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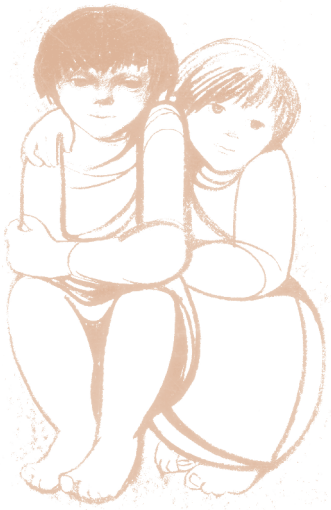

# NASCER E CRESCER
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# EDITORIAL

## Transforming to strengthen trust in the NHS

### Transformar para reforçar a confiança no SNS

Pedro Lopes Ferreira[1]

*The NHS is an inalienable moral heritage of our democracy because it is indispensable to citizenship, individual dignity and collective justice.*

António Arnaut

In recent decades, much has changed in the health systems of various countries and various challenges and problems have arisen. These include demographic ageing, the management of available resources, the emergence of the knowledge society, the explosion of digital tools and platforms, advances in medical technology, the perspectives, expectations and ambitions of new generations of professionals and the greater awareness and willingness of citizens to manage their own health and participate in the decisions that affect them. Everything has become extremely more complex in recent decades and has intensified during Covid, with ever greater and more centralized financial control.

The National Health Service (NHS) is one of the greatest achievements since April 25, 1974 and one of the main factors in the cohesion of society in democratic Portugal. In order to guarantee its sustainability for the foreseeable future, however, our SNS must undergo strategic transformations.

In general, the existence of an NHS has positive aspects. The first of these is universal access, guaranteeing all citizens, regardless of their financial situation, access to essential healthcare and eliminating financial barriers. No one is left out of the healthcare system due to a lack of resources. Related to the above, an NHS promotes equity in the provision of healthcare, ensuring that people receive treatment based on their clinical needs, rather than their ability to pay, thus reducing health inequalities between socio-economic groups. Another positive aspect has to do with accessibility and the fact that healthcare costs are essentially covered by taxes, making care more affordable for individuals and families, and allowing them not to worry about catastrophic medical expenses. A fourth point relates to the NHS's mission to promote health and prevent illness, which is essential for the safety and well-being of the population. Finally, in an NHS, there is public oversight, and the government and citizens are held accountable and can have a say in what happens.

On the other hand, any NHS is also associated with some problems, which can vary according to how it is implemented and managed in each country. The first is waiting lists due to the large number of people seeking health services, which can result in delays in treatment and frustration for patients. Limited choice can also be perceived as a disadvantage by those who want more healthcare options. Moreover, as the financing of an NHS comes from taxpayers' money, it is associated with limited budgets and financial pressures to contain costs, which can necessarily lead to a lack of resources, a reduction in professionals and limitations in the coverage of medical services. Another aspect that usually coexists in any NHS is political interference and bureaucracy, which can affect decision-making and the allocation of resources in a way that is not entirely based on clinical criteria, as well as the stability and efficiency of services. In addition, private systems may have more resources to invest in the latest medical technologies, leading to possible improvements in treatment and services. Finally, the NHS may face a shortage of

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doctors, nurses and other health professionals, further increasing waiting lists and pressure on the system.

Faced with these problems, and in order to guarantee sustainability for the foreseeable future, the Portuguese NHS must undergo strategic transformations. It is true that it needs more resources for its development. But that alone is not enough. The necessary transformations need to be made to respond to today's challenges, as strategic vision and action are required, as well as a new model of governance for the health system and the SNS.

In this context, the NHS Health Foundation has identified ten theses for transforming the NHS in a changing world. Among other aspects, these transformations include life journeys, ageing, intergenerational relationships and mental health. In addition, the importance of public health is emphasized, especially local public health. These transformations must aim for people-centeredness, so-called personalized care, ensuring that all health prescriptions and interventions consider how they interfere with people's lives and safety. This also includes the development of new digitalized, people-centered information systems.

We need to invest in adaptive changes in proximity, in local leadership and in the integration of care, because we need decentralized management in proximity, with adequate autonomy, in an adaptive way and according to local circumstances, through entrepreneurial leadership, which responsibly assumes decision-making autonomy in relation to the proposed framework for managing change. In this way, we must once again invest in the concept of the health center, a unit that is closed to citizens. And we need to reactivate the concept of local health systems, bringing together the various local interests, be they public, private or social, along with other sectors such as education.

The new SNS must also be concerned with creating confidence among professionals in the future and in its ability to provide them with attractive and motivating professional careers. This includes remuneration, working conditions, diversity of working arrangements and working hours, as well as effective processes for detecting situations of professional dissatisfaction and suffering and responding in time to correct them.

Technological innovation must be present, encompassing a commitment to people's digital inclusion, strict respect and defense of digital rights and principles, and the establishment of a clear strategy for incorporating technology into the NHS. On the other hand, it is necessary to go beyond budgetary logics focused solely on the creation of gross wealth, regardless of its quality and the underlying inequalities. We need to start funding well-being goals for our population, with concrete short- and medium-term objectives, which requires a different approach when preparing the State Budget. The NHS must be seen not simply as an expense, but above all as an important multi-annual investment to guarantee the economic development and well-being of the population.

Finally, traditional governance models must be overcome, with disjointed, fragmented and sectoral responses. Today, the various levels of care are still organized in "silos" between which users are lost.

Personally, I have high hopes for the medium- and long-term direction that the new NHS Executive Board has in mind. However, the biggest problem is currently the short term and the resolution of the problems that are greatly affecting the people who use health services.

In conclusion to this personal reflection on the situation we are currently experiencing with the NHS, it is possible and urgent to help protect our NHS for the future. For the sake of the health and well-being of the entire population, the country's economy, social cohesion and democracy itself.

The future is at risk. We must join forces and everyone is needed. There is no time for guerrilla warfare motivated by petty interests. Considering the Portuguese reality, I argue that we have no alternative to a strong NHS, which responds to the needs of the people who come to it and in whom they have confidence.

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*O SNS é um património moral irrenunciável da nossa democracia porque é indispensável à cidadania, à dignidade individual e à justiça coletiva.*

António Arnaut

Nas últimas décadas, muito mudou nos sistemas de saúde dos vários países e surgiram vários desafios e problemas. De entre estes, podemos destacar o envelhecimento demográfico, a gestão dos recursos disponíveis, o surgimento da sociedade do conhecimento, a explosão das ferramentas e plataformas digitais, o avanço da tecnologia médica, as perspetivas, expectativas e ambições das novas gerações de profissionais e a maior consciência e vontade dos cidadãos em gerir a própria saúde e em participar nas decisões que a eles dizem respeito. Tudo se tornou extremamente mais complexo nestas últimas décadas e se intensificou aquando da Covid, com um controlo financeiro cada vez maior e mais centralizado.

O Serviço Nacional de Saúde (SNS) é uma das maiores conquistas após o 25 de abril de 1974 e um dos principais fatores de coesão da sociedade do Portugal democrático. Para garantir a sua sustentabilidade para os próximos tempos, o nosso SNS tem, no entanto, necessariamente de passar por transformações de natureza estratégica.

Em geral, a existência de um SNS tem aspetos positivos. O primeiro deles é o acesso universal, garantindo a todos os cidadãos, independentemente da sua situação financeira, um acesso a cuidados de saúde essenciais e eliminando barreiras financeiras. Ninguém é deixado de fora do sistema de saúde devido à falta de recursos. Relacionado com o anterior, um SNS promove a equidade na prestação de cuidados de saúde, fazendo com que as pessoas recebam tratamento com base nas suas necessidades clínicas, e não na sua capacidade para pagar, reduzindo assim as desigualdades de saúde entre grupos socioeconómicos. Outro aspeto positivo tem a ver com a acessibilidade e com o facto de os custos dos cuidados de saúde serem cobertos essencialmente por impostos, fazendo com que os cuidados sejam mais acessíveis para indivíduos e famílias, e permitindo-lhe que não se preocupem com despesas médicas catastróficas. Um quarto ponto está relacionado com a missão do SNS de promover a saúde e prevenir a doença, essencial para a segurança e bem-estar da população. Por fim, num SNS existe supervisão pública sendo prestadas contas ao governo e aos cidadãos, podendo estes ter uma palavra a dizer.

Por outro lado, qualquer SNS está também associado a alguns problemas, que podem variar de acordo com a forma como é implementado e gerido em cada país. O primeiro são as listas de espera devido ao grande número de pessoas que procuram os serviços de saúde, de que podem resultar atrasos no tratamento e frustração para os doentes. A escolha limitada pode também ser percebida como uma desvantagem por aqueles que desejam mais opções de cuidados de saúde. Além disto, como o financiamento de um SNS tem origem no dinheiro dos contribuintes, está associado a orçamentos limitados e a pressões financeiras para conter custos, podendo necessariamente levar à falta de recursos, à redução de profissionais e a limitações na cobertura de serviços médicos. Um outro aspeto que normalmente coexiste em qualquer SNS são as interferências políticas e as burocracias, o que pode afetar as tomadas de decisão e a alocação de recursos de forma não totalmente baseada em critérios clínicos, assim como a estabilidade e a eficiência dos serviços. A acrescentar, os sistemas privados podem ter mais recursos para investir em tecnologias médicas mais recentes, podendo levar a possíveis melhorias no tratamento e nos serviços. Finalmente, os SNS podem enfrentar uma escassez de médicos, enfermeiros e outros profissionais de saúde, fazendo com que aumente ainda mais as listas de espera e a pressão sobre o sistema.

Face a estes problemas, e para garantir a sustentabilidade para os próximos tempos, o SNS português tem necessariamente de passar por transformações de natureza estratégica. É um facto que necessita de mais recursos para o seu desenvolvimento. Mas isso, só por si, não é suficiente. É preciso fazer as transformações necessárias para responder aos desafios da atualidade, pois são necessárias visão e ação estratégicas e um novo modelo de governança do sistema de saúde e do SNS.

Neste contexto, a Fundação para a Saúde SNS identificou dez teses para a transformação do SNS num mundo em mudança. Entre outros aspetos, estas transformações incluem os percursos de vida, o envelhecimento, as relações intergeracionais e a saúde mental. Além disto é realçada a importância da saúde pública, em especial de uma saúde pública local. Estas transformações devem ter como alvo a centralidade nas pessoas, os denominados cuidados personalizados, assegurando que toda a prescrição e intervenção em saúde têm em conta a forma como interferem com a vida e a segurança das pessoas. Isto inclui também o desenvolvimento de novos sistemas de informação digitalizados e centrados nas pessoas.

Há que apostar em mudanças adaptativas de proximidade, nas lideranças locais e na integração de cuidados, pois é necessária uma gestão descentralizada de proximidade, com adequada autonomia, de forma adaptativa e de acordo com as circunstâncias locais, através de lideranças empreendedoras, que assumam responsavelmente a autonomia de decisão face ao enquadramento proposto para a gestão da mudança. Deste modo, há que voltar a apostar no conceito de centro de saúde, uma unidade de proximidade dos cidadãos. E há que reativar o conceito de sistemas locais de saúde, agregando os vários interessas locais, sejam eles públicos, privados ou socias, juntamente com outros setores como o da educação.

O novo SNS tem também de se preocupar com a criação nos profissionais de uma confiança no futuro e na capacidade deste lhes proporcionar carreiras profissionais aliciantes e motivadoras. Isto inclui retribuições, condições de trabalho, diversidade de regimes e horários de trabalho, para além de processos eficazes para detetar situações de insatisfação e sofrimento profissional e de responder, a tempo, para as corrigir.

A inovação tecnológica tem de estar presente, englobando a aposta na inclusão digital das pessoas, num rigoroso respeito e defesa dos direitos e princípios digitais, e no estabelecimento de uma estratégia clara de incorporação tecnológica para o SNS. Por outro lado, é necessário ir além das lógicas orçamentais apenas centradas na criação de riqueza bruta, independentemente da sua qualidade e das desigualdades subjacentes. É preciso começar a financiar metas de bem-estar para a nossa população, com objetivos concretos a curto e a médio prazo, exigindo-se ara isso uma outra abordagem na preparação do Orçamento do Estado. O SNS deve passar a ser encarado não simplesmente como uma despesa, mas, sobretudo, como um importante investimento plurianual para se garantir o desenvolvimento económico e bem-estar das populações.

Por fim, há que superar os modelos de governação tradicionais, com respostas desarticuladas, fragmentadas e setoriais. Os diversos níveis de cuidados ainda se mantêm hoje organizados em “silos” entre os quais navegam perdidos os utentes.

Pessoalmente, tenho muitas esperanças na orientação que a nova Direção Executiva do SNS tem em mente, a médio e a longo prazo. No entanto, o maior problema é, atualmente, o curto prazo e a resolução dos problemas que muito estão a afetar as pessoas que recorrem aos

serviços de saúde.

Em conclusão a esta reflexão pessoal da situação que vivemos hoje em dia com o SNS, é possível e urgente contribuir para que o nosso SNS se proteja do futuro. Para bem da saúde e bem-estar de toda a população, da economia do país, da coesão social e da própria democracia.

O futuro está em risco. Temos de unir esforços e todos são necessários. Não é tempo para guerrilhas motivadas por interesses pequenos. Considerando a realidade portuguesa, defendo que não temos alternativa a um SNS forte, que responda às necessidades das pessoas que a ele ocorrem e no qual têm confiança.

# ORIGINAL ARTICLES

## Feeding and eating difficulties in early childhood – Characterization of a child psychiatry consultation

### Dificuldades alimentares em crianças com menos de seis anos – Caracterização da consulta de pedopsiquiatria

Pedro Carvalho e Marques[1], Maria do Rosário Monteiro[1], Márcia Rodrigues[1], Graça Fernandes[1], Vânia Martins[1]

## ABSTRACT

**Introduction:** Feeding difficulties in early childhood are among the most common problems reported by parents and may reflect the child's own characteristics or a relational problem. They are associated with problems in later life, such as behavioral disorders, cognitive deficits, and eating disorders.

**Materials and Methods:** This study was a retrospective, descriptive analysis of sociodemographic and clinical data of children under six years of age with feeding or eating problems evaluated at a first consultation in a child psychiatry unit of a tertiary hospital between January 2019 and May 2021. Children with a diagnosis or suspected diagnosis of autism spectrum disorder were excluded.

**Results:** Of a total of 647 children evaluated, 57 (8.81%) were classified as having feeding difficulties. Their median age was 24.5 months. Food selectivity was the most frequently reported problem (45.6%), followed by difficulties in self-regulation at mealtimes (43.9%) and decreased appetite (33.3%). Among the mothers, 21% had a history of depressive disorders and 7% had a history of anxiety disorders. Forty-nine percent of children had patterns of interaction with their primary caregiver that were considered worrisome or disruptive. Fifty-four percent of the therapeutic interventions provided were child-parent psychotherapy.

**Conclusions:** Early identification and intervention are needed for children with feeding problems. Feeding problems are common in early childhood and a multidisciplinary approach must always be considered as they can affect several domains of the child's health and development.

**Keywords**: child psychiatry; feeding difficulty; early childhood; eating disorder; mental health

## RESUMO

**Introdução:** As dificuldades alimentares na primeira infância estão entre as principais queixas dos pais e podem refletir características intrínsecas da criança ou um problema relacional. Estas dificuldades estão associadas a problemas subsequentes no desenvolvimento da criança, como problemas comportamentais, défices cognitivos e perturbações do comportamento alimentar.

**Materiais e Métodos:** Foi realizada uma análise retrospetiva e descritiva dos dados sociodemográficos e clínicos de crianças com menos de seis anos de idade avaliadas em primeira consulta de Pedopsiquiatria de um hospital terciário por dificuldades alimentares entre janeiro de 2019 e maio de 2021. Crianças com diagnóstico ou suspeita de perturbação do espetro do autismo foram excluídas.

**Resultados:** De um total de 647 crianças avaliadas, 57 (8,81%) foram classificadas como tendo dificuldades ou problemas alimentares. A mediana de idades foi de 24,5 meses. A seletividade alimentar foi o problema alimentar mais comum (45,6%), seguida de dificuldades na autorregulação durante as refeições (43,9%) e apetite reduzido (33,3%). Vinte e um por cento das mães apresentava antecedentes de

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perturbação depressiva e 7% apresentava antecedentes de perturbação de ansiedade. Quarenta e nove por cento das crianças incluídas no estudo apresentava padrões de interação com o cuidador principal preocupantes ou perturbados. Em 54% das crianças, a orientação terapêutica mais comum foi psicoterapia criança-cuidador.

**Conclusões:** É necessária deteção e intervenção precoce para crianças com dificuldades alimentares. As perturbações alimentares são comuns na primeira infância e deve ser sempre considerada uma abordagem multidisciplinar das mesmas, uma vez que podem ter impacto em vários domínios do desenvolvimento e saúde da criança.

**Palavras-chave**: dificuldade alimentar; pedopsiquiatria; perturbação do comportamento alimentar; primeira infância; saúde mental

## INTRODUCTION

Feeding difficulties in early childhood are among the most common problems reported by parents.[1] Up to 40% of typically developing children experience feeding difficulties, with the percentage rising to 80% in children with developmental delays.[1,2] These difficulties include refusal to eat, decreased appetite, food selectivity, difficulty self-regulating at mealtimes, fear of eating, and vomiting, among others.[1-4] Feeding disorders are associated with problems later in life, such as behavioral disorders, cognitive deficits, and eating disorders.[4]

Identifying the etiology of the feeding problem can be challenging because it may reflect the child's own characteristics and/or a dysfunctional dyadic or family relationship.[5] The child may have difficulty self-regulating at mealtimes, difficulty with transitions and changes, sensory processing disorders, food refusal secondary to invasive medical procedures, or medical conditions that predispose to feeding problems.[2,5] Because it involves an interaction between the caregiver and the child, feeding difficulties may also reflect a relational problem.[5,6] For young children, food goes beyond its nutritional value, as its quality affects the child's sense of security, autonomy, and basic trust.[5] Disturbed patterns of interaction between mother and child in cases of feeding and eating disorders were described as early as 1983 by Chatoor and colleagues.[7] During mealtimes, there is an increasing conflict over autonomy and control between parent and child, exacerbated by the development of separation and individuation.[8] In the case of feeding disorders, there are usually inconsistent and non-contingent responses from caregivers who fail to read the infant's signals, leading to increased dyadic conflict and struggle for control.[7,8] There are also reports of disturbed triadic parent-child interactions in families of children with feeding disorders, with increased tension and negative affect, which impairs the children's self-regulatory abilities.[9]

Chatoor and colleagues proposed a diagnostic classification of feeding disorders divided into six categories: feeding disorder of state regulation, feeding disorder of reciprocity, infantile anorexia, sensory food aversion, feeding disorder associated with concurrent medical condition, and post-traumatic feeding disorder.[4] Later, the authors described a classification of feeding difficulties using a systematic approach in which the child's eating behavior is classified as restricted appetite, selective feeding, or fear of feeding, and the caregiver's feeding style is classified as responsive, controlling, indulgent, or neglectful.[3]

In the Diagnostic and Statistical Manual of Mental Disorders, the various presentations of feeding disorders can be grouped into a single avoidant/restrictive feeding intake disorder.[10] The Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-5™) defines three main diagnostic categories of eating disorders: overeating disorder, undereating disorder, and atypical eating disorder.[1]

The aim of this study was to conduct a descriptive analysis of a sample of children under the age of six who were seen in a child psychiatry consultation for feeding and eating difficulties.

## METHODS

A retrospective descriptive analysis of sociodemographic and clinical data of children under six years of age with feeding or eating problems, evaluated at a first consultation in a child psychiatry unit of a tertiary hospital between January 2019 and May 2021, was performed. Children with previous child psychiatry follow-up and children with a diagnosis or suspected autism spectrum disorder were excluded from the study.

Patient data were retrieved from their medical records. Patient anonymity and confidentiality were maintained during data collection.

Sociodemographic data of the patients and their parents were collected and described. Several data on feeding patterns were assessed: child's feeding behavior (food selectivity, difficulty with self-regulation at mealtimes, limited appetite, difficulty with transition to solid foods, vomiting or anticipatory gagging, fear of feeding, and chewing without swallowing), failure to thrive, prolonged mealtimes, disruptive and stressful mealtimes, nighttime feeding, breastfeeding, and duration of breastfeeding. Psychomotor development was also assessed using the Griffiths III Mental Development Scale.

Data on parental psychiatric history and parental history of food selectivity or eating disorders were also collected. The Graffar scale was used to stratify family social characteristics.

Attachment style was assessed using an adaptation (in three stages) of the Mary Ainsworth's Strange Situation Procedure.[11]

The Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC:0-5™) was used to classify patients' diagnosis.[1] There are several diagnostic axes in this manual. Axis I refers to the clinical diagnosis, while Axis II is used to characterize the relational context. The latter has two parts: an assessment of the level of adaptation of the primary caregiving relationship(s) (Part A) and an assessment of the level of adaptation of the broader caregiving environment (Part B). The levels of adaptive functioning in Part A define ranges of relationship adaptation, and in Part B define ranges of qualities of the caregiving environment.[1]

Therapeutic interventions were examined and classified as mother-child psychotherapy, occupational therapy with sensory integration, speech therapy, day care, and parent counseling only. Follow-up status was described as improved, stabilized, or worsened.

## RESULTS

Of a total of 647 children assessed at a first visit to an early childhood psychiatry unit, 57 (8.81%) were classified as having feeding problems or difficulties, of whom 31 (54.4%) were male. The median age was 24.5 months. The age distribution is shown in **Table 1**. Children under 36 months were the most common group with feeding problems (80.6%), with the majority in the third year of life. A large percentage of children with feeding problems were under twelve months of age (n=14; 24.5%). In this age group, the most common feeding problems were difficulties with self-regulation at mealtimes (n=8), followed by parent-perceived decreased appetite (n=7), and vomiting or anticipatory gagging (n=6). Of the 14 children less than one year of age, 11 were singletons, eight were breastfed, and nine were fed at night. Five infants younger than 12 months had a diagnosis of gastroesophageal reflux disease. The most common diagnosis in this age group was undereating disorder (n=11). Regarding the relational context, nine children under one year of age had relationships with their primary caregiver that were considered strained to dysfunctional (Levels 2 and 3 on Axis II of the DC:0-5™). Child-parent psychotherapy was provided to nine children in this age group.

Regarding first consultations, 41 (71.9%) were from inpatient referrals, ten (17.5%) were from outpatient referrals, and only six (10.5%) were from primary care referrals.

The types of feeding problems identified in this cohort are described in **Table 2**. For 31 children (54.4%), parents reported more than one type of feeding problem. Eleven children (19.3%) were reported to have failure to thrive or weight loss. Twenty-five parents (43.9%) reported long mealtimes, and 31 (54.4%) found mealtimes to be disruptive or stressful. Nocturnal feeding was reported in 14 cases (24.6%).

Breastfeeding was reported in 47 cases (82.5%), with the majority of infants (56.5%) being breastfed until six months of age. Twenty-nine infants (50.9%) were cared for at home, 27 (47.4%) were in day care, nursery, or kindergarten, and one infant was institutionalized. Twenty-eight infants (49.1%) were singletons, 24 (42.1%) had one sibling, and five (8.8%) had two or more siblings.

**Tables 3 and 4** show the main diagnoses registered in Axis I and II, respectively, based on DC:0-5™. In Axis I, undereating disorders and sensory processing disorders were the two most prevalent diagnoses. Noteworthy, in Axis II, 49.1% of children exhibited patterns of interaction with the primary caregiver that were considered worrisome or disruptive (Level 2).

Regarding medical conditions, nine children (15.8%) had a diagnosis of gastroesophageal reflux disease, nine (15.8%) were born prematurely, two (3.5%) had a nasogastric tube for enteral nutrition, and five (8.8%) had a diagnosis of cow's milk protein allergy. Of the total study population, 33 children were assessed using the Griffiths III Mental Development Scale. The results of this assessment is shown in **Table 5**.

**Table 6** depicts parental sociodemographic data, psychiatric history, and history of food selectivity or feeding disorders. The most common classification of family socioeconomic status was low/middle class (34.6%), followed by middle class (30.8%) according to the Graffar scale.

In 13 cases (22.8%) the attachment style was assessed using Mary Ainsworth's Strange Situation Procedure. Five cases (38.5%) were classified as secure attachment and eight (61.5%) as insecure attachment. In the insecure attachment group, half of cases were classified as avoidant insecure attachment and the other half were classified as ambivalent/resistant insecure attachment.

The therapeutic interventions evaluated in this study were not mutually exclusive, as it was possible to use different interventions in the same case, depending on the symptomatology and relationship difficulties observed. Child-parent psychotherapy was the most common intervention, used in a total of 31 cases (54.4%). A total of 24 children (42.1%) were referred to occupational therapy, with sensory integration being the second most frequently recommended therapeutic intervention. Ten children (17.5%) were referred for speech therapy. Seven children (12.3%) were referred for nutritional pediatrics. Day hospital care was indicated in two cases (3.5%), and parent counseling and psychoeducation with no other intervention was provided in three cases (5.3%).

At follow-up, 38 children (67%) had a favorable outcome with the intervention provided, while 18 (31%) showed no change. Only one child (2%) had a worsened outcome.

