1000 words, starting with a description of the case followed by the question: What is your Diagnosis? This should be followed by patient's diagnosis, disease management, and a brief discussion. A maximum of 10 references are allowed. The abstract should have a maximum of 150 words and should follow the descriptium of the case, before references. A maximum of five keywords are allowed.

**Letters to the Editor**

Letters to the Editor consist of a comment regarding an article published in Nascer e Crescer – Birth and Growth Medical Journal or a short statement regarding a clinical case or subject. They should not exceed 500 words and five references and may include one figure or table. Regarding comments to articles published in the journal, they should refer to articles published during the last semester and article authors will be subsequently invited to reply. Both the letter and authors' reply will be published in the same journal issue.

**Current Perspectives**

Perspectives are commissioned by the Editorial Board and address current topics of interest in line with the scope of the journal. They should not exceed 1200 words and ten references and may include one figure or table. If an author wishes to submit this type of article, he must first send a summary to the editor-in-chief, indicating authors, affiliations, and article title, for assessment of work relevance.

**General Rules**

- Abbreviations used must be adequately specified. When their use is necessary, they must be defined at first mention. If more than six are used, an explanatory table should be included with all abbreviations. Abbreviations should not be used in the title.
- Measurements or values must be expressed in international units (SI units, The SI for the Health Professions, WHO, 1977), using the respective abbreviations adopted in Portugal.
- Numbers 1 to 10 must be written in full, except when used as measurement units or have decimals. Numbers greater than ten shall be written in Arabic numerals, unless at the beginning of a sentence.
- Results should not be duplicated in the text and in tables/figures; only the main results should be highlighted in the text.

**REFERENCES**

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

Examples:

a) Medical journal: give the six first authors, followed by *et al* (in italic) in case of seven or more authors, manuscript title, journal name, publication year, volume, number, and pages. Ex.: Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, *et al*. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-65.

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

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

d) Electronic reference: journal article in electronic format. Ex.: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. January, 2010. (Assessed May 8, 2013). Available at: http://www.uptodate.com.

**FIGURES AND TABLES**

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

**ACKNOWLEDGMENTS AND CLARIFICATIONS**

Acknowledgements, declaration of interest statement, and funding source should be mentioned in the last page of the article.

**MODIFICATIONS AND REVISIONS**

In the case of articles accepted for publication but requiring modifications, changes should be made by authors within fifteen days.

Proofs will be sent to the authors in electronic format, with indication of the revision deadline according to editorial requirements of Nascer e Crescer – Birth and Growth Medical Journal.

Non-compliance with the time limit determined by the journal disobliges authors from performing the revision, which will be exclusively performed by the journal's editorial staff.

## ARTICLE STRUCTURE - AUTHOR GUIDELINES

| Publication type | Abstract | | Keywords | Text | | Figures and Tables | References |
|---|---|---|---|---|---|---|---|
| | Maximum word count | Structure | | Maximum word count (excluding References and illustrations) | Structure | Maximum number | Maximum number |
| Editorial | - | - | - | 1200 | - | 1/2 | 15 |
| Original Articles | 250 | Introduction/Objetives<br>Material and Methods<br>Results<br>Discussion/Conclusions | 3 to 7 | 5000 | Introduction/Objetives<br>Material and Methods<br>Results<br>Discussion<br>Conclusions | 8 | 40 |
| Review Articles | 250 | Introduction<br>Objetives<br>Text<br>Conclusions | 3 to 7 | 5000 | Introduction<br>Methods<br>Text<br>Discussion (with conclusions) | 8 | 80 |
| Clinical Cases | 150 | Introduction<br>Clinical Case(s)<br>Discussion/Conclusions | 3 to 7 | 2500 | Introduction (brief)<br>Clinical Case(s)<br>Discussion (with conclusions) | 5 | 15 |
| Imaging Cases | 150 | Introduction<br>Clinical Case(s)<br>Discussion/Conclusions | 3 to 5 | 1000 | Case/History<br>Diagnosis<br>Comments/Discussion (conclusions) | 2/3 | 10 |
| Letters to Editor | - | - | - | 500 | - | - | 5 |
| Current Perspectives | - | - | - | 1200 | - | 1 | 10 |

# INSTRUÇÕES AOS AUTORES

## OBJETIVOS E ÂMBITO

A Nascer e Crescer – Birth and Growth Medical Journal é uma revista científica, com *peer-review*, publicada em língua inglesa e propriedade do Centro Hospitalar Universitário do Porto.

Publicada trimestralmente desde 1992, encontra-se indexada na SciELO.

Tem como objetivo principal difundir informação científica, rigorosa e atualizada, promovendo a investigação nas áreas da Saúde Materno Fetal, Neonatal e Pediátrica.

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

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

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

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

## CRITÉRIOS DE AUTORIA E RESPONSABILIDADE

A Revista NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL subscreve as normas para apresentação de manuscritos a revistas biomédicas elaboradas pelo *International Committee of Medical Journal Editors* (ICMJE), e pelo *Committee On Publications Ethics* (COPE).

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

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

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

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

### Questões éticas

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

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

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

# NORMAS DE PUBLICAÇÃO

## SUBMISSÃO

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

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

Os artigos estão sujeitos a um processo de revisão por pares duplamente cego e cabe ao Editor a responsabilidade de os:

a. Aceitar sem alterações;
b. Aceitar após modificações propostas pelos revisores;
c. Recusar.

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

As páginas devem ser numeradas segundo a sequência referida anteriormente.

**Na primeira página**

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

**Na segunda página**

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

## TEXTO

**Editoriais**

Submetidos a convite do Editor ou Conselho Editorial, constituem comentários sobre tópicos atuais. Não podem exceder as 1200 palavras, um máximo de duas figuras ou tabelas e 15 referências bibliográficas no máximo. Não possuem resumo.