**Table 1** - Age distribution of the study population

| **Age** | **n (%)*** |
|---|---|
| < 12 months | 14 (24.5) |
| 12 - 24 months | 13 (22.8) |
| 25 - 36 months | 19 (33.3) |
| 37 - 48 months | 4 (0.7) |
| > 48 months | 8 (0.14) |

*N=57

**Table 2** - Types of feeding problems in the study population

| **Feeding problem** | **n (%)*** |
|---|---|
| Food selectivity | 26 (45.6) |
| Difficulty in self-regulation during mealtimes | 25 (43.9) |
| Limited appetite | 19 (33.3) |
| Difficulty transitioning to solid foods | 16 (28.1) |
| Vomiting or anticipatory gagging | 15 (26.3) |
| Fear of feeding | 3 (5.3) |
| Chewing without swallowing | 2 (3.5) |

*N=57

**Table 3** – Axis I diagnosis according to the DC:0-5™

| **Axis I diagnosis** | **n (%)*** |
|---|---|
| Undereating disorder | 25 (43.4) |
| Sensory processing disorder | 23 (40.4) |
| Relationship-specific disorder of infancy/early childhood | 5 (8.8) |
| Global developmental delay | 5 (8.8) |
| Night waking disorder | 3 (5.3) |
| Adjustment disorder | 2 (3.5) |
| Other anxiety disorder of infancy/early childhood | 1 (1.8) |
| Separation anxiety disorder | 1 (1.8) |
| Other mood disorder of early childhood | 1 (1.8) |
| Developmental language disorder | 1 (1.8) |

*N=57

DC:0–5™, Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood

**Table 4** – Axis II diagnosis according to the DC:0-5™

| **Axis II diagnosis** | **Level 1 n (%)*** | **Level 2 n (%)*** | **Level 3 n (%)*** | **Level 4 n (%)*** | **Unknown n (%)*** |
|---|---|---|---|---|---|
| Part A | 21 (36.8) | 28 (49.1) | 6 (10.5) | 0 (0) | 2 (3.5) |
| Part B | 27 (47.4) | 25 (43.9) | 3 (5.3) | 0 (0) | 2 (3.5) |

*N=57

DC:0–5™, Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood

Part A – Caregiver-infant/young child relationship adaptation

Part B - Caregiving environment and infant/young child adaptation

Level 1 - *Well-Adapted to Good-Enough Relationships/Environments*

Level 2 - *Strained to Concerning Relationships/Caregiving Environments*

Level 3 - *Compromised to Disturbed Relationships/Caregiving Environments*

Level 4 - *Disordered to Dangerous Relationships/ Caregiving Environments*

**Table 5** - Development assessment according to the Griffiths III Mental Development Scale

| **Scale** | **Under average (<88 points) n (%)** | **Average or above average (>88 points) n (%)** |
|---|---|---|
| Locomotor scale | 8 (24.2) | 25 (75.8) |
| Personal-social | 12 (36.4) | 21 (63.6) |
| Language | 9 (27.3) | 24 (72.7) |
| Eye and hand coordination | 15 (45.4) | 18 (54.6) |
| Performance | 14 (42.4) | 19 (57.6) |
| Global quotient | 15 (45.4) | 18 (54.6) |

*N=33

**Table 6** - Parental sociodemographic data, psychiatric history, and history of feeding problems

| | **Mother** | **Father** |
|---|---|---|
| Average age (years) | 34.7 | 35.8 |
| Academic background<br>Total, n=57 (%) | | |
| Middle school | 7 (12.3) | 15 (26.3) |
| High school | 22 (38.6) | 20 (35.1) |
| College | 21 (36.8) | 16 (28.1) |
| Masters degree | 6 (10.5) | 4 (7) |
| Postgraduate | 1 (1.8) | 2 (3.5) |
| Psychiatric history<br>Total, n=57 (%) | | |
| No history of psychiatric disorder | 41 (71.9) | 45 (78.9) |
| Depressive disorder | 12 (21.0) | 2 (3.5) |
| Anxiety disorder | 4 (7.0) | 5 (8.7) |
| Neurodevelopmental disorder | 0 (0) | 1 (1.8) |
| Personality disorder | 2 (3.5) | 2 (3.5) |
| Feeding and eating disorder | 1 (1.8) | 0 (0) |
| Substance use disorder | 1 (1.8) | 1 (1.8) |
| Other | 0 (0) | 2 (3.5) |
| Background of food selectivity/feeding disorder<br>Total, n=57 (%) | | |
| No | 5 (8.8) | 6 (10.5) |
| Yes | 4 (7) | 1 (1.8) |
| Unknown | 48 (84.2) | 50 (87.7) |

## DISCUSSION

This study sought to characterize a population of children with feeding difficulties evaluated in a child psychiatry unit.

Approximately 25% of children are identified by parents as having feeding difficulties, with only 1-5% meeting criteria for a feeding disorder.[3] Benjasuwantep *et al.* studied 402 healthy children aged one to four years and found a prevalence of feeding problems of 26.9%.[12] In a study designed to investigate the prevalence of feeding disorders in typically developing young children, the authors used a parental questionnaire with high reliability and validity in detecting feeding problems (Behavioral Pediatrics Feeding Assessment Scale) and found that 8.2% had an abnormal total frequency score and 26.6% had an abnormal total problem score.[13] Wright *et al.* conducted a cross-sectional analysis of 455 children from a population-based cohort at 30 months and found feeding difficulties in 20% of parent reports.[15] This study found a prevalence of feeding difficulties of 8.81%, which is significantly lower than the above studies. These differences may be explained by the different methodologies used, as most studies used a questionnaire-based approach with cross-sectional analysis, unlike the present study. In addition, the present study focused on a clinical population and, to the authors' knowledge, similar studies in the literature have been conducted only in normal and typically developing children.[12-15] Furthermore, the definition of feeding difficulties/problems is highly variable and non-specific across studies, and some studies assess a population of children older than the one included in this study. This makes it difficult to compare results.

The results of this study reflect a low number of referrals of children with feeding difficulties to child psychiatry consultation. A high prevalence of children with feeding difficulties would be expected because these difficulties are among the most common referrals of infants and toddlers to child psychiatry units.[5] The low number observed in this study may be explained by a lack of awareness among general practitioners and pediatricians that child psychiatry can provide effective assessment and intervention for childhood

feeding and eating problems. Another explanation is that parents may tolerate certain disruptive eating behaviors in children without recognizing that they may constitute a disorder and therefore do not seek medical care. Mental health stigma regarding children and infants may be another reason for low referral of children with feeding problems for medical follow-up.

Children under 36 months were found to be the main group with feeding problems, with most occurring in the third year of life. During this period, the child's increasing sense of autonomy and individuation often presents a challenge and a period of conflict for caregivers during mealtimes. In a study of 108 children by Benjasuwantep *et al.*, feeding problems were most common in the second year of life.[12] These discrepancies may be explained by differences in methodology and inclusion criteria between among studies, as children in the latter study were between one and four years of age.

A large percentage of children with feeding problems in this study (24.5%) were under twelve months of age. Feeding problems have been reported in 1-2% of infants under one year of age, which is a significantly lower percentage than that found in this study.[4] These results may be explained by the fact that a significant proportion of cases included in the study were assessed in an Early Childhood Mental Health Unit consultation, a specialized outpatient tertiary referral service for infants under three years old. In addition, the first year of life is marked by a profound change in feeding patterns, with complementary foods introduced at around six months. This leads to changes in feeding routines and increased infant autonomy, which can be challenging for some parents to adjust to. If this process is not well coordinated between infant and caregiver, a feeding disorder may emerge.

More than half of children in this study had more than one feeding problem reported by their parents, making it difficult to differentiate which types of feeding problems may have the greatest impact. The most common type of feeding problem was food selectivity, identified in 45.6% of children, a percentage significantly higher than that reported in the literature.[12,14] This may be explained by the fact that this study was based on a clinical population with challenging feeding and behavioral problems. In a study of 959 healthy children aged 1.5 to 6 years, 25.1% were classified as picky eaters.[14] However, this study excluded children with psychiatric or psychological disorders. In another study, highly selective feeding was the most common type of feeding problem, similar to the present study, found in 15.4% of children with feeding problems.[12] Carruth *et al.* conducted a cross-sectional study of 3022 children without psychiatric or developmental problems and found that the percentage of children identified as picky eaters increased from 19% to 50% from four to 24 months.[16] Physicians must acknowledge that food selectivity (or picky eating) is a very common and normal part of child development, but in some severe cases it can be an important cause of feeding difficulties and possible failure to meet adequate nutritional or energy needs.[17] Benjasuwantep and colleagues described that energetic children with little interest in eating and limited appetite represented the second and third most common types of feeding problems, respectively, which is consistent with the present study's findings.[12] After food selectivity, difficulties in self-regulation at mealtimes and reduced appetite were the most common types of feeding problems. Overall, 33.3% of parents reported reduced appetite in their children, which is a significantly higher percentage than that found by Wright and colleagues in a healthy population (10.9%).[15]

Only 10% of cases were referred from primary care, highlighting the need for increased awareness of feeding difficulties in early childhood among primary care providers, which can be achieved through psychoeducational approaches among these professionals.

Almost 20% of the children assessed for feeding and eating difficulties had poor weight growth, highlighting the need for these cases to be assessed in a collaborative and multidisciplinary approach between child psychiatry and pediatrics.

One quarter of the children studied were fed at night. A higher prevalence of night feeding (79.6%) was found in a study of children with feeding problems.[12] This feeding practice is very common among caregivers who are concerned that their child is not getting enough nutritional intake during the day. However, it has several consequences, such as the risk of early childhood obesity and decreased nighttime sleep duration.[18,19]

Half of the population in this study did not attend day care or kindergarten. Since many feeding difficulties are related to disrupted parent-child dynamics, it is not surprising that 50% of children spent the entire day in the care of their parents.[7-9]

Prolonged mealtimes are common among children with feeding problems, as documented in the present and previous studies.[12,15] In this study, 43.9% of parents reported prolonged mealtimes, which is significantly higher than the 10.9% found by Wright and colleagues.[15] However, that study was conducted with typically developing children and not in a clinical population such as the present one. Furthermore, in a study of children aged one to four years, those with feeding problems had mealtimes longer than 30 minutes compared to typically developing children, which is consistent with the findings of this study.[12]

Mealtimes are often perceived as stressful by parents, as shown in this study, where more than half of parents (54.4%) perceived mealtimes as disruptive. This is significantly higher than the 6.5% reported by Wright *et al.*,[15] which again may be explained by differences in the study populations (clinical vs. non-clinical). Toddlers with feeding difficulties are perceived by caregivers as having more difficult temperamental characteristics, requiring more attention, and being more prone to negative affect.[20] Differences in perceptions between mothers and fathers were not explored in the present study.

As expected, the two most common diagnoses in this study were undereating disorders (43.4%) and sensory processing disorders (40.4%). Up to 40% of caregivers report that their children have feeding problems, namely lack of interest or refusal to eat, food selectivity, slow feeding, and difficulty regulating their state during

feeding.[1,2] These complaints are part of the criteria for undereating disorders.[1] Sensory processing disorders are diagnosed when the infant or toddler exhibits behaviors that reflect alterations in sensory input regulation and interfere with daily functioning, such as at mealtimes.[1] It has been described that children with sensory processing disorders, such as sensory over-responsivity disorder, may manifest severe feeding problems.[1] Also, sensory processing difficulties are more commonly observed in young children with feeding problems, and there is an association between increased sensory sensitivity and food selectivity.[20-25] Therefore, a high number of children with sensory processing disorders would be expected in this study.

The most common type of intervention was child-parent psychotherapy. Almost half of the children included in this study had patterns of interaction with their primary caregiver that were considered worrisome or disruptive, and in these cases, child-parent psychotherapy was a valuable intervention. This type of intervention is also used when there is no clear indication of a disturbed relationship, but there is evidence of worrisome aspects of the dyadic interaction that may lead to a troubled child-caregiver relationship. Feeding difficulties tend to reflect a problematic dyadic relationship, and therefore a relational approach needs to be incorporated into the management of feeding and eating disorders in early childhood.[3]

Children with apparent sensory processing difficulties were referred for assessment (and further intervention) by sensory integration occupational therapy. Of the population studied, 24 children (42.1%) were referred for this intervention, making it the second most common recommended therapeutic intervention. Many children with feeding difficulties have sensory processing problems that affect the child's ability to process multiple sensory stimuli from food.[21,22] Indeed, there is a need for a multidisciplinary approach that includes sensory assessment of infants and toddlers with feeding difficulties.

One of this study's main findings was that 21% of the mothers had a history of depressive disorder and 7% had a history of anxiety disorder. An association between maternal depression and anxiety and infant feeding difficulties has been described.[5,26] Chatoor *et al.* also pointed out that mothers who are depressed or anxious have more difficulty managing their child's feeding difficulties at mealtimes.[4]

Assessment of attachment patterns was only performed in 13 cases in this study, with 61.5% classified as having insecure attachment. In previous studies by Chatoor and colleagues, infants with infantile anorexia had higher rates of insecure attachment, which may exacerbate feeding problems. However, feeding difficulties can also occur within securely attached child-parent dyads.[6,20] The literature also describes an association between insecure attachment and the development of eating disorders later in life.[27-29]

This study has several limitations. Being a retrospective and descriptive study based on clinical reports, it was not possible for the authors to perform a complete and individualized assessment of the cases included. The use of validated questionnaires would be helpful to provide more measurable and comparable data.[13] It was also difficult to make valid comparisons between study results and those found in the literature because of the large variance in definitions used to characterize feeding difficulties, discrepancies in study methodologies and outcome measures, and different age ranges of participants in different studies. Therefore, conclusions regarding the prevalence of feeding difficulties should be drawn with caution.

A strength of the study is that it was based on a clinical population and, to the authors' knowledge, is one of the few studies conducted in a clinical setting. Most studies on the prevalence of feeding problems in infants and toddlers are based on healthy and typically developing children.[12-14]

## CONCLUSION

Although the estimated prevalence of children with feeding problems in this study was lower than that reported in the literature, it still represents a significant proportion of the cases referred to the child psychiatry unit in question. A multidisciplinary approach must always be considered, as feeding problems may have a relational, organic, or sensory processing etiology and may affect multiple domains of the child's health and development. This work highlights the importance of early identification and intervention for children with feeding difficulties.

## AUTHORSHIP

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# ORIGINAL ARTICLES

## Five years of universal newborn hearing screening: An incidence study

### Cinco anos de rastreio auditivo neonatal universal: Estudo de incidência

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## ABSTRACT

**Introduction:** Universal newborn hearing screening (UNHS) is an essential tool for early diagnosis and prognosis of hearing loss. The aims of this study were to estimate the incidence of sensorineural hearing loss (SNHL) in the Baixo Vouga region, to evaluate the importance of first-degree parental consanguinity (FDPC) as a risk factor for hearing loss in the UNHS program of Centro Hospitalar do Baixo Vouga (CHBV), and to determine the quality of hearing screening program and the main difficulties experienced in its implementation.

**Methods:** Retrospective incidence study of all newborns born in a level II hospital between 2014 and 2018. According to the presence or absence of risk factors (RF) for early childhood hearing loss, each newborn was included in one of two groups: with RF and without RF. FDPC was included in addition to the recommended RF. All newborns underwent hearing screening. Those with abnormal screening or with RF also performed diagnostic audiologic evaluation.

**Results:** Eight thousand seven hundred and twenty-seven newborns were evaluated, of whom 90.88% had no RF. The incidence rate of SNHL was 2.4/1000 infants without RF and 27.6/1000 infants with RF. Screening had an effectiveness of 99.86%, a false positive rate of 0.34%, and a referral rate to an otolaryngologist of 1.24%. FDPC was the third most common RF and the first in infants with SNHL. The missed diagnostic evaluation rate was 44.56%.

**Discussion:** The reported incidence of SNHL is similar to that reported in the literature. The CHBV UNHS program meets national guidelines for quality screening. FDPC is an important RF in this population. The rate of missed diagnostic evaluations was identified as a priority area for improvement.

**Keywords:** consanguinity; hearing loss; neonatal screening; sensorineural hearing loss

## RESUMO

**Introdução:** O rastreio auditivo neonatal universal é uma ferramenta essencial no diagnóstico precoce e no prognóstico da surdez. Os objetivos deste estudo foram estimar a incidência de hipoacusia sensorioneural (HSN) na região do Baixo Vouga, avaliar a importância da consanguinidade parental em primeiro grau (CPPG) como fator de risco para surdez e verificar a qualidade do programa de rastreio e as principais dificuldades na sua implementação.

**Métodos:** Estudo retrospetivo de incidência de todas as crianças nascidas num hospital de nível II entre 2014 e 2018. Cada recém-nascido foi incluído num de dois grupos em função da presença ou ausência de fatores de risco (FR) para surdez: com FR e sem FR. Para além dos FR

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recomendados foi incluída também a CPPG. Todos os recém-nascidos foram submetidos a rastreio; aqueles com rastreio anormal ou com FR, realizaram também avaliação audiológica diagnóstica.

**Resultados:** Foram estudados 8,727 recém-nascidos, 90,88% dos quais sem FR. A taxa de incidência de HSN foi de 2,4/1000 crianças sem FR e 27,6/1000 crianças com FR. O rastreio apresentou uma efetividade de 99,86%, um índice de falsos positivos de 0,34% e uma taxa de referenciação para consulta de otorrinolaringologia de 1,24%. CPPG foi o terceiro FR mais comum e o mais prevalente entre as crianças com HSN. A taxa de não comparência à avaliação diagnóstica foi de 44,56%.

**Discussão:** A incidência de HNS está de acordo com o descrito na literatura. O programa de rastreio cumpre as diretrizes nacionais para um rastreio de qualidade. A CPPG é um importante FR na população considerada. A taxa de não comparência à avaliação diagnóstica é um foco prioritário de otimização.

**Palavras-chave:** consanguinidade; hipoacusia; hipoacusia sensorioneural; rastreio neonatal

## INTRODUCTION

Hearing is a fundamental perception for the normal bio-psycho-social development of a child.[1-2] It depends on the functioning of the auditory system, which consists of the ears and the auditory pathway.[2] The ear ensures the capture of sound and its conversion into an electrical signal that travels along the auditory pathway to the auditory cortex, where it is integrated and interpreted.[1-3] Because the functionality of the auditory system is known from birth, several assessment methods based on electrophysiological measurements have been developed to provide a reliable estimate of hearing in newborns and infants.[1,4-6]

Since permanent hearing loss affects 1-2 per 1000 newborns, a Universal Newborn Hearing Screening (UNHS) program has been developed to diagnose these cases.[1,4-5] In Portugal, the first national guidelines of the Group for Screening and Intervention of Child Deafness (GRISI) were published in 2007, with the aim of prioritizing screening, diagnosis, and intervention for hearing loss at the national level.[5,7] Since then, the UNHS program has been widely disseminated in the Portuguese National Health Service.[8]

There are sensitive periods during which the central auditory pathway undergoes significant neuroplasticity, and critical time windows for audiological intervention have been defined to ensure adequate development of the central auditory pathway.[2] Accordingly, all newborns must be screened in the first month of life to diagnose hearing loss by three months of age and initiate early intervention by six months of age.[4-5] These timelines allow for normal language development.[1,3-4] However, recent international recommendations suggest a more ambitious goal for hospitals that already meet these requirements, advocating screening in the first month, diagnosis by two months, and intervention by three months.[4]

Currently, there are two validated electrophysiologic techniques for screening this population: otoacoustic emissions (OAE) and automated auditory brainstem response (AABR).[4,5] OAE assesses a smaller portion of the auditory system because it only detects changes in the external auditory canal (EAC), middle ear, and inner ear up to the outer hair cells, unlike AABR, which also examines the auditory pathway.[2-4,6]

Hearing loss can be classified as conductive hearing loss (CHL), sensorineural hearing loss (SNHL), or mixed hearing loss (MHL). Severity can be mild, moderate, severe, or profound.[1-4] Several factors are known to increase the risk of congenital, progressive, or late-onset hearing loss. These are called risk factors and, when present, warrant a differential screening protocol consisting of a high-risk screening. These children require audiologic diagnostic evaluation even if they pass the initial screening.[4]

The aims of this study were to (i) estimate the incidence of SNHL in the Baixo Vouga region; (ii) determine whether the UNHS program of Centro Hospitalar do Baixo Vouga (CHBV) meets the GRISI quality criteria; (iii) assess the importance of first-degree parental consanguinity as a risk factor for hearing loss in the UNHS program; (iv) assess children's age at screening and diagnosis; (v) identify the main difficulties in implementing the hearing screening protocol; and (vi) identify areas for protocol improvement.

## MATERIAL AND METHODS

This was a retrospective incidence study of all infants born between January 2014 and December 2018 in the Baixo Vouga region, specifically at CHBV, and at other private maternity hospitals in the region without hearing screening available. Electronic clinical records from CHBV UNHS computer platform were reviewed, and demographic and clinical data were collected, including gestational age, mode of delivery, gender, birth weight, risk factors, hearing screening results, diagnostic results (when available), and age at screening and diagnosis. For children born in private hospitals, only data on gender, risk factors, hearing screening results, diagnostic results, and age at screening or diagnosis could be collected. In these cases, missing data were assumed for the remaining variables.

Risk factors included those recommended by GRISI and first-degree parental consanguinity, as a significant number of cases of hearing loss have been identified in this context in previous years (**Table 1**).

**Table 1 –** Risk factors for childhood hearing loss included in the protocol

| Risk factors for childhood hearing loss |
|---|
| Family history of childhood hearing loss |
| First-degree parental consanguinity |
| ≤32 weeks gestational age |
| Very low birth weight (< 1500g) |
| 1-minute Apgar score ≤4 or 5-minute Apgar score ≤6 |
| Craniofacial malformations or others associated with hearing loss |
| In utero infections (toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis) |
| Sepsis/neonatal meningitis and/or ototoxic drugs for ≥5 days |
| Hyperbilirubinemia with exchange transfusion criteria |
| Intracranial hemorrhage |
| Invasive ventilation and neonatal intensive care for more than 48 hours |

Screening results were classified as ***pass*** (if the test result was normal) or ***refer*** (if the test did not meet the required criteria). ***Pass*** and ***refer*** thresholds were defined according to the manufacturer's rules. A Natus®MADSEN AccuScreen device was used for OAE and AABR. Diagnostic audiologic evaluation included clinical evaluation by an otolaryngologist and auditory brainstem response (ABR) using the Interacoustics Eclipse EP25 device from Interacoustics®. All screening and diagnostic testing was performed by an audiologist with pediatric experience in a controlled sound environment, preferably during spontaneous sleep.

Depending on the presence of risk factors, each infant was assigned to one of two groups: with or without risk factors. The pediatricians were responsible for identifying these risk factors. All infants underwent an initial hearing screening, preferably between 24 and 48 hours of life, using OAE (mostly) and/or AABR. Those classified as ***refer*** performed a second screening, also with OAE and/or AABR, usually by 15 days of life. All screening tests included bilateral evaluation, regardless of the differential result of the first test. Children without risk factors and classified as ***pass*** in either the first or second screening were discharged from the protocol. Otherwise, those classified as ***refer*** in both phases or in the first phase and who did not undergo the second evaluation were sent for diagnostic audiologic evaluation, which included an otolaryngologic evaluation and diagnostic testing using the auditory brainstem response method. Infants with risk factors despite screening results were also referred for diagnostic evaluation.

For descriptive analysis, mean and standard deviation were used to characterize normally distributed quantitative variables, and median and interquartile range (IQR) were used to characterize non-normally distributed quantitative variables. Normality was determined after analysis of each histogram. Qualitative variables were expressed as absolute numbers and relative frequencies. Microsoft Excel® was used for computer data entry, and IBM® SPSS® Statistics software, version 27.0, for Mac® was used for statistical analysis.

## RESULTS

During the five-year period considered, 8,727 infants were included in the CHBV UNHS computer platform, of whom 97.55% were born in CHBV and the remaining outside the hospital center. In this population, 90.88% of infants had no risk factors, 9.07% had one or more risk factors, and the presence of risk factors could not be determined in 0.05% of infants (n=4). Among children with risk factors, 81.94% had only one risk factor, 14.27% had two risk factors, and the remaining 3.79% had three or four risk factors. The three most common risk factors were a family history of childhood hearing loss (n=263), followed by neonatal sepsis/meningitis and/or ototoxic drug administration for five or more days (n=220), and a history of first-degree parental consanguinity (n=115).

Of all children included in the platform, only 19 (0.22%) did not undergo any type of screening or diagnostic evaluation. Of the children born at CHBV, 99.86% underwent a hearing screening.

In the group without risk factors (7,931 cases), 99.87% were screened, of which 90.15% had a ***pass*** result and 9.85% had a ***refer*** result. Infants classified as ***refer*** had a second screening and the vast majority (91.15%) were discharged because they were classified as ***pass***. Of the 69 infants referred for diagnostic evaluation, 23.18% had no evaluation, 28.99% had normal hearing, 18.84% had CHL, and 28.99% had SNHL.

In the group with risk factors (792 cases), 98.99% had an initial screening and 86.10% were classified as ***pass*** and 13.90% as ***refer***. The referrals were sent for a second screening and 63.30% were classified as ***pass***. Among the children with risk factors who passed the

screening, 47.58% did not complete or did not undergo a diagnostic evaluation, and this percentage decreased to 27.50% in the group of children who were classified as ***refer*** in one or both screening phases.

Of all children who underwent diagnostic evaluation (474 cases), 71.73% had a normal result. Of the remaining 134 cases, 76.87% had CHL, 20.90% had SNHL, and 2.24% had MHL. For SNHL, the incidence rate was 2.4 per 1000 infants without risk factors and 27.6 per 1000 infants with risk factors. In addition, a false positive rate of 0.34% and a referral rate to an otolaryngologist of 1.24% were identified.

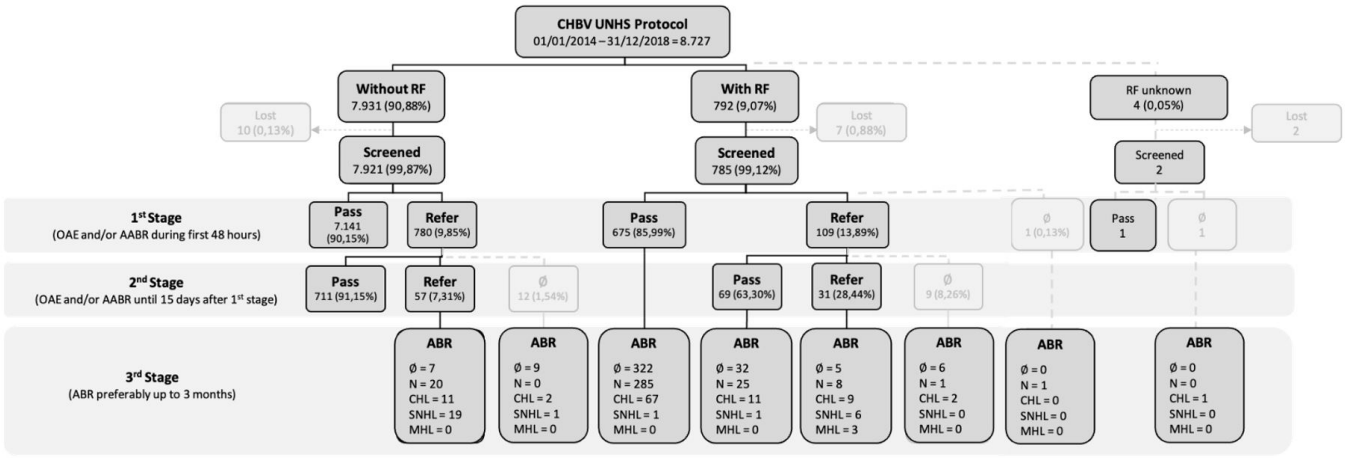


**Figure 1 –** Results of the universal newborn hearing screening protocol

AABR: automated auditory brainstem response; ABR: auditory brainstem response; CHL: conductive hearing loss; MHL: mixed hearing loss; N: normal; OAE: otoacoustic emissions; RF: risk factors; SNHL: sensorineural hearing loss; UNHS: universal newborn hearing screening; Ø: unrealized

**Table 2** shows the cases of hearing loss according to the presence of risk factors. Analysis of SNHL cases shows that the most common risk factors were first-degree parental consanguinity (n=4) and family history (n=4).

**Table 2 –** Characteristics of hearing loss cases in the study

| Risk factors | Type of hearing loss | | | | |
|---|---|---|---|---|---|
| | Sensorineural hearing loss (SNHL) n=28 | | | | Mixed hearing loss (MHL) n=3 |
| Absent n=20 | 1st OAE | Refer | | Refer | - |
| | 2nd OAE | Refer | | - | - |
| | ABR | SNHL (n=19) | | SNHL (n=1) | - |
| Present n=11 | 1st AABR | Pass | Refer | Refer | Refer |
| | 2nd AABR | - | Pass | Refer | Refer |
| | ABR | SNHL (n=1) | SNHL (n=1) | SNHL (n=6) | MHL (n=3) |
| | Risk factor | Preterm (n=1) | Consanguinity (n=1) | Sepsis (n=2)<br>Family history (FH) (n=2)<br>Consanguinity and FH (n=1)<br>Craniofacial malformation (n=1) | Consanguinity (n=1)<br>Consanguinity and FH (n=1)<br>Craniofacial malformation (n=1) |

AABR: automated auditory brainstem response; ABR: auditory brainstem response; FH: family history; MHL: mixed hearing loss; OAE: otoacoustic emissions; SNHL: sensorineural hearing loss; -: unfulfilled.

Children had a median age of two days (IQR 3) at the first screening and 22 days (IQR 16) at the second screening. At the time of diagnosis, children classified as ***refer*** at both screenings had a median age of 197 days (IQR 265.25), and at the time of diagnosis, children with an indication for this evaluation had a median age of 263 days (IQR 229.75).

Analysis of the rate of missed screenings showed that only 0.24% of infants (n=21) missed the first screening and 2.36% (n=21) missed the second screening. In the diagnostic phase, 381 of 855 infants (44.56%) missed or did not complete the diagnostic evaluation, of whom 92.91% had been classified as ***pass*** at either the first or second screening. When the results were broken down by year, a significant proportion of the 381 infants were born in 2018 (38% in the group classified as ***pass*** and 48% in the group classified as ***refer***). Conversely, between 2014 and 2017, the annual rate of missed screenings at this stage varied between 10% and 24% for children classified as ***pass*** and between 8% and 15% for those classified as ***refer***.

In infants without risk factors, screening was performed with OAE only, so it was impossible to exclude cases of auditory neuropathy. In infants with risk factors, both OAE and AABR were performed in 126 cases. Only four of these had discrepancies between the results, and all had normal ABR results. This suggests that there were no cases of auditory neuropathy in this group.

## DISCUSSION

CHBV offers newborn hearing screening to all infants born in its area of influence. This is not only an advantage for the local population, but also provides more reliable data on hearing screening and diagnosis of hearing loss in the Baixo Vouga region.

A UNHS protocol that stratifies children according to the presence or absence of risk factors for hearing loss, rather than according to their origin (nursery vs. neonatal intensive care), requires the analysis and systematic recording of risk factors in all infants. On the other hand, there may be cases where parents are unaware of the presence of risk factors at birth but recognize them later (e.g., cases of family history of hearing loss)[4], and registering them on a computer platform allows correction of the child's category and subsequent inclusion in the appropriate follow-up protocol.

Compared to other national studies, a higher prevalence of children with risk factors for hearing loss was found in this cohort, which may be due to the fact that consanguinity was considered as a risk factor and is a predominant one (one of the three most common risk factors).[9-11] Most cases of consanguinity were found in children from the Romani community. This may be explained by the prevalence of people from this community in the population supported by CHBV, as evidenced by the National Study of Romani Communities, which estimates that Aveiro district has the third highest number of resident Romani people at national level, and that the Baixo Vouga region is the group of municipalities with the fourth largest Romani population.[12]

Regarding screening results, the rate of children classified as ***pass*** and ***refer*** was similar to that reported in other national studies.[9-11] The UNHS program of CHBV was shown to meet national guidelines for quality screening, with a screening effectiveness of 99.86% (>95%), a false-positive rate of 0.34% (<3%), and a referral rate for otolaryngologic consultation of 1.24% (<4%). The results of this UNHS program were also similar to those of international programs (**Table 3**).[13] It should be noted that the present study design did not allow estimation of the rate of false-negative screening results.

**Table 3 -** Comparison of CDC and CHBV universal newborn hearing screening programs[13]

| Universal newborn hearing screening items | Data | |
|---|---|---|
| | **CDC (2018)** | **CHBV (2014-2018)** |
| **Documented hearing screening** | | |
| Percent screened (screenings/births) | 98.3% (n = 3,681,776) | 99.86% (n = 8,501*) |
| Percent referred (referrals/screenings) | 1.6% (n = 60,258) | 1.25% (n = 109) |
| **No documented hearing screening** | | |
| Percent without documented screening (loss to follow-up/births) | 1.7% (n = 63,039) | 0.14% (n = 12*) |
| **Documented diagnosis** | | |
| Percent diagnosed (diagnoses/referrals) | 64.1% (n = 38,634) | 75.23% (n = 82) |
| **No documented diagnosis** | | |
| Percent without documented diagnosis (no documented diagnoses/ referrals) | 35.9% (n = 21,624) | 24.77% (n = 27) |

CDC: Centers for Disease Control and Prevention; CHBV: Centro Hospitalar do Baixo Vouga
*Only infants born at CHBV were considered.

The diagnosis of SNHL reached 2.4 per 1000 children without risk factors and 27.6 per 1000 children with risk factors, which is in line with the incidence of hearing loss described in the literature.[5] The detection of SNHL cases in children without risk factors reinforces the importance of universal screening as advocated in recent decades, as opposed to selective screening for risk groups, as initially established.[4] The diagnosis of SNHL in children with risk factors and a ***pass*** result also reaffirms the need for diagnostic evaluation in this group of patients and raises increased concern about missed screening in this population.

In the present study, four out of 11 children with SNHL and risk factors had first-degree family consanguinity, which was the only risk factor in half of them. This could be explained by the fact that approximately 50% of all cases of deafness have a genetic etiology, 70% of which are non-syndromic, and 80% from these are autosomal recessive.[2] Therefore, in these cases there is no family history of the disease, and parental consanguinity is an important clue to the possibility of recessive inheritance.[2,14] Furthermore, in one of these cases, the result of the first screening was ***refer*** but the result of the second screening was ***pass***, which means that if this risk factor had not been considered, this child would have been discharged from the protocol and would not have undergone diagnostic assessment. Following these findings, this research group developed a cohort study during the same time period to evaluate the importance of defining first-degree parental consanguinity as a risk factor for childhood hearing loss. This study found that children with first-degree parental consanguinity were three times more likely to have a ***refer*** result at screening than children without risk factors.[15] Although additional studies are needed, the identification of a significant number of cases of parental consanguinity among children diagnosed with SNHL in CHBV is relevant. Therefore, it seems prudent to continue to consider parental consanguinity as a risk factor for hearing loss.[16]

The rate of missed hearing screenings comprised (i) children who did not undergo screening (due to neonatal death, transfer to more differentiated services, or absence from consecutive appointments when it was impossible to perform screening in the maternity ward) and (ii) children who did not undergo a second screening or diagnostic evaluation when indicated (including children born in CHBV but not living in its area of influence, children who changed residence, cases who had no means of contact or did not respond after several contact attempts, and children for whom it was impossible to perform diagnostic evaluation because of sleep interruption). These different reasons for not completing the protocol require different approaches for correction.

The rate of missed hearing screenings was shown to increase significantly at the second screening and diagnostic evaluation. At this stage, the highest rate of non-compliance was observed in the group with risk factors who was classified as ***pass*** in screening. This could be justified by the fact that the result could somehow falsely reassure parents and health professionals.[17] In addition, the time constraints of screening all children with risk factors by six months of age, as recommended at the time of the study, prioritizes children classified as ***refer*** in both screenings. This ensures a more timely diagnosis of children who are more likely to have hearing loss, but also delays the diagnostic evaluation of the remaining children to more advanced ages, resulting in the need for multiple diagnostic evaluations before a definitive result is obtained (due to greater difficulty with spontaneous sleep and higher incidence of middle ear effusion with age). Missed hearing screenings in this group of children may be related to parental difficulty in understanding that children with hearing loss may respond to auditory stimulation, depending on the severity of the hearing loss. Beyond this point, an altered screening result is sometimes attributed to transient CHL without recognizing the possibility of its coexistence with a sensorineural deficit.[17-18] These points reinforce the need for ongoing professional training and parental awareness.

The discrepancy between the missed hearing screening rates in 2018 and previous years can be explained by the fact that data collection was completed in 2019, which may not have been sufficient to ensure adequate follow-up of children born in the previous year, thus affecting the results.

Regarding the UNHS program time targets, CHBV achieved the target of screening in the first month of life. However, the median time to diagnosis for ***refer*** cases was 6.5 months instead of the currently recommended 3 months. This highlights the missed opportunity to act at an ideal time window and reinforces the need to implement measures to reduce the rate of missed hearing screening at diagnostic assessment. This is also recognized as a reality internationally, as reported in a study where screening referrals failed to meet the recommended goal of assessment by six months of age in two-thirds of cases.[17]

When comparing the two screening techniques, the dissonance in results can be explained by the immaturity of the auditory pathways at the time of the first evaluation.

The CHBV computer platform allows several actions, including changing the category to which each child belongs (with vs. without risk factors) at any time, defining the incidence and prevalence of hearing loss in the population, and saving human and material resources. A future national online platform would be of great value to facilitate the monitoring of children followed in more than one hospital and in situations of change of residence.[4]

No less important, the presence of a multidisciplinary team is highly recommended for the success of a UNHS program.[4]

## CONCLUSIONS

Universal newborn hearing screening is an essential tool for early diagnosis and prognosis of hearing loss. Stratifying infants according to the presence or absence of risk factors for hearing loss may be a valuable improvement to the current national protocol. First-degree parental consanguinity is an important risk factor in this population.

Improving the rate of missed diagnostic screenings is a priority area for intervention.

## AUTHORSHIP

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# ORIGINAL ARTICLES

## Serotonin selective reuptake inhibitors and suicide risk in a Portuguese adolescent sample

### Inibidores seletivos de recaptação da serotonina e risco de suicídio numa amostra portuguesa de adolescentes

Nuno Duarte[1], Sarah Amaral[1], Marta Abrantes[1]

## ABSTRACT

**Background:** The adolescent population is at high risk for depressive disorders, and suicide is a leading cause of death in this age group worldwide. Selective serotonin reuptake inhibitors (SSRIs) remain the only approved pharmacological approach, despite concerns about suicidality.

**Objectives:** This study aimed to understand the relationship between antidepressant use and suicidality in an adolescent population from an Adolescent Psychiatric unit in Lisbon, Portugal.

**Methods:** A total of 296 medical reports of adolescent patients with depressive symptoms in psychiatric follow-up at the considered unit were reviewed. Two demographically and clinically similar samples were obtained, one exposed to SSRI treatment and one control group.

**Results:** A risk of suicide attempt of 0.006 was found in the group exposed to SSRIs versus 0.025 in the control group, corresponding to a relative risk of suicidality of 0.248. This difference did not reach statistical significance, despite a Bayes factor of 4.57 and a Pearson's r of -0.078.

**Conclusions:** The study results suggest that SSRIs do not increase the risk of suicide attempt in adolescents with depressive symptoms.

**Keywords:** antidepressant; attempt; depression; depressive disorder; second generation; suicide

## RESUMO

**Introdução:** A adolescência está associada a um risco elevado de perturbações depressivas, sendo o suicídio uma das principais causas de morte nesta faixa etária globalmente. Os inibidores seletivos de recaptação da serotonina (SSRIs) são a única terapêutica farmacológica aprovada internacionalmente neste contexto, apesar das preocupações com o risco de suicídio.

**Objetivos:** Este estudo procurou identificar a relação entre o uso de antidepressivos e o risco de suicídio numa amostra de adolescentes com sintomas depressivos seguidos numa Unidade de Psiquiatria da Adolescência em Lisboa, Portugal.

**Métodos:** Foram analisados os processos clínicos de 296 doentes com sintomatologia depressiva em seguimento na consulta de Psiquiatria da Adolescência. Foram obtidas duas amostras demográfica e clinicamente semelhantes, uma exposta a tratamento com SSRIs e outra sem exposição aos fármacos (grupo controlo).

**Resultados:** Os resultados revelaram um risco de suicídio de 0.006 no grupo exposto aos psicofármacos e 0.025 no grupo controlo, correspondente a um risco relativo de suicídio de 0.248. Esta diferença não foi estatisticamente significativa, apesar do fator de Bayes de 4.57 e do r de Pearson de -0.078.

**Conclusões:** Os resultados sugerem que os SSRIs não aumentam o risco de tentativa de suicídio entre adolescentes com sintomas depressivos.

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**Palavras-chave:** antidepressivo; depressão; perturbação depressiva; suicídio, tentativa

## INTRODUCTION

According to the World Health Organization (WHO), adolescence is the developmental period from childhood to adulthood.[1] Globally, one in seven 10-19 year olds experience a mental disorder, accounting for 13% of the global burden of disease in this age group.[2,3] Adolescence has the highest incidence of affective disorders, particularly depressive disorders, and suicide is a leading cause of death among 15-24 year olds worldwide.[2,4,5]

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) defines Major Depressive Disorder (MDD) as a syndrome that includes at least five symptoms (such as depressed mood and suicidal thoughts, among others).[6] Therefore, MDD is associated with several symptoms and risks, including suicidality.[4] According to the WHO's International Classification of Diseases-11 (ICD-11), several manifestations of suicidality can be considered (**Table 1**).[7]

**Table 1 -** ICD-11 definition of suicidal events[7]

| Event | Definition |
|---|---|
| Non-suicidal self-injury | Intentional self-injury inflicted to the body with the expectation that it will only lead to minor physical harm. |
| Suicidal ideation | Thoughts about the possibility of ending one's life. |
| Suicidal behavior | Concrete actions taken in preparation for ending one's life, without constituting suicidal attempt. |
| Suicidal attempt | Concrete behavior with the conscious goal of ending one's life. |

The international guidelines suggest managing mild depression in adolescents with psychological therapies, while antidepressants are not recommended at this stage.[8] Clinicians are instructed to manage moderate to severe depression with a combination of psychological therapy and an antidepressant.[8,9] Selective serotonin reuptake inhibitors (SSRIs) are the only antidepressants approved for pediatric patients and are the most commonly prescribed in the clinical practice.[8-10]

Although the adolescent serotonin system is thought to be similar to that of adults, some studies have shown several findings that suggest some differences, such as an important decrease in serotonin 1A (5-HT1A) binding and increased expression of the serotonin transporter in non-serotoninergic brain areas.[4] Maturation of the noradrenaline system is also thought to be delayed.[4]

Although SSRIs are known to improve several depressive symptoms, their use in children and adolescents has been questioned due to safety concerns, namely suicidal ideation and behavior.[10-13] Concerns peaked in 2004 when the United States Food and Drug Administration (FDA) issued a warning after a meta-analysis of 372 clinical trials showed increased suicidal ideation and behavior in patients receiving antidepressant treatment.[13] This led to a decrease in antidepressant prescriptions among adolescents and a paradoxical increase in suicide attempts.[11,13] Several studies have since challenged this warning.[4,11]

The last report of the Portuguese authorities on suicide accounted for 9.5 per 100,000 people in the year 2019.[14] Portugal has a high rate of antidepressant use compared to other European countries, with an increase of 83.5% between 2010 and 2020.[15] As is the case worldwide, SSRIs − most commonly sertraline − are the most prescribed antidepressants in the country.[16]

The aim of this study was to understand the relationship between antidepressant use and suicidality in an adolescent population followed at an Adolescent Psychiatric Unit in Lisbon, Portugal.

## MATERIALS AND METHODS

### *Study participants*

This study was conducted in patients who were referred to a psychiatric consultation at the Adolescent Psychiatry Unit – Clínica da Juventude, Hospital Dona Estefânia. Only patients with a first appointment during the year 2021 were included. Exclusion criteria comprised (1) ongoing antidepressant treatment at the first appointment, (2) absence of depressive symptoms at referral and/or at the first clinical assessment; and (3) insufficient data. Depressive symptoms were identified according to the ICD-11 symptomatology described for depressive disorders: depressed mood, decreased interest in activities, feelings of worthlessness, excessive guilt, hopelessness, recurrent thoughts of death, and reduced energy.[7]

### *Study procedures*

A controlled retrospective cohort study was conducted to examine how adolescents with depressive symptoms respond to SSRIs. All patients had an identification number that allowed for the collection of digital and physical records. Anonymity was maintained to ensure confidentiality. Data extraction was performed by child and adolescent psychiatry trainees.

### *Assessment*

Data collected included sociodemographic information (age and gender), symptomatology prior to referral and initiation of antidepressant therapy (depressive symptoms, nonsuicidal self-injury, suicidal behavior, and suicide attempts), pharmacologic therapy (antidepressant and date of initiation, as well as antipsychotic and anxiolytic medications), and posterior suicide attempts within the next three months (**Figure 1**).

Descriptive statistics were initially used to describe participants' age and gender, psychiatric background, treatment, and outcomes to compare samples and calculate relative risk. Two-tailed tests were used to determine statistical significance at the 5% level between variables and outcome, and Bayesian analysis of independent samples was used to obtain a measure of the strength of evidence. Pearson correlation r was calculated to measure the correlation between the two variables. Data analysis was performed using IBM SPSS Statistics (version 26, Armonk, New York).

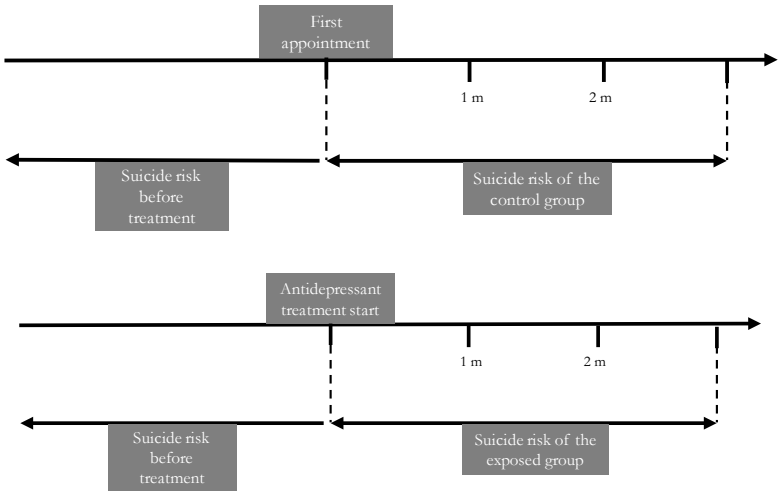


**Figure 1 –** Study timeline of the observation period
A - control group; B - exposed group

## RESULTS

A total of 503 adolescents were initially enrolled, of whom 13 were excluded for insufficient data and 14 were excluded for already being on antidepressant treatment at the first appointment (**Figure 2**). After analysis of referral letters and first appointment notes, 190 patients were excluded for lack of depressive symptoms, leaving a final sample of 286 participants.

Of the 286 study participants, 213 were girls and 73 were boys. The mean age was 15.02 years. The exposed population consisted of 164 adolescents, and the control group consisted of 122 adolescents. **Table 2** shows the characteristics of the study population.

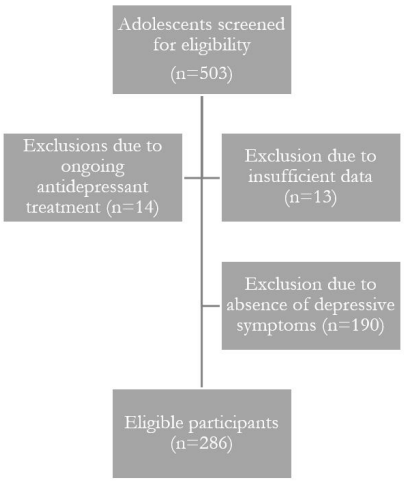


**Figure 2 -** Flowchart of patient enrolment in the study

**Table 2 -** Characteristics of the study population

| | **Exposed group** | **Control group** | **Total population** |
|---|---|---|---|
| Population (N) | 164 | 122 | 286 |
| Gender (m:f ratio) | 30:130=0.23 | 43:80=0.54 | 73:213=0.34 |
| Mean age (years) | 15.12 | 14.89 | 15.02 |
| History of non-suicidal self-injury (N, %) | 79 (49%) | 73 (59%) | 152 (53%) |
| History of suicidal ideation (N, %) | 70 (43%) | 47 (38%) | 117 (41%) |
| History of suicidal behavior (N, %) | 23 (14%) | 14 (11%) | 37 (13%) |
| History of suicidal attempts (N, %) | 24 (15%) | 15 (12%) | 39 (14%) |
| Antipsychotic treatment (N, %) | 113 (69%)<br>Quetiapine 50 (30%)<br>Risperidone 34 (21%)<br>Olanzapine 21 (13%)<br>Aripiprazole 7 (4%) | 67 (54%)<br>Quetiapine 28, (23%)<br>Risperidone 23 (19%)<br>Aripiprazole 6 (5%)<br>Olanzapine 5 (4%)<br>Paliperidone 4 (3%)<br>Clozapine 1 (0%) | 180 (63%) |
| Anxiolytic treatment (N, %) | 62 (38%)<br>Loflazepate 36 (22%)<br>Alprazolam 14 (9%)<br>Diazepam 7 (4%)<br>Lorazepam 5 (3%) | 31 (25%)<br>Loflazepate 26 (21%)<br>Clonazepam 2 (2%)<br>Diazepam 2 (2%)<br>Alprazolam 1 (0%) | 93 (33%) |
| SSRI treatment (N, %) | 164 (100%)<br>Sertraline 95, (58%)<br>Escitalopram 40 (24%)<br>Fluoxetine 29 (18%) | 0 | 164 (56%) |

There were no cases of suicide in the study population. Conversely, four suicide attempts were reported during the three-month follow-up period. One suicide attempt was recorded in the antidepressant exposure group (1/164=0.006) and three in the control group (3/122=0.025). **Figures 3** and **4** show the risk of suicide attempt among adolescents exposed and not exposed to antidepressants and according to gender. Overall, the relative risk of suicide attempt was 0.248. The Bayesian test for independent samples retrieved a Bayes factor of 4.57. The p-value for a 95% confidence interval for this risk was 0.189 and Pearson's r was -0.078.