**Artigos Originais**

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

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

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

**Casos de imagem**
Dedicada a casos clínicos em que a imagem se revele fundamental para o diagnóstico. As imagens (duas ou três) podem ser relativas à observação clinica do doente ou a meios complementares de diagnóstico. Num texto escrito com o máximo de 1000 palavras, deve iniciar com uma descrição do caso, que finaliza com a pergunta: Qual o seu Diagnóstico? Segue-se a revelação do diagnóstico, orientação do doente e breve discussão. Poderá incluir até 10 referências bibliográficas. O Resumo, com o máximo de 150 palavras, segue a estrutura do texto antes das referências. As palavras-chave serão no máximo cinco.

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

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

**Normas gerais**

- As abreviaturas utilizadas devem ser objeto de especificação. Quando necessária a sua utilização, devem ser definidas na primeira vez que são mencionadas no texto. Se utilizadas mais do que seis, recomenda-se a inclusão de um quadro onde todas serão explicadas. Não se aceitam abreviaturas nos títulos dos trabalhos.
- Os parâmetros ou valores medidos devem ser expressos em unidades internacionais (*SI units, The SI for the Health Professions, WHO, 1977*), utilizando as respetivas abreviaturas adotadas em Portugal.
- Os números de 1 a 10 devem ser escritos por extenso, exceto quando se utilizam como unidades de medida ou estão acompanhados de decimais. Números superiores a dez, são escritos em algarismos árabes, exceto se no início da frase.
- Relativamente aos resultados, a informação não deverá ser referida em duplicado no texto e nos quadros / tabelas, bastando salientar no texto os resultados principais.

**REFERÊNCIAS BIBLIOGRÁFICAS**

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

Seguem-se alguns exemplos:

a. Revista médica: listar os primeiros seis autores, seguidos de *et al* (em itálico) se ultrapassar seis, título do artigo, nome da revista, ano, volume, número e páginas. Ex.: Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, *et al*. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-65.
b. Capítulo em livro: autor(es), título do capítulo, nome(s) do(s) Editor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação, primeira e última páginas do capítulo. Ex.: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.
c. Livro: autor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação e número de páginas. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on guide. 2nd. London: Taylor & Francis; 2013. p. 120.
d. Referência electrónica: artigo de revista em formato electrónico. Ex.: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. Janeiro, 2010. (Acedido em 8 de maio de 2013). Disponível em: http://www.uptodate.com.

**FIGURAS E QUADROS**

- Apresentadas em página individual, em formato digital de boa qualidade, acompanhado de título e legenda explicativa quando necessário.
- Cada quadro e figura deverão ser numerados sequencialmente, em numeração árabe, por ordem de referência no texto.
- Todas as abreviaturas ou símbolos necessitam de legenda.
- Se a figura ou quadro é cópia integral ou modificada de uma publicação, deve ser mencionada a sua origem e autorização para a utilização quando apropriado.
- Fotografias ou exames complementares de doentes deverão impedir a sua identificação, sendo acompanhadas de

autorização para a publicação, dada pelo doente ou seu responsável legal.
- O total de figuras e quadros não deve ultrapassar os valores indicados para cada tipologia de artigo.

**AGRADECIMENTOS E ESCLARECIMENTOS**

Os agradecimentos, a declaração de conflito de interesse e a informação sobre as fontes de financiamento do estudo devem figurar na última página.

**MODIFICAÇÕES E REVISÕES**

No caso de o artigo ser aceite, mas sujeito a modificações, estas devem ser realizadas pelos autores no prazo de quinze dias.

As provas tipográficas serão enviadas aos autores em formato eletrónico, contendo a indicação do prazo de revisão em função das necessidades de publicação da Revista.

O não respeito do prazo desobriga a aceitação da revisão dos autores, sendo a mesma efetuada exclusivamente pelos serviços da Revista.

## ESTRUTURA DOS ARTIGOS - NORMAS DE PUBLICAÇÃO

| Tipo de Artigo | Resumo | | Palavras-chave (Português e Inglês) | Texto | | Figuras e Quadros | Bibliografia |
|---|---|---|---|---|---|---|---|
| | Número máximo de palavras | Estrutura | | Número máximo de palavras (excluindo Referências e Ilustrações) | Estrutura | Número total máximo | Número máximo de referências |
| Editorial | - | - | - | 1200 | - | 1/2 | 15 |
| Artigos Originais | 250 | Introdução/Objetivo<br>Material e Métodos<br>Resultados<br>Discussão/Conclusões | 3 to 7 | 5000 | Introdução/Objetivo<br>Material e Métodos<br>Resultados<br>Discussão<br>Conclusões | 8 | 40 |
| Artigos de revisão | 250 | Introdução<br>Objetivos<br>Desenvolvimento<br>Conclusões | 3 to 7 | 5000 | Introdução<br>Métodos<br>Desenvolvimento<br>Discussão (com conclusões) | 8 | 80 |
| Casos Clínicos | 150 | Introdução<br>Caso(s) clínicos(s)<br>Discussão/Conclusões | 3 to 7 | 2500 | Introdução (breve)<br>Caso(s) clínicos(s)<br>Discussão (com conclusão) | 5 | 15 |
| Casos Imagem | 150 | Introdução<br>Caso(s) clínicos(s)<br>Discussão/Conclusões | 3 to 5 | 1000 | Caso/Historial<br>Diagnóstico<br>Comentários/Discussão (Conclusões) | 2/3 | 10 |
| Carta ao editor | - | - | - | 500 | - | - | 5 |
| Perspetivas Atuais | - | - | - | 1200 | - | 1 | 10 |