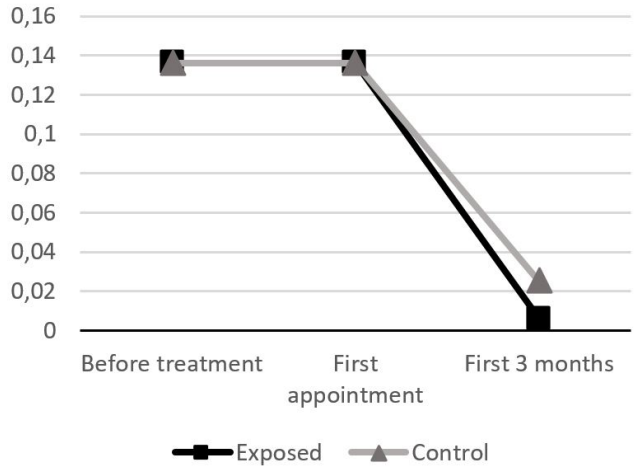


**Figure 3 –** Risk of suicide attempt in adolescents exposed and not exposed to antidepressants during the study period

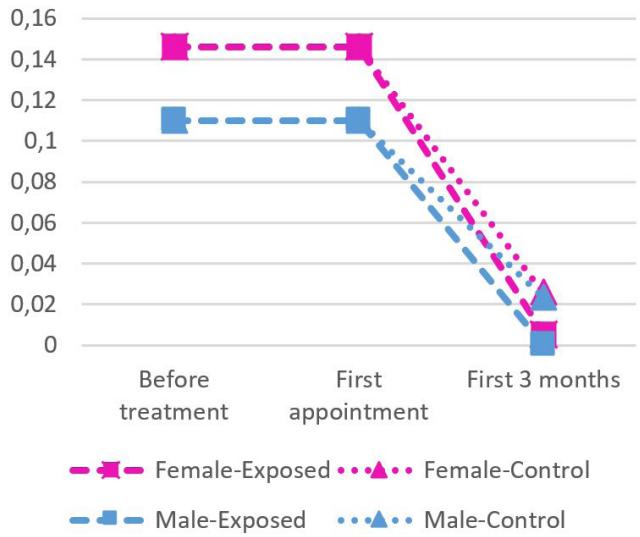


**Figure 4 –** Risk of suicide attempt in adolescents exposed and not exposed to antidepressants during the study period, according to gender

## DISCUSSION

The results of this study, including Pearson's r close to 0, do not support an association between antidepressant treatment and suicide attempt. The higher incidence of suicide attempt in the control group was not statistically different from the incidence in the exposed group and could be due to chance. Bayesian analysis suggested moderate evidence for the study hypothesis.[17] The results suggest that antidepressants might have a small protective effect against suicide attempt, but lack power to draw conclusions, even when female and male adolescents are analyzed independently. The group exposed to antidepressants had a higher male-to-female ratio, which may support the results, as female adolescents are thought to be more prone to suicide attempts.[18] The size of the study sample did not allow conclusions to be drawn regarding the effect of age and concomitant antipsychotic and anxiolytic treatment on suicide risk. The results are in line with those of several recent studies suggesting that SSRIs do not increase the risk of suicidal behavior.[10]

This study has several limitations that should be acknowledged: (1) despite similarities, the control group has several differences from the exposed group; (2) clinicians decide whether and how to initiate antidepressant treatment according to their clinical judgment; (3) antidepressant dosage and titration were not taken into account, nor were concomitant psychological therapies such as cognitive behavioral therapy and concomitant antipsychotic or anxiolytic medication; (4) suicide risk before exposure to antidepressant treatment was calculated within a longer time frame than suicide risk after exposure to antidepressant treatment; and (5) comorbidities were not considered.

Importantly, in addition to psychopharmacological treatment, patients and their families were regularly followed up with psychosocial support, which usually continued for more than three months until clinical discharge.

Although the lack of a difference in the suicide attempt rate between males and females is an important study finding, a larger sample would potentially allow for more significant results, and a randomized controlled trial might lead to stronger conclusions.

## CONCLUSION

The study findings suggest that SSRIs do not increase the risk of suicide attempt among adolescents.

## AUTHORSHIP

Nuno Duarte – Conceptualization; Resources; Data curation; Formal Analysis; Methodology; Project administration; Writing – original draft; Writing – review & editing

Sarah Amaral – Conceptualization; Resources; Data curation;

Writing – original draft; Writing – review & editing
Marta Abrantes – Conceptualization; Resources; Data curation; Writing – original draft; Writing – review & editing

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# REVIEW ARTICLES

## Decoding the Human Genome

### Descodificando o Genoma Humano

Diogo Fernandes da Rocha[1], Gustavo Rocha[2], Pedro Louro[1,3]

## ABSTRACT

The neonatologist is often the first clinician to identify genetic disorders without prenatal diagnosis. Technological advances in genetics over the past few decades have opened up possibilities never before imagined. Gone are the days when we could offer our patients little more than a peripheral blood karyotype. Newer methods, such as comparative genomic hybridization or Sanger sequencing and next-generation sequencing, allow a more detailed analysis of the human genome, both at the level of large rearrangements (deletions, duplications) and potentially pathogenic point variants. High-tech technologies have been useful in uncovering genes involved in diseases that have long been known to have a genetic origin, but whose etiology has remained elusive. Despite the promise of these technologies, no method is self-sufficient, and all have limitations. The aim of this review is to update clinicians on the genetic tests that are currently available and in use. Given that the first human genome was sequenced just over twenty years ago, what news will the next twenty years bring?

**Keywords**: comparative genomic hybridization; DNA; fluorescence *in situ* hybridization; high-throughput nucleotide sequencing; karyotype; multiplex polymerase chain reaction; polymerase chain reaction; sequence analysis

## RESUMO

O neonatologista é frequentemente o primeiro clínico a confrontar-se com condições genéticas não diagnosticadas no período pré-natal. Os avanços tecnológicos no campo da genética nas últimas décadas trouxeram possibilidades nunca antes imaginadas. Distantes estão os tempos em que pouco mais poderia ser oferecido aos doentes do que um cariótipo de sangue periférico. Metodologias mais recentes, como hibridização genómica comparativa ou sequenciação de Sanger e sequenciação de nova geração, permitem analisar mais detalhadamente o genoma humano, quer ao nível dos grandes rearranjos (deleções, duplicações), quer de variantes pontuais potencialmente patogénicas. Estas tecnologias de ponta têm sido úteis na descoberta de genes implicados em doenças há muito entendidas como de origem genética, mas cuja etiologia permanecia desconhecida. Apesar dos bons presságios, nenhum método é autossuficiente e todos apresentam as suas limitações. O objetivo desta revisão é atualizar os clínicos sobre os testes genéticos atualmente disponíveis e utilizados. Recordando que o primeiro genoma humano foi sequenciado há pouco mais de vinte anos, que novidades trarão os próximos vinte?

**Palavras-chave:** amplificação de sonda dependente de ligação *multiplex*; cariótipo; hibridização genómica comparativa; hibridização *in situ*

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fluorescente; reação de polimerização em cadeia; sequenciação de nova geração; sequenciação de Sanger

## INTRODUCTION

Genetic disorders presenting in the neonatal period are chronic conditions with a significant impact on the lives of patients and their families. Their clinical presentation is heterogeneous, and early diagnosis can facilitate clinical management and provide timely prognostic counseling to families. Over the past few decades, the availability of diagnostic tests has expanded, making it difficult for neonatologists (and other non-geneticists) to keep up with this progress. Appropriate use and understanding of the expanding array of genetic testing modalities require ongoing education. Herein, the authors present an overview of genetic tests currently used in the Neonatal Intensive Care Unit (NICU) and provide background on their characteristics and use in clinical practice, from classical cytogenetics to the evolving role of next-generation sequencing (NGS).

### Copy number variants and single nucleotide variants

Changes in the human genome can be broadly divided into two groups: copy number variants (CNVs) and single nucleotide variants (SNVs). A CNV corresponds to a loss (deletion) or gain (e.g., duplication) of genetic information, usually greater than 50 base pairs (bp).[1-6] On the other hand, a SNV refers to a point change in the genome.[1,5] For example, if we think of the genome as a set of 46 instruction manuals, searching for CNVs is like looking for extra or missing chapters, while searching for SNVs is like looking for changes in the letters of each word. Similarly, SNVs can be categorized as deletions, insertions, or substitutions. Considering the functional impact of SNVs on protein translation, they can be further classified as follows:[5,7]

- Base pair substitutions:
  - Silent: a base pair exchange does not imply a change in amino acid translation (given the redundant nature of the genetic code). However, not all silent changes are benign (e.g., if they occur near exon-intron transitions, they can generate alternative splicing sites).
  - Missense: the most common change, consisting of a base pair exchange that results in a variation in the amino acid sequence.
  - Nonsense: a base pair exchange that results in a premature STOP codon.
- Small insertions/deletions (less than 50 bp): when an addition or subtraction of base pairs occurs, respectively. If both occur simultaneously, it is called an indel (insertion + deletion). These insertions/deletions can be further classified as follows:
  - In-frame: when the reading frame is maintained, i.e., the amount of deoxyribonucleic acid (DNA) lost or gained is divisible by three.
  - Out-of-frame: when the reading frame is altered for all subsequent nucleotides.
    - Frameshift: insertion or deletion of nucleotide bases in numbers that are not multiples of three, usually forming a STOP codon downstream.
- Splice site: all variants that affect exon-intron transitions, thereby altering the transcribed genetic information.

Considering their relationship with the patient's clinical status, both CNVs and SNVs can be classified into five classes based on their likelihood of pathogenicity:[4, 8-11]

- Class 1: Benign (B).
- Class 2: Likely benign (LB).
- Class 3: Uncertain clinical relevance (Uncertain significance) (VUS).
- Class 4: Likely pathogenic (LP).
- Class 5: Pathogenic (P).

By convention, only the P and LP variants and VUS should be reported in laboratory reports, while the B and LB variants are usually not included.[8] The classification of variants is based on available data and may therefore change over time (which is why the clinical relevance of previously identified VUS should be periodically reassessed).[10,12]

In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) published the updated standards and guidelines for the clinical interpretation of SNVs. There are 28 criteria in the ACMG/AMP guidelines, classified by weight and type of evidence. Depending on the weight of evidence, pathogenic criteria are classified as very strong (PVS1), strong (PS1–4), moderate (PM1–6), and supportive (PP1–5), while benign criteria are classified as stand-alone (BA1), strong (BS1–4), and supportive (BP1–6). These criteria are then combined according to the scoring rules to translate into the five-tier system (P/LP/VUS/LB/B).[10]

However, because there is a great deal of variability in the application of these criteria, the ACMG has recently proposed a quantitative approach to reduce the classification discrepancies between different laboratories.[4,10,11] In the case of CNVs, a score metric has been developed that assigns points to each observed piece of evidence supporting or refuting pathogenicity. CNVs with a

final score ≥0.99 are considered P, while scores between 0.90 and 0.98 are considered LP. VUS are the broadest category, corresponding to scores between -0.89 and 0.89, while refuting evidence with scores between -0.90 and -0.98 or ≤-0.99 are considered LB and B, respectively.[4] For SNVs, a Bayesian approach to combining rules has been incorporated, allowing the calculation of a posterior probability (Post_P). The ranges of these Post_P allow variants to be classified as P with Post_P >0.99; LP with Post_P between 0.90 and 0.99; LB with Post_P between 0.001 and 0.10; B with Post_P <0.001; and VUS with Post_P in the remainder interval.[11]

The next sections focus on the techniques that can be used to detect point and/or copy number variants.

## CYTOGENETICS

### *Cell culture*

Cell cultures are grown in a favorable artificial environment from cells obtained from an animal or plant tissue. These cultures are used as models to study cell physiology and biochemistry, as well as the effects of drugs and toxic compounds on cells.[13] In human genetics, cell cultures are used to analyze tissues for clinical and/or genetic diagnosis and are an essential step in the preparation of a karyotype.[9,14] Cells can be obtained from peripheral blood leukocytes, bone marrow, amniotic fluid, or other solid tissues. Typically, the goal of these cultures is chromosome condensation and subsequent cell synchronization. Various drugs have been used for this purpose, such as methotrexate (for cell arrest in S-phase) or colchicine (to block mitotic spindle formation).[14]

### *Karyotype*

In the human species, the karyotype of a diploid cell consists of 46 chromosomes – 22 pairs of autosomes and a 23rd pair of sex chromosomes (XX, female or XY, male). Chromosomes are identified by their size, centromere position, and banding pattern.[5,14]

Although the karyotype is very useful, its use as a first-line genetic test is rapidly decreasing, being currently indicated for aneuploidies (such as trisomy 13, trisomy 18, trisomy 21, monosomy X [Turner syndrome]), sexual differentiation abnormalities, and balanced chromosomal rearrangements (**Figure 1**).[5,8] The most commonly used staining technique is G-banding. Other staining techniques, such as Q, C (constitutional heterochromatin), R (reverse), or NOR bands (satellite chromosomes and acrocentric portions of chromosomes), can also be used.[5,8,14]

Currently, all karyotypes are obtained with high resolution bands. This is possible by staining the chromosomes before they reach their maximum condensed state (i.e., when they are still in prophase or prometaphase). In this way, the chromosomes are more stretched, allowing a greater number of bands to be evaluated and smaller losses or gains of genetic material to be detected.[5]

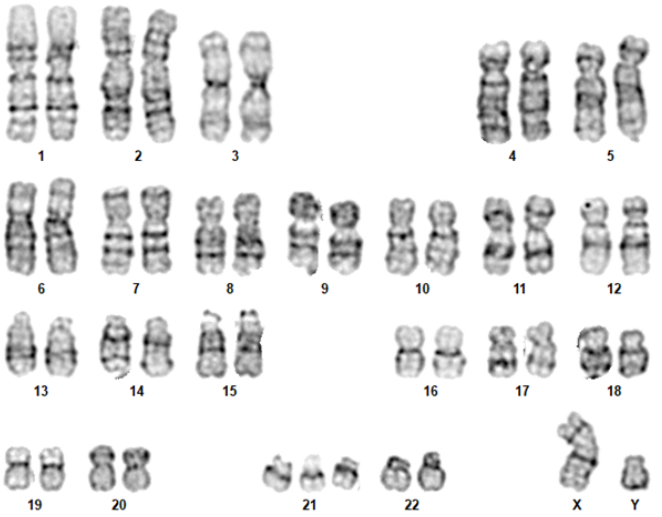


**Figure 1 –** Karyotype of trisomy 21

### *Fluorescence in situ hybridization*

Fluorescence in situ hybridization (FISH) is a rapid analysis that uses fluorescent probes that bind to chromosomal regions with a high degree of complementarity.[5, 12] (**Figure 2**) This technique must be targeted (i.e., clinicians must first specify which chromosomal region they wish to evaluate), which is different from karyotyping, where all chromosomal regions are assessed. However, both techniques are currently being abandoned in favor of other molecular techniques. Nevertheless, FISH remains one of the best methods for detecting low-grade mosaicism and is useful for describing balanced rearrangements and subtelomeric cryptic rearrangements, as well as for studying satellite chromosomes, which are not detected by comparative genomic hybridization and may also not be detected by karyotyping.[3,8]

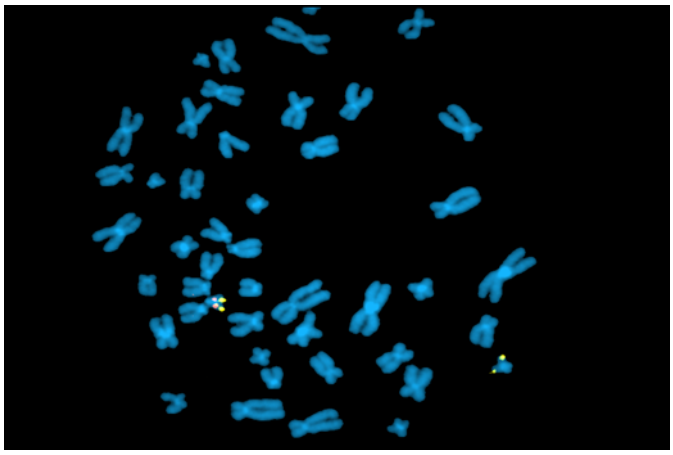

**Figure 2 -** Fluorescence in situ hybridization (FISH) with probes for 22q11.2 (LSI TUPLE1 - red) and control (LSI ARSA - yellow). 22q11.2 microdeletion syndrome

## MOLECULAR BIOLOGY

***Comparative genomic hybridization***

Oligonucleotide array comparative genomic hybridization (oligo-array CGH or simply array CGH) allows global analysis of all chromosomes by searching for CNVs.[9,14] Array CGH is the first-line test in some clinical settings, such as intellectual disability, autism spectrum disorders, or polymalformative syndromes, and is useful in the diagnosis of conditions such as 22q11.2 microdeletions (DiGeorge syndrome), 7q11.23 microdeletions (Williams syndrome), and 1p36 microdeletions.[2,5,8,9]

This test may also be required in other contexts, such as clarification of karyotype findings (marker chromosomes, apparently balanced translocations with an associated phenotype, breakpoint characterization) or prenatal screening of high-risk pregnancies (echographic abnormalities, intrauterine growth restriction, cardiac malformations, increased nuchal translucency).[8]

As a comparative technique, array CGH involves hybridizing the DNA of a control patient (of the same sex, stained red) with the DNA of the case being studied (stained green).[2,5,12] On the plate where both DNAs are placed for hybridization, there are multiple wells (each containing a probe for a specific region of the genome).[2] In situations where there is a deletion, the well will be red. If there is a duplication, the well turns green. Clinical interpretation of the results is performed using appropriate software and consulting international databases (DGV, OMIM, PubMed, DECIPHER, ClinGen), taking into account the clinical data provided by the clinician (**Figure 3**).[4,9]

The resolution of array CGH depends on the number of probes included. In the case of 4x180K array CGH, a total of 180,000 probes are distributed across the genome at average intervals of 13Kbp. In the case of 8x60K array CGH, the 60,000 probes are distributed at 41Kbp intervals.[2,5] On the other hand, higher resolution arrays (such as 750K array CGH) tend to include probes for both CNVs and SNPs (see below). The combination of oligo/SNP arrays has gained notoriety for its ability to simultaneously identify CNVs and loss-of-heterozygosity-associated regions (i.e., chromosomal regions that are very similar to each other because they are derived from the same ancestor).[9] Typically, low-resolution array CGH is used in the prenatal context, while high-resolution array CGH is used postnatally.[2,5]

In turn, single-nucleotide polymorphism genotyping arrays (SNP arrays) determine an individual's genotype at specific polymorphic sites (i.e., loci where there are 2 or more alleles with a population frequency greater than 1%).[9] The great advantage of this array technique is that it uncovers regions of homozygosity by comparing the profiles of different polymorphisms at specific chromosomal regions. This makes it possible to detect cases of parental consanguinity, uniparental isodisomy, or copy number neutral changes.[9,15]

Over time, because of its higher diagnostic yield (15–20%), array CGH has largely replaced the role once played by the karyotype (~3% yield).[9] This has been supported by the ability of array CGH to detect changes as small as 100 Kbp versus deletions up to 3–5 Mb or duplications greater than 5 Mb in the case of karyotype.[2,8,9] However, array CGH has some technical limitations, such as the inability to detect balanced rearrangements, low-grade mosaicism, and supernumerary chromosomes composed of heterochromatin.[3,5,8,9]

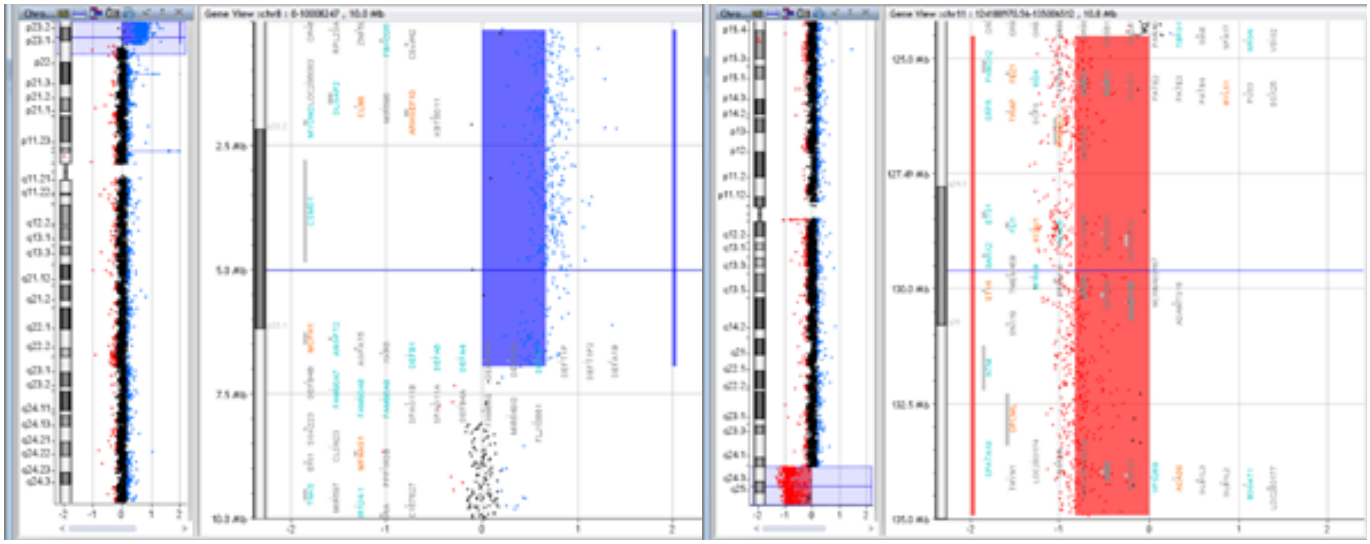

**Figure 3 -** Case of a 15-year-old female patient with intellectual deficit, dysmorphic appearance, short stature, and normal karyotype, whose array CGH revealed a 6.7Mb deletion of the 8p23.1 region and a 10.4Mb duplication of the 11q24.2 region [arr 8p23.1-pter(176,814-6,939,296)x3, 11q24.2-qter(124,518,113-134,927,114)x1] resulting from a balanced translocation in the father

***Polymerase chain reaction***

One of the fundamental steps in any molecular biology protocol is polymerase chain reaction (PCR), which allows to target and amplify a genomic region of interest.[5] PCR was first developed by Kary Mullis in the mid-1980s.[16,17] The following components are required to perform a PCR: two oligonucleotide primers flanking the DNA strand (both a forward, which attaches to the DNA in the 5'-3' direction, and a reverse primer, which attaches to the DNA in the opposite direction), thermostable polymerase, nucleotides, buffer (to create an optimal pH), and water.[5,17,18]

The PCR reaction can be repeated several times, with each cycle consisting of three critical steps:[5,16,17,19]

- Denaturation (~95°C): Separation of the DNA strands by melting the double-stranded templates apart. Melting temperature depends on template length and sequence, as well as melting time.
- Annealing (55-60°C): Attachment of primers targeting specific DNA sequences. Temperature depends on the primers used. Protocols often use a temperature a few degrees below the melting temperature to allow the formation of stable complexes with the target sequences and to avoid binding to other sequences.
- Elongation (72ºC): Synthesis of new DNA strands using DNA polymerase to anneal the primers while stabilizing the complex.

Experimental conditions are therefore critical to the outcome of the PCR reaction. For example, if the annealing temperature is too high, there may be insufficient primer-template hybridization. If it is too low, non-specific products may be generated.[17] Another point to consider is that although the PCR reaction allows for semi-quantitative evaluation, it does not allow for precise quantification of the amplified DNA. For this purpose, a quantitative PCR (qPCR) reaction can be performed. Also known as real-time PCR, qPCR was developed in 1992 and works by measuring fluorescent dyes or probes.[17,18] This allows a proportional comparison of the amount of product generated by amplification and the number of cycles required to generate a threshold amount of amplified DNA. qPCR is particularly useful in cases where there is a known CNV and the need to look for it in other family members.[3,8]

Another PCR variant is triplet repeat primed PCR (TP-PCR). TP-PCR is used to detect expanded alleles in diseases whose pathological mechanism depends on triplet expansion (such as fragile X syndrome [FRAXA] or spinocerebellar ataxia). TP-PCR is particularly useful when the conventional PCR reaction identifies only one allele size (as in homoallelism, where both alleles have the same number of triplet repeats) or when allele loss is suspected (as in larger expansions).[20,21] Special probes, called triplet-primed PCR, allow the generation of fragments with a size amplitude proportional to the number of triplets that make up the expansion. The different fragments are then run on a capillary electrophoresis device, which will show a decremental pattern in the case of expanded alleles.[21] If there is an interest in quantifying the expansion, long-range PCR or Southern blotting should be performed.[22]

***Multiplex ligation-dependent probe amplification***

Multiplex ligation-dependent probe amplification (MLPA) is a type of multiplex assay that quantifies the change in DNA copy number by hybridizing a probe to a target sequence.[8,12,23] Currently, this molecular technique is the first-line test for the diagnosis of Duchene/Becker muscular dystrophy and suspected cases of spinal muscular atrophy (SMA).[3]

MLPA probes consist of two adjacent halves, one that binds to the 5' region and another that binds to the 3' region of the target sequence. In a first step, the target DNA is denatured, with subsequent hybridization of the two adjacent halves to the target region. After joining the two halves, they are combined into a single larger sequence. The resulting probe is amplified by PCR reaction. The copy number of each genomic region can be determined by comparing the amount of DNA amplified from the target region with the amount amplified from a standard sample (**Figure 4**).[3,12] As a comparative method, MLPA is highly susceptible to technical errors. False negative results can also occur if there are polymorphisms in the probe binding sites.[3]

A variation of this method, methylation-specific MLPA (MS-MLPA), is used to study epigenetic/methylation defects.[3,8,24] DNA methylation abnormalities can result in inappropriate expression or silencing of genes.[24] This test is used in disorders associated with methylation abnormalities, such as Beckwith-Wiedemann, Prader-Willi, Angelman, and Silver-Russel syndromes.[3]

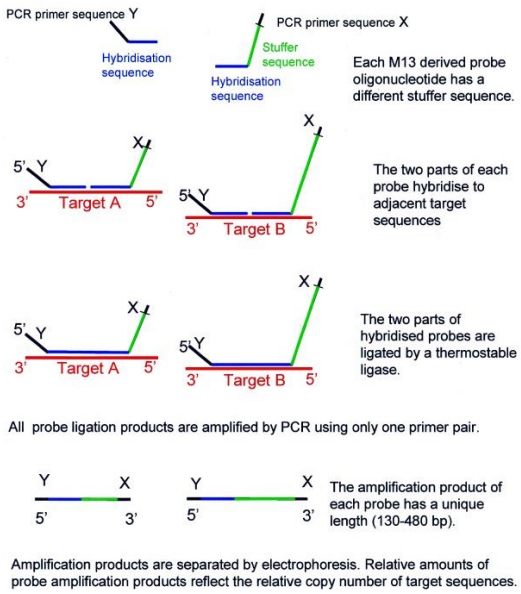


**Figure 4 -** Multiplex ligation-dependent probe amplification (MLPA) scheme. Reprinted from Schouten JP *et al*.[23]

***Sanger sequencing***

In the 1970s, Frederick Sanger described the first sequencing technique, which became the basis for the Human Genome Project (HGP).[25,26] Sanger sequencing (also known as the chain termination method) uses special nucleotides called dideoxy terminators (ddNTPs), which are characterized by the absence of the free OH group at the 3' carbon of the pentose.[5,25,27] When these ddNTPs are added to a growing DNA sequence, the sequence is prevented from continuing to grow. This results in DNA sequences of different sizes which, after amplification, are run on an agarose gel.[5,27] Depending on the radioactivity of each fragment and its size, it is possible to determine the genetic sequence of the target region nucleotide by nucleotide.[5,25]

Nowadays, instead of using radioactive ddNTPs or agarose gels, automated methods based on fluorescent ddNTPs and running fragments in multichannel capillary electrophoresis devices are used (**Figure 5**).[25,27] This method is still time-consuming and very expensive if the intention is to sequence a large number of genes (justifying the years and billions of dollars spent on the HGP to sequence a single genome).[12,26] However, this does not invalidate its value, with this method currently considered not only the most reliable, but also the gold standard (often used as a confirmatory test for NGS). In addition, Sanger sequencing can be used for family studies, especially when a pathogenic variant has been identified in the affected proband.[10,11]

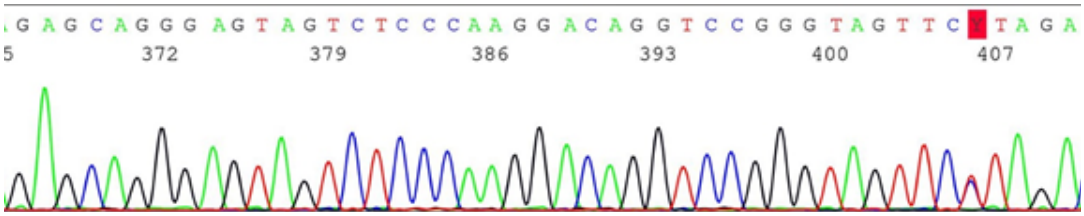


**Figure 5 -** Electropherogram. Sanger sequence obtained by automated approach that detected a single nucleotide variant (SNV) involving nucleotide 406

***Next-generation sequencing***

NGS, or high-throughput nucleotide sequencing, is based on the parallel sequencing of different genomic sequences. This is done by fragmenting the genome into smaller sequences (about 100-200 bp) that are amplified simultaneously (short reads, collectively called a DNA library). The subsequent alignment of the different fragments into a single sequence allows the detection of variants in an exon or exon-intron transition (by mapping the DNA short reads to the reference genome).[5,25] Thus, the main advantage of NGS is its ease of use and speed in obtaining results, since it can sequence the entire human genome in a single day (with the associated time and cost expected to decrease in the coming times).[26,28]

Today, a larger number of second-generation NGS platforms are available. Overall, second-generation methods can be divided into two major groups: sequencing by hybridization and sequencing by synthesis.[25,27] Most commercially available sequence by synthesis platforms use reversible nucleotides that can reverse the temporary block of DNA strand growth (unlikely ddNTPs). Of these, the following can be highlighted:[25,27,28]

- Ion Torrent: Also known as ion exchange sequencing. A hydrogen ion is released upon incorporation of a new nucleotide, which changes the medium pH. This voltage change is detected by a pH sensor, which instantly converts the sequencing phenomenon into digital information, speeding up the process.
- Illumina technology: The most widely used method of sequencing by synthesis due to its greater ease of use. It is based on the concept of bridged PCR using fluorescent nucleotides.[29]

One of the major limitations of NGS is its inability to sequence large fragments. While Sanger sequencing can read sequences from 600 to >1000 bp, NGS methods can only read shorter sequences (from 300 to 500 bp).[25,27] In this sense, third- and fourth-generation methods (such as PacBio or Nanopore) have been developed in recent years in an effort to combine the advantages of NGS – sequencing multiple fragments simultaneously – with those of Sanger – sequencing larger fragments, reducing the probability of reading errors.[25,28,30,31]

Because NGS allows multiple genes to be analyzed simultaneously, they are grouped into gene panels for clinical convenience:[5,8,9]

- Gene-specific panel: assesses all genes associated with a given phenotype, from only a few to hundreds of genes.
- Mendeliome or clinical exome: assesses all gene exons associated with OMIM phenotypes (which represent approximately 1-2% of the entire human genome and include approximately 85% of all variants described to date).
- Whole exome sequencing (WES): assesses all gene exons, even those of unknown function. Useful for non-specific phenotypes and when all other tests are negative.
- Whole genome sequencing (WGS): assesses the entire genome and may in the future replace the role currently played by array CGH and WES. WGS is currently used in clinical research and has

little applicability in clinical practice.

Both WES and WGS can be performed alone or, for example, in trio (simultaneously comparing the genome of a child and its parents).[5,10,32] The rationale for this strategy is to reduce the amount of useless information generated by sequencing methods (for example, if the VUS identified are inherited, they are less likely to be disease-causing because a healthy parent is also a carrier).[5] This is because the larger the panel examined, the lower its specificity and the greater the number of VUS identified.[9,12] The large amount of data generated by NGS, as well as its difficult interpretation, causes serious and complex problems that overload not only the workflow of laboratory pipelines, but also the medical team, which spends a lot of time discussing and trying to assign meaning to these variants.[33] Other limitations of NGS should also be considered, such as the inability to detect balanced rearrangements, nucleotide expansions, uniparental disomy, or methylation defects.[8,9,33]

## CRITICAL CONSIDERATIONS ABOUT GENETIC TESTING

When ordering a genetic test, the pros and cons should always be weighed. To avoid misdiagnosis, a targeted diagnostic test (e.g., Sanger sequencing, FISH, MLPA, or gene panels) should be ordered when a specific syndrome is suspected.[32,34] Advantages include better coverage of the gene(s) of interest and less chance of equivocal results.[9,12] Examples of targeted diagnostic tests include MLPA for SMA, *FBN1* gene sequencing for Marfan syndrome, or multigene panels for Noonan syndrome.[5,12]

However, an untargeted test may be useful if the clinical presentation is nonspecific (e.g., karyotype, array CGH, WES, or WGS). When performing some of these more comprehensive studies (especially WES or WGS), one should consider the possibility of incidental findings that may reveal pathogenic variants unrelated to the phenotype (e.g., predisposition to cancer or neurodegeneration). Carrier status should also be considered.[33,35] These findings should be given the greatest relevance. Patients should receive genetic counseling throughout the process and their autonomy should be respected.[4,5,12] In some countries, such as Portugal, genetic counseling is mandatory before genetic testing is ordered for certain conditions.[36] In the case of minors, when genetic testing is recommended for diagnostic purposes, parents must consent to the results they wish to receive after discussing the benefits and risks.[5,36]

The best interests of the child should not be disregarded. When appropriate, the child should be given the opportunity to express his/her opinion on the request for genetic studies, and his/her will should not be devalued, whatever it may be.[37] The American Academy of Paediatrics (AAP) and the ACMG emphasize that predictive genetic testing is inappropriate for asymptomatic minors at risk for adult-onset diseases for which early treatment has no beneficial effect, because it denies the child's autonomy.[5,12,37,38] The same concerns are shared by the Portuguese law.[36]

Another aspect to be considered is the confidentiality of genetic data. Several countries have anti-discrimination laws both in access to health insurance and in employment. This means that everyone can know their genetic data and make important lifestyle and medical decisions without fear of genetic discrimination.[39,40]

## CONCLUSIONS

Technological advances in the field of genetics over the past few decades have opened up previously unimagined possibilities. In clinical practice, comparative genomic hybridization has largely replaced the role once played by the karyotype in detecting unbalanced rearrangements. NGS has made an unprecedented contribution to the identification of new monogenetic causes of disease, which would have taken years of collaborative work using Sanger sequencing alone. However, it is not enough to simply read the genome. It is necessary to interpret it and understand whether certain individual variants are simply different versions of the normal or disease-causing. Thus, collaboration between different specialties and fields of knowledge is essential in the arduous mission of decoding the human genome.

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## GLOSSARY

*Acrocentric chromosomes*: chromosomes in which the centromere is not in the middle but near the end. Humans usually have five pairs of acrocentric autosomes (chromosomes 13, 14, 15, 21, 22). The Y chromosome is also acrocentric.

*Allele*: one of two or more versions of a DNA sequence (a single base or a segment of bases) at a given genomic location.

*Allele dropout:* event that occurs when there is a polymorphism in the site where the primers should bind, resulting in poor or no amplification of one or both alleles for a given individual.

*Aneuploidy*: abnormal number of chromosomes in a cell that does not include a difference of one or more complete sets of chromosomes (e.g., having 45 or 47 chromosomes).

*Balanced rearrangement*: type of chromosomal structural variant (e.g., translocation, inversion, or insertion) without apparent cytogenetic gain or loss of chromatin.

*Cell synchronization*: process by which cells at different stages of the cell cycle are brought to the same phase.

*Codon:* nucleotide triplets that correspond to amino acids or stop signals during translation.

*Constitutional heterochromatin*: chromatin thought to maintain a condensed and transcriptionally inert chromatin conformation (formed primarily at gene-poor pericentromeric regions).

*Copy-neutral change*: phenomenon whereby one of two homologous chromosomal regions is lost, but various mechanisms have ensured the presence of two identical copies of such a region in the genome, thus making it copy neutral.

*Marker chromosomes*: structurally abnormal, extra pieces of unidentified chromosomal material that usually occur in addition to the normal chromosomal complement. Also referred to as supernumerary chromosomes.

*Mosaicism*: a condition in which the same person has two or more sets of cells that are genetically different. If 20–40% of cells are abnormal, it is considered low-grade mosaicism.

*Nucleotide expansion*: diseases associated with nucleotide expansions occur when the number of triplets present in a mutated gene is greater than the number found in a normal gene. These are called dynamic mutations.

*OMIM:* catalog of all known human genes and genetic phenotypes, freely available and updated daily. The official home is omim.org.

*Reading frame:* the division of a sequence of nucleotides into a set of consecutive, non-overlapping triplets.

*Satellite chromosome*: the end of a chromosome that is separated from the rest of the chromosome by a secondary constriction. Found in acrocentric chromosomes.

*Sequencing by hybridization*: indirect sequencing method in which sets of oligonucleotides are hybridized under conditions that allow the detection of complementary sequences in the target nucleic acid.

*Sequencing by synthesis*: polymerase-dependent sequencing approach in which the sequencing reaction generates a newly synthesized DNA strand.

*Subtelomeric cryptic rearrangement*: chromosomal rearrangement involving the end of chromosomes (telomeres).

*Supernumerary chromosome*: the same as Marker chromosome.

*Thermostable polymerase*: a special type of polymerase that can withstand the higher temperatures used in polymerase chain reaction (PCR) while maintaining enzymatic activity.

*Uniparental disomy*: when the two copies of a chromosome come from the same parent, rather than one from the mother and one from the father. In uniparental isodisomy, the two copies come from one chromosome, while in uniparental heterodisomy, the two copies come from each chromosome.

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# REVIEW ARTICLES

## Immunoglobulin A vasculitis (Henoch-Schönlein purpura) in children - A Literature Review

### Vasculite de imunoglobulina A (púrpura de Henoch-Schönlein) em Pediatria - Revisão da Literatura

Patrícia Sousa[1], Susana Correia de Oliveira[1], Ângela Dias[1], Cláudia Tavares[1]

## ABSTRACT

Immunoglobulin A vasculitis (IgAV) is a small-vessel vasculitis that primarily affects children. Major manifestations include purpuric rash, proteinuria/hematuria, arthralgia, and abdominal pain. In this article, the authors review data on the epidemiology, diagnosis, and treatment of IgAV in children.

IgAV affects 10 to 56 children per 100,000 per year. The mean age at presentation is six years. Both genetic and environmental factors contribute to its pathogenesis, but the deposition of immune complexes containing abnormal glycosylated immunoglobulin (Ig) A1 plays a predominant role.

The course of the disease is usually benign and supportive care is sufficient. Short-term complications are mostly related to gastrointestinal involvement, including the risk of perforation and bleeding. Long-term morbidity is due to chronic kidney disease and hypertension. Corticosteroids are not recommended for prevention of renal involvement, but may be useful as a treatment strategy, as well as more aggressive immunosuppressive drugs.

**Keywords:** child; diagnosis; epidemiology; IgA vasculitis; physiopathology; therapy

## RESUMO

A vasculite de imunoglobulina A (VIgA) é uma vasculite de pequenos vasos que afeta sobretudo crianças. As principais manifestações clínicas são exantema purpúrico, proteinúria/hematúria, artralgia e dor abdominal. Este artigo apresenta uma revisão dos dados mais recentes de epidemiologia, diagnóstico e abordagem da VIgA em pediatria.

A VIgA afeta 10 a 56 por 100.000 crianças/ano, manifestando-se inicialmente na idade média de 6 anos. Tanto fatores genéticos como ambientais contribuem para a sua patogénese, sendo que a deposição de imunocomplexos contendo imunoglobulina A1 anormalmente glicosilada desempenha um papel preponderante. Atendendo ao curso habitualmente benigno da doença, o tratamento conservador é geralmente suficiente. As complicações a curto prazo estão sobretudo relacionadas com envolvimento gastrointestinal, incluindo risco de perfuração e hemorragia. A morbilidade a longo prazo está associada a doença renal crónica e hipertensão. Os corticosteroides não estão recomendados na prevenção do envolvimento renal, mas podem ser úteis no tratamento, assim como outros fármacos imunossupressores.

**Palavras-chave:** criança; diagnóstico; epidemiologia; fisiopatologia; terapêutica; vasculite IgA

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## INTRODUCTION

Henoch-Schönlein purpura (HSP), or immunoglobulin A vasculitis (IgAV), is the most common small-vessel vasculitis in children.[1] It was formerly known as anaphylactoid purpura, although anaphylaxis is not involved in its pathophysiology.[2] The disease was first described by Schönlein in 1837 as a triad of purpura, joint pain, and nephritis.[3] Thirty-seven years later, his student Henoch recognized the association with gastrointestinal involvement, but it was not until 1948 that the role of immunoglobulin A (IgA) in its pathogenesis was demonstrated.[4,5] Current diagnostic criteria require the presence of a palpable nonthrombocytopenic purpuric rash associated with gastrointestinal symptoms and/or arthritis and/or proteinuria/hematuria and/or histologic evidence of predominant IgA deposition.[6] Central nervous system (CNS), respiratory, and genital involvement are rare. Both genetic and environmental factors have been suggested as triggers, with respiratory infections being the most important.[7] The pathogenesis is not fully understood, but small vessel deposition of immune complexes containing galactose-deficient IgA is of great importance.[8]

The disease course is usually self-limited and only symptomatic treatment is required. In severe cases, especially in the presence of renal dysfunction, immunosuppression may be required, including corticosteroids, mycophenolate mofetil, cyclosporine, rituximab, and dapsone.[8,9]

In the acute phase, the outcome depends mainly on the extent of gastrointestinal involvement, while the long-term prognosis depends mainly on the extent of renal involvement. Recurrence occurs in approximately one-third of patients, but long-term follow-up is warranted in high-risk patients.[2,10]

## OBJECTIVES

The aim of this study was to review the current evidence on the epidemiology, risk factors and pathophysiology, most common and less common clinical manifestations, diagnostic criteria, differential diagnosis, treatment options, and follow-up of IgAV.

## EPIDEMIOLOGY AND RISK FACTORS

IgAV is mostly a disease of childhood, with 90% of affected individuals under the age of 10 and a mean age of diagnosis of six years.[2,9] The incidence is probably underestimated at 10-56 children per 100,000 per year due to underreporting.[11,12] There is a predominance of cases in winter.[1,9] Several risk factors for renal involvement have been described, and the most important contributors include: older age of onset (especially over 10 years) and wintertime, longer interval between symptom onset and diagnosis, rural residence, persistent purpura, severe gastrointestinal symptoms, recurrence, angioedema, obesity, and decreased C3.[1,10,13] Data on sex predominance are conflicting, but most studies suggest a slight male predominance of 1.2-1.8:1.[11] The role of sex in renal manifestations is uncertain.[11] IgAV is reported worldwide, but is less observed in subjects of African descent.[2,8]

In most cases, the precipitating cause is not identified, but there is often an association with preceding infections, usually in the upper respiratory tract.[7,14] A correlation between virtually all respiratory pathogens and IgAV has been observed.[9] Associated pathogens are listed in **Table 1** and include *Streptococcus*, particularly Group A *β-hemolytic Streptococcus*, parvovirus B19, hepatitis B virus, hepatitis C virus, human immunodeficiency virus 1, *Bartonella henselae*, *Salmonella spp*, *Shigella*, *Staphylococcus aureus*, and *Mycoplasma pneumoniae*.[9] Less common viral pathogens include Epstein–Barr virus, adenovirus, coxsackie virus, hepatitis A, varicella zoster virus, citomegalovirus, influenza, rotavirus, norovirus, and bocavirus.[2,8,14-16] Besides infections, also foods, immunizations, drugs, and allergens can trigger IgAV.[1] Drug-induced cases are more common in adults, and angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (losartan), antibiotics (clarithromycin), L-dopa, chlorpromazine, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been implicated.[2,14] Cases of IgAV have been reported following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in children, and one case following coronavirus disease-19 vaccination in an adult.[17-19] At least five cases have been reported following hymenoptera sting.[20]

**Table 1 -** Most common pathogens associated with IgAV

| Bacteria |
|---|
| *Streptococcus* (group A *β-hemolytic Streptococcus)* |
| *Staphylococcus aureus* |
| *Bartonella henselae* |
| *Salmonella spp.* |
| *Shigella spp.* |
| *Mycoplasma pneumoniae*. |
| Viruses |
| Adenovirus |
| Bocavirus |
| Cytomegalovirus |
| Coxsackie virus |
| Epstein–Barr virus |
| Hepatitis A virus, hepatitis B virus, hepatitis C virus |
| Human immunodeficiency virus 1 |
| Influenza virus |
| Norovirus |
| Parvovirus B19 |
| Rotavirus |
| Varicella zoster virus |

**Pathophysiology**

IgAV is a non-granulomatous leukocytoclastic vasculitis that affects small vessels.[14] Leukocytoclasia originates from partially disintegrated neutrophil granulocytes in the vessel walls that are deposited around the extravasated erythrocytes that cause purpura.[9]

Although the detailed pathogenic mechanisms of IgAV are not fully understood, IgA plays an important role. IgA deposition has been found in patients with IgAV, IgA nephritis (IgAN), skin-limited IgA, and systemic IgA, suggesting a common pathophysiology.[2,8] An inherited defect is likely the initial trigger for the glycosylation abnormalities that occur in the O-linked oligosaccharides of the IgA1 hinge region, particularly in galactose and sialic acid levels.[14,21] The abnormal IgA1 is inappropriately catabolized in the liver, leading to its accumulation and deposition. In addition, IgA1 is particularly polymeric, facilitating the formation of immune complexes with unaltered IgA1 and IgG.[21] Environmental triggers such as infections are thought to stimulate IgA production.[8] Both quantitative and structural abnormalities in IgA cause overexpression of RFcI (CD89), found on circulating monocytes and neutrophils, and the transferrin receptor (CD71), found on mesangial cells. IgA also forms immune complexes with CD89, which then bind to CD71 and are deposited in the walls of small vessels.[22] Once deposited, these immune complexes activate the alternative complement pathway, causing C3 deposition and further damaging the endothelial lining by promoting mesangial cell proliferation and the local inflammation in the glomeruli responsible for progressive renal failure.[7,8] There are several molecules involved in local inflammation that are elevated in the acute phase of IgAV, originating from both immune and non-immune cells.[9] These include antibodies, receptors, transmembrane proteins, endothelins (ET-1), vasoconstrictor hormones and cytokines such as interleukin (IL)-1, IL-6, and IL-8, toll-like receptors (TLR)-2 and TLR-4, and tumor necrosis factor-α (TNF-α), which also induces adhesion molecules on endothelial cells and leukocytes.[2,9,13,21] The roles of IgG and IgM in IgAV are still being elucidated.[21]

The familial association in the occurrence of IgAV suggests the important role of genetic contribution, particularly mutations in the Mediterranean fever gene, which encodes the protein pyrin/marenostrin, which then regulates caspase-1 activation and IL-1B production. There is an increased risk for IgAV associated with human leukocyte antigens (HLA) A2, A11, B35, B34, and DRB1*01, and a decreased risk in carriers of HLA-A1, DRB1*07, B49, and B50.[2,9,14,16] HLA-B35 is particularly associated with renal involvement.[2]

There is recent evidence regarding the role of the digestive system in the pathophysiology of IgAV, such as the involvement of gliadin in mouse models and improvement with gluten-free diets, the activation of the innate immune response in the digestive mucosa, the association of IgAN with genes involved in immunity to intestinal microorganisms and in inflammatory bowel disease, the particular composition of the microbiota in these patients, and the improvement with ileum-targeted release formulations of budesonide.[8]

**Clinical manifestations**

The classic tetrad of IgAV consists of palpable purpura, arthralgia (joint pain), gastrointestinal complaints, and renal involvement. Skin involvement is mandatory. The order of presentation varies, but the clinical course most commonly begins with purpura and joint pain and progresses over days to weeks. In most cases, the diagnosis is made in less than four days.[1] Rarely, the CNS, testis, and lungs are also affected.[9] Less common manifestations include low-grade fever, malaise, orchitis, seizures, epistaxis, ileoileal intussusception, jejunal hemorrhage, orbital hematoma, CNS bleeding, and ischemic stroke.[2]

Skin

The rash usually begins with petechiae and palpable purpura. Non-blanching, round, oval, and retiform indurations up to 1 cm in diameter appear predominantly on the lower limbs and extensor surfaces, usually in a symmetrical distribution (**Figure 1**).[8,14,23] Slower blood flow in the dilated venules favors deposition of IgA complexes on the lower limbs and extensor surfaces, but lesions also occur on the forearms, cheeks, and ears in one-third of patients.[9] Rarely, early lesions may be erythematous maculae or urticarial, which resolve with pressure. Bullous or necrotic lesions are less common, especially in children.[2,9] Lesions resolve completely over time, but affected areas remain discolored for weeks after resolution due to hemosiderin deposition.[9] Non-pitting edema and pruritus may also be present.[2]

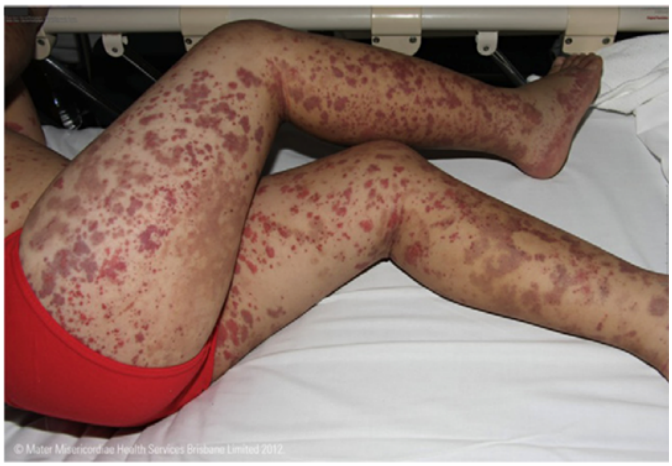

**Figure 1 -** Purpuric skin lesions in a patient with IgAV (courtesy of the author of Reference 42)

Joints

Arthralgia or arthritis affects 75% of children with IgAV and precedes the onset of purpura in up to 25% of cases and up to 14 days. The joints become painfully swollen, with limited mobility, but

spontaneous resolution occurs without joint destruction.[2,9] One or more joints may be affected, either simultaneously or not. Knees and ankles are most commonly affected, but hands and feet can also be affected.[8]

Gastrointestinal tract

In up to 40% of patients, the clinical course begins with gastrointestinal manifestations. Deposition of immune complexes in the intestinal vessel walls leads to abdominal pain, vomiting, melena, and hematemesis. Abdominal pain, usually epigastric or periumbilical, is the most common symptom.[2] Hypoalbuminemia without proteinuria, fecal calprotectin measurement, fecal occult blood testing, and imaging studies may be useful in detecting subclinical intestinal involvement.[2,8,9] Upper and lower digestive endoscopic study allows direct analysis and biopsy of lesions, which are more commonly found in the duodenum and may present as mucosal erythema, petechial purpura, areas of necrosis, or erosion.[8] In severe cases, differential diagnosis with acute surgical abdomen is necessary. Although rare, complications are more common in children than in adults and include perforation, intussusception, bowel angina, and infarction. Because of the potential severity, acute mortality associated with IgAV is mostly related to gastrointestinal involvement.[7,9,14]

Kidney (Henoch-Schönlein purpura nephritis)

IgAV nephritis (IgAVN) affects 20-80% of IgAV patients, usually within one to three months of IgAV onset, but may also occur several months later, with or without purpura relapse.[1,2,8,11] It is the most important source of morbidity associated with IgAV. Microscopic hematuria and mild proteinuria are the most common and earliest findings.[24] Nephrotic and nephritic syndrome occurs in 7% of patients and end-stage renal disease in 1-2%, possibly more than ten years after onset.[8] If renal involvement is absent within six months, long-term renal damage is highly unlikely.[9] Renal failure at diagnosis is extremely rare in children. Hypertension may develop at any time during the course of the disease.[11]

Onset over six years of age and during colder seasons, time from initial manifestations to diagnosis over eight days, persistent purpura over one month, rural residence, recurrence, angioedema, gastrointestinal bleeding, and CNS involvement are significant risk factors for renal involvement.[1,2] The course is usually self-limited and benign. However, the degree of proteinuria is the most important determinant of IgAV prognosis.[1] Age, platelet distribution width, higher CD3, lower fibrinogen, C-reactive protein, and neutrophil-to-lymphocyte ratio, and higher IgG may be useful in predicting renal involvement in IgAV patients.[11] Pathologically, it is determined by the presence of crescents or tubulointerstitial changes.[2] IgA levels do not seem to correlate with renal involvement. This is an important cause of renal failure in children, accounting for 3% of renal replacement therapy cases in pediatrics.[8]

Central nervous system

This vasculitis affects CNS tissues by causing edema, ischemia, infarction, thrombosis, and/or hemorrhage.[8,14] It usually occurs two to four weeks after the onset of HSP, mostly in patients with severe disease and concomitant multi-organ involvement.[14,25] The posterior parietal and occipital regions are more commonly involved, possibly due to facilitated IgA deposition in the posterior circulation.[14] Headache is the most common symptom, followed by seizures, irritability, dizziness, emotional instability, behavioral changes, hemiparesis and other focal deficits, nystagmus, ataxia, aphasia, and dysarthria. Rare complications include intracranial hemorrhage, mononeuropathy, chorea, acute motor sensory axonal neuropathy, and posterior reversible encephalopathy syndrome.[9,26] Despite its low prevalence, 20% of cases result in permanent sequelae, such as visual and verbal deficits, focal signs, and epilepsy.[14]

Magnetic resonance imaging may show cerebral vasculitis.[8] Lumbar puncture is usually normal but can be relevant in the differential diagnosis.[14]

Lungs

Although rare (0.8-5% of IgAV cases), pulmonary involvement is often severe, with a mortality rate of 27%, mostly due to diffuse alveolar hemorrhage, which is the most common presentation.[8] Deposition of immune complexes in the alveolar-capillary membrane causes pulmonary edema, intra-alveolar hemorrhage, interstitial fibrosis, arterial neutrophilic infiltrate, loss of nuclear staining in the alveolar walls and septa, and capillary wall necrosis.[27] Most patients also present with renal involvement, and antineutrophilic cytoplasmic antibody (ANCA) vasculitis should be considered in these cases.[8] Presentation ranges from cough, hemoptysis, dyspnea, tachypnea, and chest pain to acute respiratory failure. Occasionally, subclinical changes are noted on pulmonary function test or chest radiograph. Lung biopsy confirms leukocytoclastic vasculitis. First-line treatment is high-dose intravenous pulse methylprednisolone with or without immunosuppressive therapy.[27]

Other rare complications include parotitis, myositis, episcleritis, carditis, myocarditis, pancreatitis, cholecystitis, pseudomembranous colitis, orchitis/epididymo-orchitis, and urethritis.[8,28-30]

## DIAGNOSIS

The diagnosis of IgAV is based on clinical manifestations and histologic findings, as there are currently no proven useful biomarkers.[7,9] In 2010, the European League Against Rheumatism (EULAR), the Paediatric Rheumatology International Trials Organization (PRINTO), and the Paediatric Rheumatology European Society (PRES) published

revised criteria for the diagnosis of IgAV in children, achieving 100% sensitivity and 87% specificity.[9] Predominant purpura or petechiae in the lower limbs is a mandatory criterion, plus at least one of the following: acute-onset diffuse abdominal pain; acute-onset arthritis or arthralgia; renal involvement (proteinuria or hematuria); leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposition on histopathology.[6]

As with any cutaneous vasculitis, skin biopsy is the gold standard for the diagnosis of IgAV. IgA-predominant vascular deposits are the most characteristic IgAV finding, but are not always present and may be caused by other conditions such as vasculitic syndromes, erythema nodosum, and venous stasis.[9] Direct immunofluorescence may also show perivascular infiltration of neutrophils and mononuclear cells and C3, IgG (40% of cases), and IgM (20% of cases) deposits, reflecting the presence of immune complexes.[2,8,14] Skin biopsy is usually recommended only when clinical criteria are not met.[9] Histologic evidence of leukocytoclastic vasculitis includes inflammation and fibrinoid necrosis of the vessel walls, endothelial swelling, neutrophilic infiltrate with nuclear fragmentation, and deposition of cellular debris in the surrounding skin (**Figure 2**).[2]

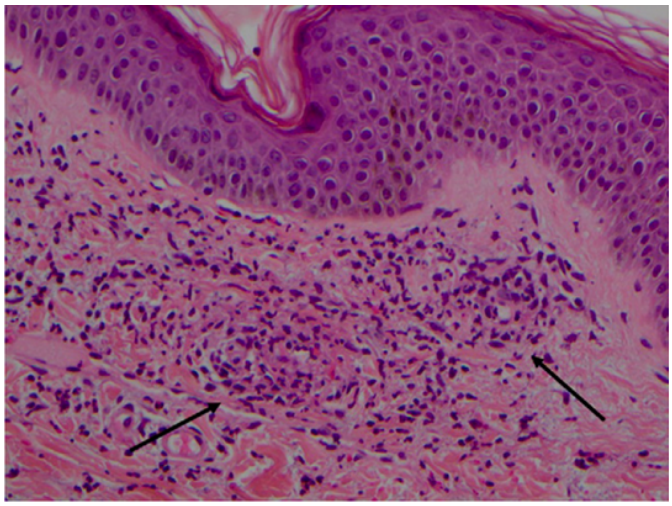

**Figure 2 -** Leukocytoclastic vasculitis of the skin in a child with Henoch–Schönlein purpura. Superficial dermal vessels with inflammatory infiltrate composed mainly of neutrophils and eosinophils (arrows). Hematoxylin/eosin; magnification × 200 (courtesy of the author of Reference 42).

Kidney biopsy is recommended in the presence of persistent severe proteinuria, but may also be considered in cases of short-term severe proteinuria, persistent moderate proteinuria, or impaired glomerular filtration rate.[31] It may show a wide variety of glomerular lesions, most commonly focal and segmental glomerulonephritis.[14] Mesangial deposits in sclerotic glomeruli allow for retrospective diagnosis.[8]

The current histologic classification for IgAVN in children considers only mesangial proliferation and crescent ratio. Therefore, some authors advocate the use of the MEST-C score according to the 2016 revision of the Oxford classification for IgAN, which considers mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and cellular/fibrocellular crescents. However, this classification awaits validation in pediatrics and IgAVN.[32]

Because biopsies are not always easily obtained and many vasculitides and glomerulonephritides share similar histopathologic findings, the development of less invasive, disease-specific, and early-detectable biomarkers is of great interest.[7,11] Laboratory tests can aid in differential diagnosis and early detection of complications.[14] A complete blood count may show moderate leukocytosis and normal or elevated platelet counts; coagulation studies are normal.[2,7] Acute phase reactants may be slightly elevated. Antinuclear antibodies are usually undetectable.[7] Serum C3 and C4 levels may be decreased, especially in children with a recent streptococcal infection.[33] Half of patients show an increase in serum IgA, but it is unclear whether these are clinically significant.[2,21] Regarding renal involvement, urinalysis should be performed at the time of diagnosis, and sequential assessments are recommended three to six months after IgAV onset. It may reveal proteinuria, and the presence of erythrocyte casts or dysmorphic red blood cells indicates the glomerular origin of hematuria.

The differential diagnosis includes acute hemorrhagic edema of infancy (AHEI), leukemia and leukemic lymphoma, acute post-streptococcal glomerulonephritis (APSGN), septicemia, disseminated intravascular coagulation, papular-purpuric gloves-and-socks syndrome, Mediterranean fever, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, and other vasculitides such as hypersensitivity, urticarial and ANCA-associated small vessel vasculitis, mixed cryoglobulinemia, cutaneous polyarteritis, rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease, juvenile dermatomyositis, or antiphospholipid antibody syndrome. The gastrointestinal presentation may be confused with causes of acute surgical abdomen.[2,7]

In AHEI, purpuric lesions involve the lower extremities as in IgAV, but also the face and are usually larger, sometimes target-shaped or developing into bullae, and preceded by facial edema. Peripheral edema is also common, and gastrointestinal or renal involvement is rare. Vascular IgA deposits are rarely seen.[2]

The signs of leukocytoclastic vasculitis may also be found in cases of leukemia and leukemic lymphoma.[2] Skin biopsy may be useful in differentiating from other vasculitides.[7] Vasculitis may be a manifestation of malignancy, either hematologic or solid tumors of gastrointestinal, respiratory, or urinary origin.[9] In the presence of hematuria, renal biopsy helps to differentiate from APSGN by showing diffuse granular IgG deposits.[2]

In the future, the study of IgA1 binding sites and other antibodies such as IgA rheumatoid factor, IgA anticardiolipin antibodies, and IgA anti endothelial cell antibodies may be relevant to the diagnosis.[7] IgA anti-beta2 glycoprotein antibodies are elevated in IgAV, especially in association with severe renal and joint involvement.[9]

**Treatment/Management**

In the absence of renal involvement, supportive treatment is the backbone of this mostly benign and self-limited disease, consisting of hydration, electrolyte balance, and nutrition.[2,7] Compression therapy and antihistamines can help reduce vasodilation and increase blood flow, thereby inhibiting immunoglobulin deposition and lesion progression. Immobilization should be limited to those with severe joint involvement, as it increases the risk of thrombosis, does not affect gastrointestinal or renal involvement, and is beneficial in containing purpuric lesions.[8] Analgesics and antispasmodics are preferred to NSAIDs because of the hemorrhagic and nephrotoxic effects of the latter.[8]

The use of corticosteroids is controversial due to side effects such as weight gain, moon facies, and generalized edema, but may be useful in cases of painful edema and incipient necrosis prior to ulcer formation.[2]

The optimal approach to IgAVN remains uncertain and is often extrapolated from IgAN, especially in cases of more severe renal involvement.[8,9] These patients may require renin-angiotensin system blockers (ACE inhibitors or angiotensin II receptor antagonists) to control blood pressure and persistent proteinuria.[8] If proteinuria remains above 1 g/day/1.73m$^2$, methylprednisolone pulses followed by a short course of oral corticosteroids are usually recommended.[34] The use of terminal ileum-targeted budesonide shows promise in providing effective results with fewer side effects.[35] Corticosteroids appear to have no effect in preventing renal damage, but have a potential benefit in improving the course of established renal involvement, significantly reducing proteinuria and subsequent end-stage renal disease, particularly if started before fibrous crescents are found.[2,36] They may be used independently or in combination with cytotoxic agents, particularly in rapidly progressive glomerulonephritis.[2] There are conflicting data regarding the benefit of cytotoxic agents. Some studies have found no benefit from the use of cyclophosphamide alone or in combination with corticosteroids, while others have demonstrated the advantage of cyclophosphamide and azathioprine in inducing remission and improving its duration.[2,9,37] Azathioprine is usually preferred to cyclophosphamide because of its lower toxicity.[2] Mycophenolate mofetil has also shown better results than cyclophosphamide in reducing proteinuria, with fewer side effects.[9,38] Rituximab, an anti-CD20 antibody, inhibits B-cells and has been effective in inducing remission in individual cases where it has been used, even in end-stage renal disease.[9]

Compared to methylprednisolone, cyclosporine A showed no difference in biopsies at two years, but more frequent and faster regression of proteinuria.[9] It may be used in corticosteroid-dependent patients.[2] Anticoagulants have also been studied for their potential role in limiting fibrin accumulation, but are generally not recommended due to the risk of adverse effects.[2,9,37] O-aminocaproic acid, methotrexate, and hydroxychloroquine have been studied in adults with IgAV.[2,8] Ongoing studies are evaluating the contribution of colchicine in skin-limited vasculitis.[39] The prophylactic role of tonsillectomy has been discussed but is not usually recommended.[9] The use of immunoglobulins and plasmapheresis reduces circulating immune complexes and appears to be beneficial in combination with other therapies, but more studies are needed to clarify their role.[2,8,9]

Glucocorticoids may be helpful for abdominal and joint pain after symptomatic measures have failed.[2,8] In particularly severe cases and after corticosteroid failure, further immunosuppressive strategies may be considered.[38] Abdominal surgery may be necessary for gastrointestinal complications.[9] After exclusion of glucose-6-phosphate deficiency, dapsone has been used in specific cases of persistent and severe purpuric lesions, with complete resolution.[8,9]

**Prognosis and follow-up**

The acute phase of IgAV usually lasts one to four weeks.[2] Although it is mostly a benign disease, 12% of children develop chronic kidney disease within three to four years, and 20% of these progress to end-stage renal disease.[2] Follow-up and close monitoring are recommended until complete clinical and laboratory resolution.[8] Thereafter, the risk of renal impairment decreases dramatically, and there is no consensus regarding follow-up, but annual observations have been advocated.[8,40] Children with renal involvement should be followed long-term.[12] Factors associated with poor prognosis include nephrotic and nephritic syndrome, acute kidney injury at presentation, hypertension, proteinuria/creatinuria ratio greater than 1 g/g, and more than 50% crescent or interstitial fibrosis on renal biopsy.[2,8] In contrast, children who do not present with urinary abnormalities within the first six months rarely have a decline in renal function.[8] Recurrence is defined by the recurrence of symptoms at least two weeks after resolution, but usually occurs within three to four months and affects approximately 15-40% of patients.[2] The most common manifestations are gastrointestinal and cutaneous. Predicting recurrence is challenging as there are currently no validated biomarkers with prognostic value and the association with older age is controversial.[8,41] Low-dose corticosteroids in alternate-day regimens and dapsone may have a role in preventing relapse.[2]

## CONCLUSIONS

IgAV primarily affects children, often following a respiratory infection as trigger.[7] In the absence of renal involvement, supportive treatment is sufficient.[7] Corticosteroids may be useful in cases of severe gastrointestinal manifestations, but do not alter the incidence

of nephritis and are therefore not recommended for the prevention of kidney disease.[2] Despite its usually benign course in children, IgAV has the potential to induce chronic kidney disease and even end-stage renal disease.[8] The extent of renal involvement greatly influences the long-term prognosis.[10] As new evidence emerges, a better understanding of the physiopathology underlying IgAV is gained and better therapeutic options arise. However, there is still an important lack of early and non-invasive diagnostic and prognostic biomarkers to guide the optimal management of these patients.[11]

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# CASE REPORTS

## Nijmegen breakage syndrome: The importance of follow-up

### Síndrome de quebras de Nijmegen: A importância do seguimento

Sara Leite[1], Cláudia Lemos[1], Rita Dias[2], Raquel Faria[3,4], Laura Marques[5]

## ABSTRACT

Nijmegen breakage syndrome (NBS) is a rare genetic disorder caused by mutations in the *NBN* gene, which is inherited in an autosomal recessive pattern. The condition results in inadequate DNA repair and is characterized by immunodeficiency with recurrent sinopulmonary infections, increased radiosensitivity, and predisposition to malignancy, particularly of lymphoid origin. The main clinical feature is progressive and severe microcephaly, which affects the facial phenotype, characterized by prominent midface, sloping forehead, and retrognathia. Mild to moderate intellectual impairment is often present and female patients usually develop primary ovarian failure. The diagnosis requires a high index of suspicion and is confirmed by molecular genetic testing. Herein are presented two cases of Nijmegen breakage syndrome followed in a tertiary center.

**Keywords:** immunodeficiency; Nijmegen breakage syndrome; microcephaly

## RESUMO

A síndrome de quebras de Nijmegen (NBS) é uma doença genética rara que ocorre devido à presença de variantes patogénicas no gene *NBN*, herdado de forma autossómica recessiva. Esta condição leva à reparação inadequada do DNA e caracteriza-se por imunodeficiência com infeções pulmonares recorrentes, hipersensibilidade à radiação e predisposição para neoplasias, particularmente de origem linfoide. As características fenotípicas principais são a microcefalia grave, que influencia o fenótipo facial, com andar médio da face proeminente e retrognatismo. A perturbação ligeira a moderada do desenvolvimento é frequente e os doentes do sexo feminino geralmente desenvolvem insuficiência ovárica primária. O diagnóstico requer um elevado índice de suspeição e pode ser confirmado por análise genética. São apresentados dois casos de síndrome de quebras de Nijmegen seguidos num hospital terciário.

**Palavras-chave:** imunodeficiência; síndrome de quebras de Nijmegen; microcefalia

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## INTRODUCTION

Nijmegen breakage syndrome (NBS) is a rare genetic disorder (1:100000) caused by mutations in the *NBN* gene, which is inherited in an autosomal recessive pattern.[1] With more than 60 variants described, the *NBN* gene, located on chromosome 8q21, is the only gene identified to date in the genetic basis of NBS.[2] The protein product of the *NBN* gene is nibrin, which plays a key role in regulating the activity of proteins involved in the end-processing of normal and mutated DNA double-strand (DDS) breaks caused by ionizing radiation.[2,3] When DDS breaks are not repaired, they result in genomic instability, gene mutations, or chromosomal rearrangements that can lead to malignancy, particularly of lymphoid origin.[4] Nibrin also plays a role in lymphocyte maturation and immunoglobulin class switching, resulting in immunodeficiency characterized by recurrent sinopulmonary infections and increased radiosensitivity.

The main clinical feature of NBS is progressive and severe microcephaly, which affects the facial phenotype, resulting in a prominent midface, sloping forehead, and retrognathia.[2] The nose is usually long and beaked, but may also be upturned with anteverted nostrils.[2] Mild to moderate intellectual impairment is often present, and female patients usually develop primary ovarian insufficiency.[2]

The diagnosis requires a high index of suspicion and is confirmed by molecular genetic analysis.

## CASE REPORTS

**Case 1**. An 18-month-old male of Ukrainian ancestry was referred to the hospital for severe microcephaly noted at birth. He presented a "bird-like" face (**Figure 1a**) and a *café au lait* spot on the right lumbar region. He had severe lymphopenia (686/mm$^3$) with low CD4$^+$ counts (CD4 375/mm3; CD4% 28.4; **Table 1**). There was no relevant family history and the parents were not consanguineous. Molecular genetic analysis revealed a homozygous pathogenic variant, c.657_661delACAAA(p.Lys219Asnfs*16), confirming the diagnosis of NBS.

The child maintained regular follow-up. He is currently six years old, has moderate speech delay, and is receiving speech therapy and global developmental stimulation. Microcephaly was progressive (less than the 3$^{rd}$ percentile, standard deviation -4.86) and the boy maintained severe lymphopenia with low CD4$^+$ counts. Prophylactic cotrimoxazole was administered during the first three years of life. To date, he had no severe infections or signs of malignancy.

**Case 2**. A four-year-old girl was referred to the immunodeficiency center for recurrent respiratory infections. She had severe microcephaly (below the 3$^{rd}$ percentile, standard deviation -3.79), prominent midface, sloping forehead, receding mandible, and long, prominent nose (**Figure 1b**). The initial study revealed immunoglobulin deficiency and lymphopenia with low CD4 counts (**Table 1**). At the age of five, she was hospitalized for severe autoimmune hemolytic anemia, with good response to steroids. She had a favorable course throughout childhood and adolescence, with moderate intellectual disability and recurrent respiratory tract infections, which were treated in the outpatient setting. The girl was transferred to the adult immunodeficiency clinic at the age of 18 years, clinically stable.

At the age of 33, she presented with severe hemolytic anemia and severe lymphopenia and cryoglobulinemia, and was diagnosed with lymphoplasmocytic lymphoma. She was treated with a chemotherapy regimen (five cycles of rituximab, cyclophosphamide, and prednisone), with initial clinical remission. Six months later, a control computed tomography (CT) scan showed pulmonary relapse and the girl was started on a new chemotherapy regimen (four cycles of rituximab and bendamustine). She experienced clinical deterioration since cycle four, and a new biopsy of a mass lesion confirmed progression to high-grade diffuse large B-cell lymphoma. She was started on palliative treatment with cyclophosphamide and rituximab, with no response and a fatal outcome in four months.

The patient fulfilled clinical and analytical criteria for NBS and had several chromosomal abnormalities: 46,XX,t(2;13)(p21;q14),t(6;10)(q21;p15),t(7;11)(q32;q23.2). Molecular genetic testing for the most common abnormalities in the *NBN* gene at that time (including the founder mutation in exon 6, c.657_661del5) was negative. Genomic array (array-CGH) showed the presence of the 6q23.1-q23.2 deletion associated with lymphoplasmocytic lymphoma.


**Figure 1** – Phenotypic features of the two patients considered (a. male, Case 1; b. female, Case 2)

**Table 1** – Immunologic profile of the two patients

| | Case 1 | Case 2 |
|---|---|---|
| **Immunoglobulin** | | |
| IgA (mg/dL) | 39 | 548 |
| IgG (mg/dL) | 631 | 891 |
| IgM (mg/dL) | 58 | 70 |
| IgE (UI/mL) | <2 | <2 |
| **Lymphocyte population (/mm$^3$)** | | |
| CD3 | 560 | 1127 |
| CD4 | 375 | 520 |
| CD8 | 84 | 590 |
| CD19 | 286 | 121 |

## DISCUSSION

The diagnosis of NBS is based on characteristic clinical manifestations, chromosomal instability, increased cellular sensitivity to ionizing radiation *in vitro*, cellular and humoral immunodeficiency, and homozygous pathogenic variants in the *NBN* gene.

Patients have a high susceptibility to infections, usually involving the respiratory tract (chronic sinusitis, recurrent bronchitis, pneumonia). Opportunistic infections are also common. Early diagnosis of NBS is important to prevent severe recurrent infections.

There is no specific treatment for NBS. Intravenous immunoglobulin may be given if immunoglobulin levels are low, and appropriate antibiotic prophylaxis may be instituted.

Unnecessary exposure to all forms of ionizing radiation for diagnostic purposes should be avoided unless absolutely necessary. Because of the high sensitivity to radiation treatment and chemotherapy, the radiation dose should be limited and chemotherapy protocols should be tailored to individual tolerance.[2,4] In these patients, it is reasonable to reduce the chemotherapy dose by up to 50%, especially with anthracyclines, methotrexate, alkylating agents, and epipodophyllotoxins. The use of monoclonal antibodies and kinase inhibitors or bone marrow transplantation with reduced-intensity conditioning can be considered in selected cases to replace radiotherapy and some antineoplastic agents, as performed in Case 2.[1,4]

The major complication associated with chromosomal instability is the development of cancer, primarily of lymphoid origin. As many as 40% of malignancies are diagnosed before the second decade of life, and the most common types are non-Hodgkin lymphoma, predominantly diffuse large B-cell lymphoma, and T-cell lymphoblastic lymphoma.[4] Patient prognosis remains poor.

Malignancy should be carefully assessed, as it may occur several decades after diagnosis. The patient in Case 2 presented with lymphoma in the third decade of life, with an initial remission followed by a fatal course, which is common in these patients. Early diagnosis must be made by examinations that do not involve the use of ionizing radiation. However, this patient underwent two chest X-rays and three CT scans between diagnosis and follow-up because these studies are more accessible than magnetic resonance imaging. The impact of this amount of ionizing radiation on the final outcome is unknown.

The present two cases illustrate the importance of close and long-term follow-up of NBS patients from childhood to adulthood, as some comorbidities may be prevented or reduced with early treatment. In addition, genetic counseling should be offered to parents of affected patients, as NBS is an autosomal recessive disorder and prenatal testing for increased risk pregnancy or preimplantation genetic diagnosis for NBS can be performed.[2]

## AUTHORSHIP

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# CASE REPORTS

## Congenital chylothorax: A series of eight cases

### Quilotórax congénito: Uma série de oito casos

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## ABSTRACT

**Introduction:** Congenital chylothorax (CC) is the accumulation of lymph in the pleural space. The aim of this study was to review the cases of CC diagnosed in newborns admitted to a level III neonatal intensive care unit between January 2014 and December 2020.

**Results:** Eight cases of CC were identified, all with prenatal diagnosis. After postnatal confirmation of the diagnosis, supportive care and conservative therapy were initiated. Six cases underwent mechanical ventilation, two were treated with surfactant and inhaled nitric oxide, four required inotropic support, and one underwent extracorporeal membrane oxygenation. Five newborns were effectively treated with octreotide. One patient with hydrops fetalis died after birth.

**Discussion:** The prognosis of CC depends on the severity of the effusion and on associated abnormalities. Medical treatment is based on supportive and conservative treatment. Although the use of octreotide is not unanimous, it proved to be an effective and safe adjuvant therapy in these patients.

**Keywords:** chylothorax; congenital abnormality; hydrops fetalis; neonatal; octreotide; pleural effusion

## RESUMO

**Introdução:** O quilotórax congénito consiste na acumulação de linfa no espaço pleural. O objetivo deste estudo foi analisar os casos de recém-nascidos com diagnóstico de quilotórax congénito admitidos numa unidade de cuidados intensivos neonatais de nível III entre janeiro de 2014 e dezembro de 2020.

**Resultados:** Foram identificados oito casos de quilotórax congénito, todos com diagnóstico pré-natal. Após confirmação pós-natal do diagnóstico, foi iniciado tratamento de suporte e conservador. Seis casos foram submetidos a ventilação mecânica invasiva, dois foram tratados com surfactante e óxido nítrico inalado, quatro tiveram necessidade de suporte inotrópico e um recebeu oxigenação por membrana extracorporal. Cinco casos foram efetivamente tratados com octreótido. Um recém-nascido com hidrópsia fetal faleceu após o nascimento.

**Discussão:** O prognóstico do quilotórax congénito depende da gravidade do derrame pleural e das anomalias associadas. O tratamento inicial deve ser de suporte e conservador. Embora a utilização de octreótido não seja consensual, demonstrou ser uma terapêutica efetiva e segura nesta amostra de doentes.

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**Palavras-chave:** anomalia congénita; derrame pleural; hidrópsia fetal; neonatal; octreótido; quilotórax

## INTRODUCTION

Congenital chylothorax (CC), defined as the accumulation of lymph fluid in the pleural space, is an uncommon condition with a reported incidence of approximately 1 in 24,000 newborns.[1] It is associated with increased prenatal and postnatal morbidity and mortality, accounting for around 1:2,000 neonatal intensive care unit (NICU) admissions.[2,3]

Clinical manifestations of neonatal chylothorax can range from asymptomatic to severe respiratory distress and are related to the severity of pleural effusion/hydrops and eventual impaired lung development, which may lead to pulmonary hypoplasia and pulmonary hypertension, especially if the condition occurs during early fetal development.[2,4-6]

The management of CC is not standardized and varies among neonatal units. Published reviews and case series agree that the first-line management of CC should be conservative and include supportive measures combined with dietary changes ranging from total parenteral nutrition (TPN) to medium-chain triglyceride (MCT) formulas, provided that the neonate can be orally fed.[2,4,5,7-9] Octreotide, a second-line treatment, is a synthetic somatostatin analog that is thought to reduce lymphatic flow by causing mild vasoconstriction of splanchnic vessels.[2,10,11] Case studies have reported marked variability in its use in different clinical conditions, with no currently established treatment protocols for chylothorax.[4,6,10] A 2010 Cochrane meta-analysis reported that octreotide does not have sufficient evidence to be considered an established treatment option.[12] However, a systematic review with data from multiple NICUs reported widespread use of octreotide as an effective and safe approach.[8] Failure of medical therapy, severe metabolic and nutritional complications, and overall clinical deterioration may be indications for surgical treatment.[2]

The purpose of the present study was to review the management and clinical course of cases of CC diagnosed in a level III NICU over a seven-year period.

## METHODS

A retrospective descriptive review of institutional records of newborns diagnosed with CC admitted to a level III NICU of Maternidade Dr. Alfredo da Costa, in Lisbon, Portugal, between January 1, 2014 and December 31, 2020 was performed. Patients with other known causes of chylothorax, such as trauma and surgery, were excluded. Parameters analyzed included gender, prenatal diagnosis of chylothorax and interventions, gestational age (GA), mode of delivery, Apgar score, birth weight, associated conditions, clinical presentation, characterization of pleural effusion, clinical course, treatment, and adverse effects. Inclusion criteria were based on biochemical and cultural analysis of the pleural fluid and included (i) sterile pleural fluid, (ii) more than 1,000 cells/µL, (iii) more than 80% lymphocytes, and (iv) triglycerides greater than 110 mg/dL, if feeding was enteric. Informed consent was obtained from the parents of all patients included in the study. Descriptive analysis was performed using Microsoft Excel®.

The management of CC at the considered NICU is based on supportive care consisting of respiratory and cardiovascular support and correction of anemia, coagulation disorders, and hypoalbuminemia, if present. In cases of metabolic acidosis with bicarbonate levels below 12 mEq/L, bicarbonate solution is used to maintain water-electrolyte balance. Thoracentesis and pleural drainage combined with pain management are performed in cases of moderate-to-severe pleural effusion or symptomatic newborns. In mild and asymptomatic cases, a MCT formula supplemented with parenteral nutrition is started and tapered according to clinical improvement. In more severe or symptomatic cases, initial treatment includes fasting and individualized prescription of TPN. After one week of TPN, octreotide therapy is used in cases where a large effusion persists. If the pleural drainage volume after birth is ≥ 50 mL/kg/day, octreotide may be considered earlier, between the third and fifth day. If the drained volume is <10-20mL/Kg/day, formulas with MCT are introduced. Intravenous immunoglobulin is used in newborns with prolonged pleural effusion and hypoglobulinemia.

## RESULTS

Eight cases of CC were identified in this seven-year review, predominantly in male patients (n=5). All cases had prenatal suspicion of this diagnosis at a mean (standard deviation [SD]) GA of 27.2 ± 5.8 weeks, with ultrasound evidence of fetal pleural effusion. In addition, cases 3 and 5 had prenatal diagnosis of bilateral hydronephrosis, and case 6 had prenatal diagnosis of hepatomegaly and ascites. Case 8 was diagnosed with hydrops fetalis at 20 weeks GA and underwent pleuroamniotic shunting due to its severity. As no improvement was noted, intrauterine fetal thoracentesis twice weekly was started at 26 weeks GA. This was the only case requiring *in utero* intervention. Prenatal data are summarized in **Table 1**.

**Table 1 -** Prenatal findings in neonata chylothorax cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Sex** | M | F | M | F | M | F | M | M |
| **Prenatal diagnosis of pleural effusion** | Yes (22 w) | Yes (27 w) | Yes (20 w) | Yes (33 w) | Yes (31 w) | Yes (32 w) | Yes (33 w) | Yes (20 w) |
| **Other prenatal ultrasound findings** | -- | -- | Hydronephrosis | -- | Pericardial effusion | Hepatomegaly, ascites | -- | Hydrops fetalis |
| **Antenatal interventions** | No | No | No | No | No | No | No | Yes (Pleuroamniotic shunt + fetal thoracentesis) |

F – female; M – male; W – weeks

The median GA at birth was 35 weeks (range 30-40), and 50% of patients were born by eutocic delivery. Birth weight ranged from 1,950 to 4,595 grams. Half of cases required immediate resuscitation. Three cases were diagnosed with other conditions: cases 1 and 3 with bilateral hydronephrosis and case 5 with Down syndrome associated with septal heart defects and bilateral cryptorchidism. The demographic characterization of neonatal chylothorax cases is summarized in **Table 2**.

**Table 2** - Demographic characterization of neonatal chylothorax cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **GA** | 35w+ 1d | 40w+3d | 35w+3d | 33w+4d | 37w+1d | 36w+6d | 35w+4d | 30w |
| **Delivery Mode** | eutocic | eutocic | vacuum | eutocic | caesarean | caesarean | caesarean | eutocic |
| **AS 1/5/10´** | 6/8/8 | 9/10/10 | 8/9/10 | 5/8/9 | 8/9/10 | 5/8/9 | 9/10/10 | 2/4/6 |
| **BW, g** | 2,668 | 3,540 | 2,735 | 2,130 | 2,740 | 4,595 | 2,600 | 1,950 |
| **Associated clinical pathologies** | Bilateral hydronephrosis | -- | Bilateral hydronephrosis | -- | Down syndrome, ASD, VSD, cryptorchidism | -- | -- | -- |
| **Pleural effusion location** | Right | Right | Bilateral | Bilateral | Right | Right | Bilateral | Bilateral |

AS – Apgar score; ASD – atrial septal defect; BW – birth weight; d – days; GA – gestational age; VSD – ventricular septal defect; W – weeks

At birth, six patients showed signs of mild to moderate respiratory distress, and one (case 2) was asymptomatic. Case 8 presented with severe symptoms and died four hours after birth with severe respiratory failure despite implementation of recommended protocols.

Pleural effusion was bilateral in four cases and right-sided in the remaining cases. Biochemical and cultural analysis of the pleural fluid is shown in **Table 3**. Triglyceride levels >110 mg/dL were found only in cases 2 and 5. In both cases, the newborns had already received enteral nutrition for several days.

**Table 3 -** Characterization of pleural fluid

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Cells (cells/µL)** | 1,500 | 16,000 | 9,146 | 4,272 | 7,000 | 7,961 | 13,484 | 1,559 |
| **Lymphocytes (%)** | 95.3 | 97 | 97.1 | 97.1 | 93.3 | 88.7 | 96.7 | 92.2 |
| **Proteins (g/dL)** | 25 | 72.2 | 1.89 | 24.5 | 30 | 40.4 | 24.7 | 16.4 |
| **Triglycerides (mg/dL)** | 20 | 1064 | 44 | 43 | 637 | 53 | 20 | 17 |
| **Culture test** | Negative | Negative | Negative | Negative | Negative | Negative | Negative | Negative |

Regarding supportive care, six patients required invasive ventilation support (**Table 4**). The median duration of invasive mechanical ventilation was 15.8 days (range 1-33). Patients 1 and 8 received surfactant due to hyaline membrane disease. Case 3 required inotropic support due to hemodynamic instability since the first day of life. On day 10, the newborn's clinical condition deteriorated, with severe persistent pulmonary hypertension refractory to aggressive ventilation with 100% oxygen, nitric oxide treatment, and inotropic support. The patient was eligible for extracorporeal membrane oxygenation, which he received for a total of 19 days, with gradual clinical improvement. Cases 1 and 7 also presented with hypotension requiring inotropic support for five and nine days, respectively. All infants required chest drains with a mean duration of insertion of 13 days (SD ± 9.9). Initial treatment for all newborns included fasting and individualized prescription of TPN. When clinically stable, oral feeding with a high MCT formula was initiated.

**Table 4** - Supportive treatment of neonatal chylothorax cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Invasive ventilatory support (days)** | Yes (11) | No | Yes (33) | Yes (6) | No | Yes (11) | Yes (33) | Yes (1) |
| **Surfactant** | Yes | No | No | No | No | No | No | Yes |
| **Cardiovascular support** | Yes (inotropic agents) | No | Yes (inotropic agents + ECMO) | No | No | No | Yes (inotropic agents) | Yes |
| **Chest drainage duration (days)** | 13 | 7 | 33 | 3 | 13 | 11 | 27 | 1 |

ECMO – extracorporeal membrane oxygenation

Five patients did not respond to conservative treatment and were treated with continuous octreotide infusion. Octreotide administration was initiated at a median age of six days (range 5–27) and continued for a median of 29 days (range 17–46). The initial dose was 1-2 µg/kg/h, with progressive increases according to therapeutic response. Case 7 responded effectively to the maximum dose of 12 µg/kg/h. None of the most commonly reported side effects of octreotide therapy was observed. Resolution of chylothorax was achieved in all five patients. Full enteral feeding with MCT formulas was achieved at a mean age of 39 days (SD ± 15). Octreotide treatment is summarized in **Table 5**.

Complications were present in almost all CC cases (**Table 6**): pneumothorax in four, late-onset culture-negative sepsis in one, late-onset sepsis due to coagulase-negative staphylococci susceptible only to vancomycin in three, and severe hypoalbuminemia in three.

The median time to resolution of pleural effusion was 22 days (range 13–50). No patients required surgical intervention. The mean length of hospital stay was 58.1 days (SD ± 19.8). One patient did not survive (case 8).

**Table 5** - Octreotide treatment of neonatal chylothorax cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Octreotide** | No | No | Yes | Yes | Yes | Yes | Yes | No |
| **Starting day** | -- | -- | 6 | 20 | 27 | 6 | 5 | -- |
| **Total duration (days)** | -- | -- | 17 | 24 | 29 | 46 | 45 | -- |
| **Intial dose (µg/Kg/ h)** | -- | -- | 1 | 2 | 1 | 2 | 2 | -- |
| **Maximum dose (µg/Kg/h)** | -- | -- | 7 | 4 | 2,5 | 5 | 12 | -- |

**Table 6** - Complications and clinical course of neonatal chylothorax cases

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 | Case 8 |
|---|---|---|---|---|---|---|---|---|
| **Complications** | Pulmonary hypertension<br>Arterial hypotension<br>Sepsis<br>Coagulopathy<br>Hypoalbuminemia | -- | Pneumothorax<br>Pulmonary hypertension<br>Hypotension<br>Anemia<br>Thrombocytopenia<br>Hypoalbuminemia<br>Hypogammaglobulinemia<br>Acute kidney failure | PTX | Sepsis<br>Anemia | PTX<br>Sepsis<br>Anemia<br>Coagulopathy<br>Acute kidney failure | PTX<br>Hypotension<br>Sepsis<br>Hypoalbuminemia | Respiratory Insufficiency<br>Tension PTX |
| **Time to reach full enteral feeding (days)** | 24 | 16 | 39 | 35 | 42 | 61 | 49 | -- |
| **Length of stay (days)** | 29 | 62 | 47 | 50 | 79 | 79 | 65 | -- |
| **Outcome** | Discharge | Discharge | Discharge | Discharge | Discharge | Discharge | Discharge | Death |

PTX: Pneumothorax

## DISCUSSION

Congenital chylothorax, defined as the accumulation of chyle in the pleural space, results from various pathologic processes or developmental abnormalities of the lymphatic vessels or lymphatic duct that damage or obstruct this system, leading to leakage in the absence of external insults such as trauma or surgery.[1,2,4] It may be idiopathic or associated with genetic syndromes, such as trisomy 21, X monosomy, or Noonan syndrome.[2-4,13] It is a rare condition, but represents the most common cause of pleural effusion during the fetal and neonatal periods.[4]

Eight neonates with CC were identified in the present NICU, corresponding to an incidence of 1:3,000 live births. However, selection bias towards more severe cases cannot be excluded, as all patients were diagnosed prenatally and referred to our tertiary hospital for intensive postnatal care.

The authors believe that prenatal diagnosis of fetal pleural effusion is of great value in determining the severity of the effusion, associated abnormalities, and the need for *in utero* intervention. Prenatal intervention by thoracentesis, pleuroamniotic fluid drainage, or amniotic shunting depends on the GA at diagnosis, the volume and recurrence of the chylous effusion, the degree of pulmonary compression, and the presence of hydrops.[2,4,12] Infants with large or progressive pleural effusion or two or more fluid collections (ascites, pleural or pericardial effusion, generalized subcutaneous edema) -without other major congenital anomalies should be considered for fetal treatment to decompress the pleural space, allow normal lung development, and restore fetal hemodynamics.[2] It is also important

to schedule delivery at a tertiary perinatal center with experienced neonatal staff, as most of these patients may require intensive resuscitation and ventilation.[4,5]

All cases in this series had a prenatal diagnosis of CC, but only one (the case with hydrops fetalis) was considered for antenatal intervention. The initial treatment approach was conservative and consisted of supportive measures combined with nutritional management.

Respiratory support was required in 75% of cases and inotropic support in half, similar to what has been described in previous case series.[4,5,9,14]

Pleural drainage was performed in all cases, and albumin replacement due to protein loss XXX, a commonly described complication, was also performed in three patients.[1,5,9,13,14] In some cases, dietary modification is effective and allows complete resolution of the chyle effusion.[4,5,9,13] In other cases, failure of conservative treatment requires additional treatment options, as seen in this study in five of the seven surviving cases. Octreotide was used in these patients following previous reports of treatment success with this agent.[4-6,9,11,13,15] A 2010 Cochrane meta-analysis suggested a wide dose range of 20–70 µg/kg/day administered subcutaneously and 0.3–10 µg/kg/hour administered intravenously. Studies show a wide variation in the optimal timing, dose, duration, efficacy, and safety of octreotide, suggesting that there is insufficient evidence to support it as an established treatment option.[12]

The most commonly reported side effects of octreotide are arrhythmias, injection site pain, nausea, vomiting, constipation or diarrhea, hyperglycemia, hypoglycemia, transient liver dysfunction, transient hypothyroidism, and necrotizing enterocolitis.[5,12,14] In the present series, octreotide was shown to be safe and effective for the treatment of neonatal CC, even over long periods of time, as all treated cases responded effectively and without side effects. This is consistent with previous case series that have also reported no side effects associated with this agent.[1,9,15] Conversely, Bialkowski A *et al.* reported hyperglycemia and bloody stools in two of 28 infants treated with octreotide.[14]

Although surgical treatment is indicated when medical treatment fails after four to five weeks, conservative treatment with octreotide infusion was maintained in cases 6 and 7 in this study because clinical improvement was observed without recurrence of effusion . Although some case series reported successful treatment with octreotide, others described lack of response and recurrence of effusion with the need for surgical treatment.[5,9]

In conclusion, this study confirms the previously reported very low incidence of CC and documents the clinical approach to this condition in the study NICU. The authors emphasize the importance of prenatal diagnosis to assess the severity of the disease and associated conditions and to plan for possible fetal intervention. The management approach in this NICU is based on descriptions of other case series and algorithms proposed in other NICUs. Although implementation of guidelines is difficult due to the rarity of this condition, the need to optimize the therapeutic approach should prompt the development of multicenter studies.

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## LEGENDS

CC – Congenital chylothorax

GA – gestational age

MCT – medium-chain triglycerides

NICU – neonatal intensive care unit

TPN – total parenteral nutrition

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# CASE REPORTS

## Aquagenic palmoplantar keratoderma associated with cystic fibrosis gene mutation

### Acroqueratodermia aquagénica associada a mutação do gene da fibrose quística

Inês Falcão[1], Filipa Rodrigues dos Santos[1], Nuno Neto Magalhães[2], Leonor Cunha[1]

## ABSTRACT

**Introduction:** Aquagenic palmoplantar keratoderma (APK) is a rare dermatologic condition characterized by excessive palmar wrinkling that occurs within minutes of exposure to water. Cystic fibrosis (CF) or CF carrier-associated forms, drug-induced cases, and idiopathic forms have been described. The exact pathophysiology remains unknown.

**Clinical case:** A 13-year-old female patient was observed for pruritus and palmar edema after brief contact with water with one month of evolution. Symptoms resolved spontaneously 20 minutes after drying the hands. Study of the cystic fibrosis transmembrane conductance regulator (CFTR) gene revealed an F508del mutation in one allele.

**Discussion/Conclusion:** Similar to what was described in this patient, the F508del mutation has been the most commonly associated with APK in patients with CF. In the present case, APK was the sole manifestation of the patient's CF carrier status. This fact highlights the importance of considering and investigating this type of genetic alteration in these patients. Overall, CF should be considered in patients with APK, and patients with CF should be asked about symptoms of this condition.

**Keywords:** aquagenic palmoplantar keratoderma; cystic fibrosis; cystic fibrosis transmembrane conductance regulator gene; genetic screening; f508del mutation

## RESUMO

**Introdução:** A acroqueratodermia aquagénica palmoplantar (APK) é uma condição dermatológica rara caracterizada por enrugamento palmar excessivo poucos minutos após exposição a água. Têm sido descritos casos associados a fibrose quística (FC) ou formas associadas ao estado de portador de FC, bem como casos induzidos por fármacos e formas idiopáticas. A fisiopatologia da APK permanece desconhecida.

**Caso clínico:** É descrito o caso clínico de uma menina de 13 anos de idade com queixas de prurido e edema palmar após breve contacto com água com cerca de um mês de evolução. Os sintomas regrediam espontaneamente 20 minutos após a secagem das mãos. O estudo do gene regulador da condutância transmembranar da fibrose quística (CFTR) revelou a mutação F508del num dos alelos.

**Discussão/Conclusão:** À semelhança do presente caso, a mutação F508del é a mais frequentemente associada à APK em doentes com FC. A APK representou a única manifestação do estado portador de FC neste doente. Destaca-se assim a importância de considerar e pesquisar este tipo de alteração genética em doentes com APK.

Em conclusão, a FC deve ser considerada em doentes com APK, e os doentes com FC devem ser questionados sobre sintomas de APK.

**Palavras-Chave:** acroqueratodermia aquagénica palmoplantar; fibrose quística; gene regulador da condutância transmembranar da fibrose quística; mutação f508del; rastreio genético

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## INTRODUCTION

Aquagenic palmoplantar keratoderma (APK) is a rare condition characterized by edematous, flat-topped papules on the palms or, less commonly, the soles, with wrinkling after brief exposure to water that persists for 20 to 30 minutes after exposure.[1] Clinical findings are usually bilateral and symmetric.[1]

The diagnosis is relatively straightforward if one is aware of this entity.[1] While the exact pathophysiology remains unclear, several mechanisms and associations have been proposed.[1] One commonly described mechanism that may explain APK suggests that increased sodium retention in the stratum corneum results in increased water uptake capacity.[2-4] Other hypotheses include stratum corneum barrier dysfunction, possible involvement of transient vanilloid receptor type 1, and increased skin aquaporin expression.[5] Another hypothesis links APK to increased sympathetic activity and involvement of sympathetically innervated eccrine sweat glands.[5,6] This theory is supported by the fact that several anticholinergic medications have been effective in the treatment of APK.[6]

APK can be idiopathic or induced by drugs. Drug-induced APK has been associated with rofecoxib, celecoxib, aspirin, and, less often, tobramycin.[7-10] The proposed mechanism for the cases associated with rofecoxib, celecoxib, and aspirin involves cyclooxygenase-2 (COX-2) inhibition in epidermal cells, which may cause increased sodium reabsorption in a mechanism similar to the effect of COX-2 inhibitors on kidney cells.[7-9]

Histopathologic changes include orthohyperkeratosis with increased thickness and abnormal staining of the stratum corneum, dilated acrosyringia, and dermal eccrine ducts with hyperplasia of eccrine glands, clear cell changes and vacuolation, and increased capillaries around and adjacent to the eccrine glands.[11]

APK is associated with cystic fibrosis (CF) and involves the same mutations found in CF (usually ΔF508 of the CFTR gene), either homozygous or heterozygous. It has been reported that 40-84% of patients with CF have concomitant APK.[2-3]

Although APK is more common in patients with CF, Gild *et al.* described the first case associated with an isolated mutation in the CFTR gene, suggesting that APK may be a sign of CF carrier status.[12] However, APK is not specific to CF, as it is also found in other conditions such as marasmus, nephrotic syndrome, atopy, palmar hyperhidrosis, Raynaud's phenomenon, malignant melanoma, Behçet's disease, and nail psoriasis.[4,13]

## CLINICAL CASE

A 13-year-old Caucasian female patient was observed for pruritus and palmar edema after brief contact with water with one month of evolution. Symptoms were more easily triggered by hot water and resolved spontaneously 20 minutes after drying the hands. The condition fluctuated between exacerbations and periods of complete resolution. The girl had no other dermatologic history except for occasional palmar hyperhidrosis. She reported no plantar symptoms or other associated complaints (e.g., respiratory or gastrointestinal). She had no relevant medical history, including no history of atopy or chronic cardiac or respiratory disease, and denied sinus, nasal, or gastrointestinal complaints. She was not taking any regular medication, only occasional paracetamol. There was no family history of cystic fibrosis or aquagenic wrinkling of the palms.

On physical examination, the patient's skin was found to be dry with mild thickening of the palms and some subtle central white and flesh-colored papules. The remainder of the skin, scalp hair, and nails were normal. Nasal examination was normal with no nasal polyposis, and lung auscultation was unremarkable. Within five minutes of immersion in water, the patient developed wrinkling of the palmar skin, web spaces, and digits with prominent dilated ostia, which were observed with a dermoscope.

CFTR gene study revealed an F508del mutation in one allele.

Biopsy of palmar papule after water immersion showed hyperorthokeratosis, dermal edema, and dilatation of eccrine acrosin ostia. Sweat test was negative (< 60 mmol/L).

The patient was treated with topical aluminum chloride 20%, with satisfactory improvement of signs and symptoms. Considering the CF carrier status, the patient and family members were referred for genetic counseling.

## DISCUSSION/CONCLUSIONS

Skin lesions typically appear after brief contact with hot or cold water, with complete resolution shortly after drying the hands. In the absence of water contact, the palmar and/or plantar skin does not show any of the described signs or in some cases continues to show the presence of hyperlinearity and multiple white millimeter papules. Lesions are usually asymptomatic but may occasionally be associated with complaints of pruritus and burning. This entity is more common in female patients (58%), especially in young age groups (onset between 9-42 years).[4]

CF is usually diagnosed at an early age, with more than 75% of patients being diagnosed by the age of two. The diagnosis of non-classic CF in children and young adults is more challenging. To date, more than 2,000 CFTR mutations have been identified, which are classified according to their potential impact on CFTR function or according to their clinical implications.[14]

The F508 mutation is the most commonly associated with APK in CF patients. Although this is the most common CFTR gene mutation, some authors speculate that it may be a predisposing factor for APK.[4]

In the present case, APK was a unique manifestation of the patient's CF carrier status. This fact highlights the importance of considering and investigating this type of genetic mutation in these patients. These diseases should be investigated not only in CF carriers, but also

in CF patients to facilitate timely treatment. Therefore, identification of the genetic mutations underlying this disorder may help to elucidate the pathophysiological mechanisms involved. The authors believe that APK is an underdiagnosed entity that can be confused with the physiologic pallor and wrinkling of the palms and soles, usually caused by vasoconstriction associated with prolonged water exposure.

Aquagenic urticaria (AU) is one of the conditions to consider in the differential diagnosis of APK. It is a rare form of chronic inducible urticaria that is triggered by water at any temperature. Pruritic wheals develop immediately or within minutes at sites of skin contact with water (but not on the palms and soles, which is the main clinical difference from APK), regardless of temperature or source, and clear within 30-60 minutes. Sweat, saliva, and even tears can cause a reaction. Symptoms often begin during puberty, but cases presenting in childhood have also been reported. A 20-minute water challenge test at body temperature is recommended for diagnosis of AU.[15-18]

Most treatment regimens for APK focus on reducing the hyperkeratosis associated with the condition or providing a water barrier to prevent exposure. Treatments involving the application of 12% ammonium lactate creams or petroleum jelly or the use of gloves have not been shown to be effective. The use of 20% aluminum chloride solution has been shown to result in rapid improvement of symptoms in a series of three patients.[19]

Tap water iontophoresis, endoscopic thoracic sympathectomy, botulinum toxin injections, and oxybutynin are effective for refractory forms.[19] Topical salicylic acid and aluminum salts are effective but of little value as maintenance therapy.[19] Oral oxybutynin 5 mg/d is probably the best option for treating APK. The reported pathophysiologic effects of nonsteroidal anti-inflammatory drugs in this setting suggest that the use of prostaglandins may be warranted.[9]

The use of sweat chloride testing or genetic studies should be encouraged in these patients, as there is an association between APK and CF or CF carrier status, especially when APK occurs at young ages.

In conclusion, the authors suggest that sporadic isolated APK should be included in the clinical spectrum of CFTR gene mutations as a CFTR-related disorder, especially in more dubious cases. Furthermore, screening for rare mutations in the CFTR gene should be recommended in patients with isolated APK in order to adapt genetic counseling as well as management and prevention of complications.

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# CASE REPORTS

## Small deletion in the critical region of Cri-du-chat syndrome associated with cat-like cry

### Pequena deleção na região crítica da síndrome de Cri-du-chat associada a choro de gato

Catarina Freitas[1], Paula Rendeiro[2], Maria José Costa[3]

## ABSTRACT

Cri-du-chat syndrome is a rare disorder caused by a deletion of part of the short arm of chromosome 5. It is characterized by the presence of clinical features at birth, namely cat-like cry, low weight, microcephaly, and facial dysmorphism. The corresponding phenotypes vary from minimal features to a complete phenotype.

Herein is described the case of an infant who presented from birth with cat-like cry and a peculiar face with a wide nasal bridge and thin upper lip. The genetic study revealed a very small deletion on the short arm of chromosome 5, which has not been described in the literature and may represent a novel variant of this recurrent deletion. Furthermore, since the main feature of this case is the cat-like cry, the considered deletion (detected only by microarray analysis) could be associated with this specific feature.

**Keywords:** cat-like cry; chromosome 5; Cri-du-chat; facial dysmorphism; microcephaly

## RESUMO

A síndrome Cri-du-chat é uma doença rara que resulta de uma deleção no braço curto do cromossoma 5. Caracteriza-se pela presença de achados clínicos ao nascimento, como choro em miado de gato, baixo peso, microcefalia e dismorfia facial. O fenótipo correspondente varia entre a presença de algumas características e o quadro clínico completo.

É descrito o caso de uma lactente que apresentou desde o nascimento choro em miado de gato e uma fácies peculiar com ponte nasal larga e lábio superior fino. O estudo genético revelou uma pequena deleção no braço curto do cromossoma 5. Esta deleção não se encontra descrita na literatura, podendo representar uma nova variante da deleção recorrente. Para além disso, uma vez que o choro em miado de gato é a característica principal do quadro clínico, a deleção considerada (identificada apenas pelo estudo de *microarray*) pode estar associada a este fenótipo específico.

**Palavras-chave:** choro em miado de gato; Cri-du-chat; cromossoma 5; dismorfia facial; microcefalia

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## INTRODUCTION

Cri-du-chat syndrome results from a deletion of variable size on the short arm of chromosome 5 (5p-).[1,2] It is a rare entity that should be suspected in the presence of specific clinical features at birth, namely cat-like cry, low weight, microcephaly, and facial dysmorphism.[2-5] It is also associated with delayed psychomotor development and presence of cardiac, neurological, or renal malformations, which should be investigated in routine workup.[2,3] Herein is described the case of an infant who presented with cat-like cry since birth and whose genetic study was very challenging.

## CASE PRESENTATION

An eight-month-old female infant presented from birth with a high-pitched, cat-like cry and a peculiar face with wide nasal bridge and thin upper lip. She was born by eutocic delivery from a singleton pregnancy without complications and had an Apgar index of 9/10. Because of suspicion of Cri-du-chat syndrome, a genetic study was performed, first by fluorescence in situ hybridization (FISH) with a specific probe for the critical region of this syndrome at 5p15.2 (metasystem XL 5q31/5q33/5p15 FISH probe), which was negative for deletion of the short arm of chromosome 5. Following this result, chromosomal microarray analysis (aCGH) was performed, which revealed a deletion of 2.889 Mbp at 5p15.33p15.32 (genomic coordinates GRCh37: 1708529 to 4597389; **Figure 1**) involving *MIR4277*, *MEPL36*, *NDUFS6*, *LOC101929034*, *IRX4*, *CTD-2194D22.4*, *LOC100506858*, *IRX2*, *C5orf38*, *LOC105374620*, *LINC01377*, *LINC01019*, *LINC01017* and *IRX1* genes, suggesting a possible etiology for the observed phenotype. The patient was observed by a cardiologist, who excluded cardiac malformations. No morphologic changes were found in transfontanellar, abdominal, or renal ultrasound. At the time of the study, the infant was eight months old and presented with appropriate height, weight, and psychomotor development.

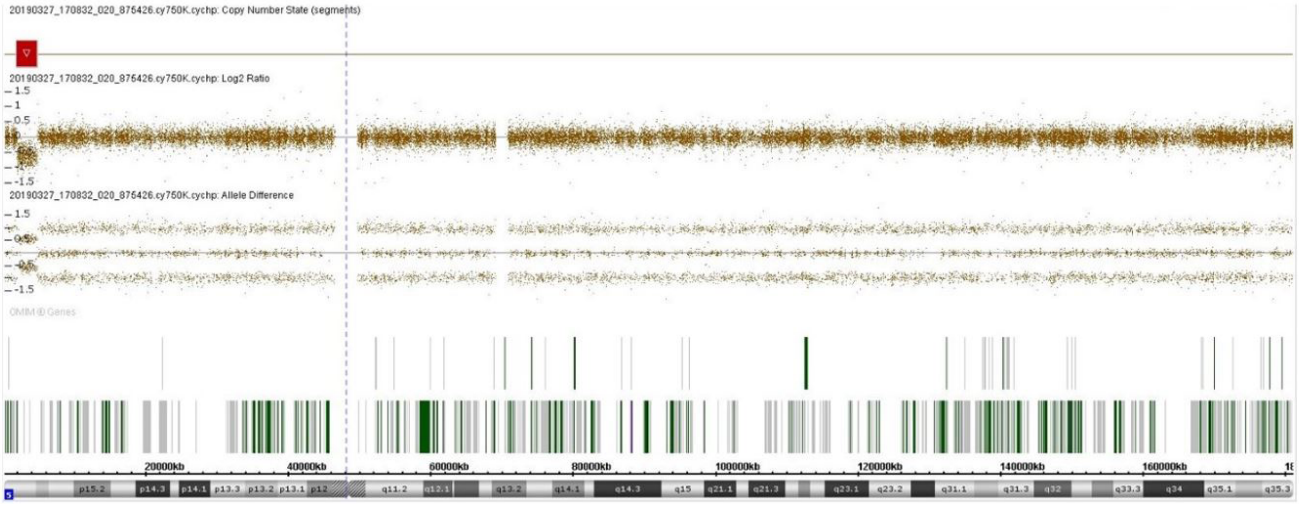


**Figure 1** – Chromosome microarray analysis of chromosome 5 (Chromosome Analysis Suite, Applied Biosystem™). The red bar at the top represents the deleted region

## DISCUSSION

Cri-du-chat syndrome results from a chromosomal abnormality with an estimated incidence of 1:15000 to 1:50000 live births.[1-5] The condition has a mortality rate of approximately 10%, mainly in the first year of life.[3] The classic phenotype is characterized by the presence of a high-pitched, cat-like cry early in life (apparently related to vocal cord abnormalities), facial dysmorphism (round face, wide nasal bridge, epicanthal folds), and microcephaly, as well as psychomotor and intellectual delay. Although a genotype-phenotype correlation has not been fully established, the disease has a variable spectrum of clinical features and severity that appears to depend on the size and gene content of the deletion.[2-5]

Most deletions on the short arm of chromosome 5 associated with Cri-du-chat syndrome are *de novo* deletions in the terminal region. Only 5% are interstitial, mostly with hereditary transmission.[5] The deletion can vary in size from as little as ~5 Mb to the entire short arm of chromosome 5, and the larger the loss and the number of

genes involved, the greater the likelihood of progression to global developmental delay.[2,4,6] The corresponding phenotypes vary from minimal features to a complete phenotype. Several genotype-phenotype correlation studies have been published to identify the genomic regions responsible for the major features of this syndrome. However, the results have not always been consistent. In the case of the typical cat-like cry, recent studies have identified 5p15.31 (specifically the *FLJ25076* gene), 5p15.32 (involving the *ADAMTS16* and *ICE1* genes), and 5p15.33 as possible critical regions.[6,8,9,10]

In this case, a smaller deletion than those described in the literature was detected, slightly less than 3 Mbp, located in the critical region of Cri-du-hat syndrome, but not involving genes previously considered essential for the presence of the cat-like cry. The region involved (5p15.33p15.32) is more distal than those originally associated with this trait.[5,6] There are descriptions in the literature of two patients with small terminal deletions of 4.79 Mbp and 5.5 Mbp, both involving the region deleted in the present case (**Figure 2**).[8,9] The patient with the 4.79 Mbp deletion did not show the typical cat-like cry, and the patient with the 5.5 Mbp deletion had this typical feature. The comparison of these two cases allowed to identify *ADAMTS16* and *ICE1* genes as possible critical genes in the development of the typical cat-like cry, but the present case seems to contradict this theory, since the observed deletion does not involve these two genes.[8] The lack of reports of cases with identical size and location to this case makes it difficult to anticipate a prognosis for this patient. However, the location of the deletion in the critical region of Cri-du-chat syndrome suggests a possible etiology for the clinical signs described (high-pitched, cat-like cry associated with wide nasal bridge and thin upper lip). It should be noted that the first FISH study did not show any alterations because the deletion in question does not involve the FISH-targeted region, since the FISH probe is located in the telomere region. Considering the variability of the size of the deletion in Cri-du-chat syndrome and the variable location in 5p, aCGH is currently the primary diagnostic tool for this clinical entity, as it is able to precisely define the location and size of the deletions.[3]

It should also be noted that the parents of some children with this syndrome have the same deletion but do not show any characteristic features or symptoms, highlighting how environmental and/or genetic factors – such as incomplete penetrance or modifying genes – can influence the phenotypic expression.[7] For this reason, the genetic study of parents is essential for genetic counseling. This was not done in the present case because the child had unknown parents, but this study would have been useful to assess the pathogenicity of the deletion in question, as there are no descriptions of identical deletions in the literature.

The study of associated malformations, namely cardiac, neurological, and renal, should not be neglected. Therefore, echocardiography and transfontanellar, abdominal, and renopelvic ultrasound should be performed.[3]

Follow-up of this case did not reveal any additional features that could be part of the syndrome, and normal growth and development were noted.

The authors emphasize the rarity of this entity and the need for a high degree of clinical suspicion in its diagnosis, highlighting the importance of the diagnostic approach that allowed to clarify the etiology in the present case. This case also highlights the need for more information on atypical deletions such as the one considered here, in order to allow a more accurate and effective genotype-phenotype correlation. Although there is no specific treatment for this syndrome, its early recognition allows for timely and more effective educational and rehabilitation intervention. This case highlights the challenge that the diagnosis of a rare genetic disease can be and the importance of valuing clinical signs and performing genetic study, namely through chromosomal microarray analysis.

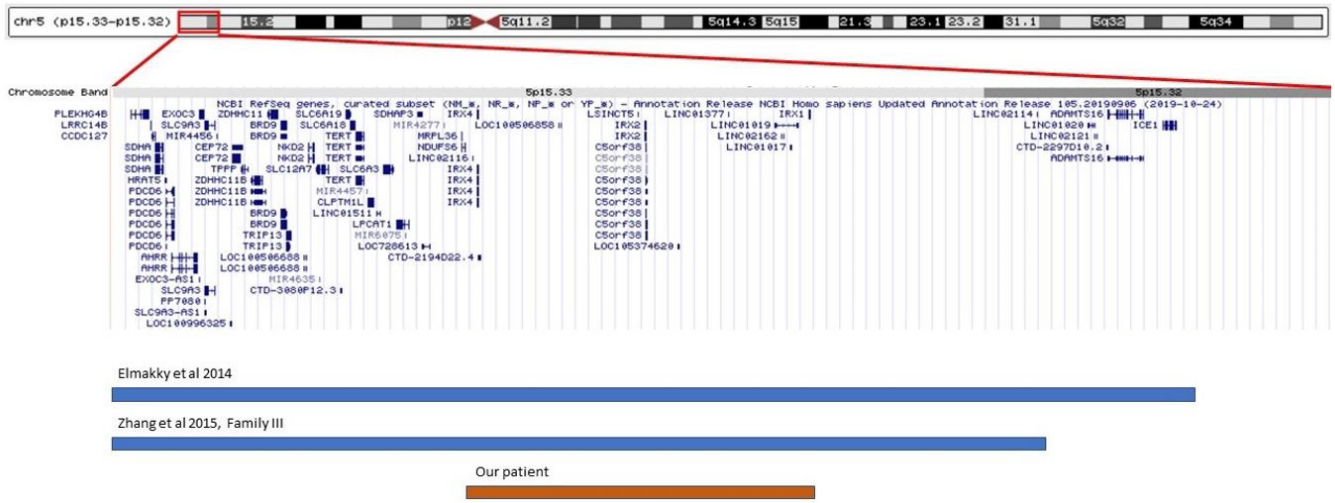


**Figure 2** – Diagram showing the relative positions of the two small deletions described by Elmakky *et al.* 2014 and Zhang *et al.* 2015 (family III) compared to the deletion reported in the present study

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# CASE REPORTS

## Delayed subaponeurotic fluid collection: An unusual cause of scalp swelling

### Coleção de líquido subaponevrótico tardio: Um caso incomum de edema do couro cabeludo

Catarina Cristina[1], Mariana Duarte[2], Mário Matos[2], Rita Machado[1]

## ABSTRACT

Delayed subaponeurotic fluid collection (DSFC) is a rare cause of scalp swelling in young infants whose exact etiology remains unknown. It is often associated with traumatic or instrumental delivery or fetal electrode monitoring. The diagnosis is clinical, with DSFC being differentiated from other causes of scalp swelling based on the characteristic history and physical examination findings. However, laboratory tests or head imaging study may be considered in the differential diagnosis.

Herein is presented the clinical case of a seven-week-old male infant brought to the pediatric Emergency Department with acute onset of large and fluctuant scalp swelling. He had been born by cesarean section after induction of labor and failure to progress. The diagnosis of DSFC was established after imaging studies.

DSFC is a very rare diagnosis, with only about 50 cases reported in the literature. Despite its acute onset, it is a benign condition that does not require additional laboratory or imaging studies. Current treatment is conservative and the condition usually resolves spontaneously.

**Keywords:** infant; scalp swelling; subaponeurotic fluid collection; subgaleal

## RESUMO

A coleção de líquido subaponevrótica tardia (CLST) é uma causa rara de edema do couro cabeludo em lactentes. A sua etiologia exata permanece desconhecida, mas está frequentemente associada a partos traumáticos ou instrumentados e à monitorização fetal com elétrodos. O diagnóstico é clínico. A CLST pode ser diferenciada de outras causas de edema do couro cabeludo através da história clínica característica e dos achados ao exame objetivo. Contudo, podem ser considerados exames laboratoriais e de imagem no diagnóstico diferencial.

É descrito o caso de um lactente de sete semanas de idade que foi levado ao Serviço de Urgência de Pediatria após manifestação aguda de edema do couro cabeludo de grandes dimensões e flutuante. O parto tinha sido realizado por cesariana após indução do trabalho de parto e falha na progressão. O diagnóstico de CLST foi estabelecido após a realização de exames de imagem.

A CLST é um diagnóstico muito raro, com apenas cerca de 50 casos descritos na literatura. Apesar do início agudo, é uma condição benigna, não necessitando de exames laboratoriais ou de imagem adicionais. O tratamento é conservador e a condição habitualmente resolve-se de forma espontânea.

**Palavras-chave:** coleção de líquido subaponevrótica; edema do couro cabeludo; lactente; subgaleal

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## INTRODUCTION

Scalp swelling is a common clinical condition in the neonatal period and in young infants. It can be caused by cephalohematoma, caput succedaneum, subgaleal hemorrhage, and delayed subaponeurotic or subgaleal fluid collection (DSFC).[1]

The scalp is divided into five layers: skin, subcutaneous tissue, galea aponeurosis, loose connective tissue, and periosteum.[1,2,10,12,14] DSFC is defined as fluid accumulation between the galea aponeurosis and the periosteum and typically manifests beyond the neonatal period.[2,3,12,14] It is a recently described entity with fewer than 50 cases reported in the literature. The first cases were described in 2002 in a case series by *Hopkins et al.*[1]

DSFC is usually described as a soft, ill-defined, mobile, fluctuant, non-tender swelling that crosses the cranial suture lines and is located over the superior occiput.[3,4,12,14] It usually develops by one to four months of age in healthy and hemodynamically stable infants with no history of recent trauma.[3,4,11,12] The exact etiology is unknown, but birth trauma, instrumental delivery, or scalp electrodes leading to disruption of venous drainage, lymphatic drainage, and/or cerebrospinal fluid (CSF) leakage have been implicated as major mechanisms.[2,3,10]

Other conditions should be considered in the differential diagnosis of DSFC, such as non-accidental injuries, coagulopathies, and other causes of neonatal scalp swelling (cephalhematoma, caput succedaneum, subgaleal hematoma).[10]

DSFC is a benign condition with a clinical diagnosis. Management is conservative, with spontaneous resolution expected in one to two months.[3,4,10]

The authors present the first case of DSFC reported in a Portuguese child, with the aim of improving its diagnosis and management, and also present a brief review of the literature on the subject.

## CASE REPORT

A seven-week-old male infant was brought to the pediatric Emergency Department with an acute onset of occipitoparietal scalp swelling with five hours of evolution. The swelling was noticed by the parents, who reported that the boy was eating, behaving, and sleeping normally and had no abnormal movements, vomiting, or infectious symptoms. There was no history of trauma or scalp manipulation and no relevant family history (e.g., coagulopathy).

The boy was born at 37 weeks' gestation by cesarean section after induced labor for fetal growth restriction and failure to progress. No fetal scalp electrodes or instruments were used during labor. No scalp swelling was noted in the scalp in the immediate neonatal period. Medical history was otherwise unremarkable.

At presentation, the patient was alert and interactive with stable vital signs. Physical examination revealed a large scalp swelling in the occipitoparietal area that was ill-defined, fluctuant, watery in consistency, and not bounded by suture lines (**Figure 1**). It was non-tender with no overlying skin changes. The systematic examination was normal, including normal anterior fontanelle and normal neurological examination. There was no evidence of physical injury or trauma.

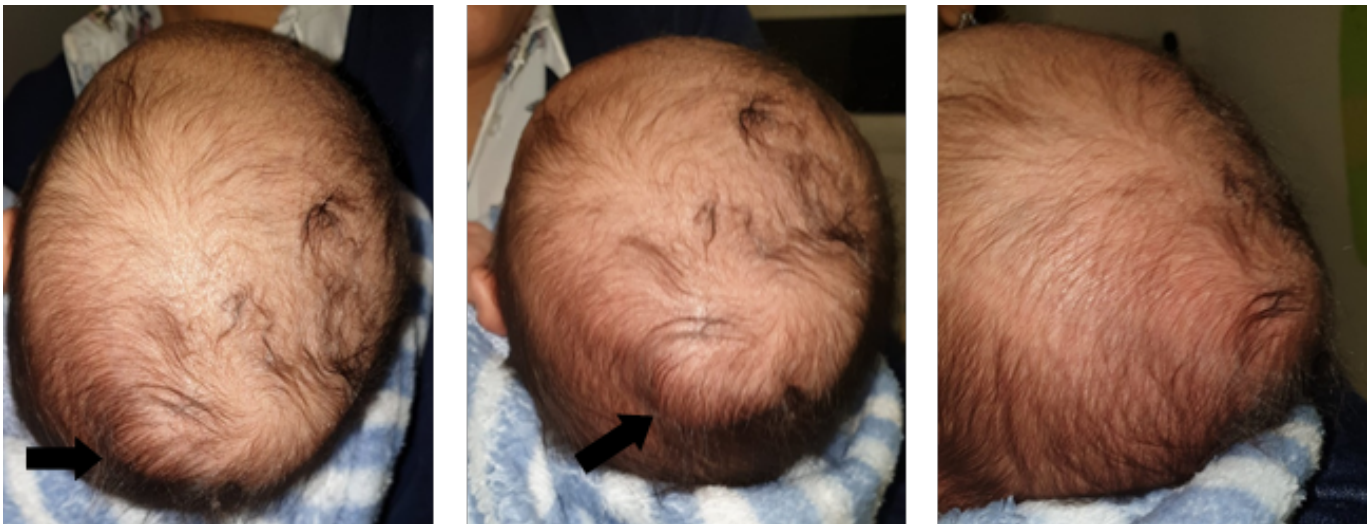

**Figure 1 -** Fluid scalp swelling in the occipitoparietal region without evidence of overlying scalp erythema or injury. The collection does not follow the cranial suture lines

Blood tests, including coagulation, were normal. Cranial ultrasound (US) revealed a compressible, hypoechoic subgaleal fluid collection approximately 7 mm across the suture lines. A non-contrast cranial computed tomography (CT) scan confirmed these findings and revealed no skull fracture or intracranial abnormality (**Figure 2**).

The patient's history, physical examination, and imaging findings were consistent with the diagnosis of benign delayed subaponeurotic fluid collection (DSFC), which was confirmed by the pediatric neurosurgeon. Conservative management was decided, and the child was discharged home after 14 hours of surveillance in the hospital.

At the first follow-up five days later, blood tests were unchanged. Cranial US showed the same fluid collection, now with approximately 11 mm. Fifteen weeks later, a control cranial CT was performed and showed a decrease in the subaponeurotic fluid collection. At the next visit, growth and developmental milestones were normal and the scalp swelling continued to decrease in size, resolving completely within 19 weeks of onset.

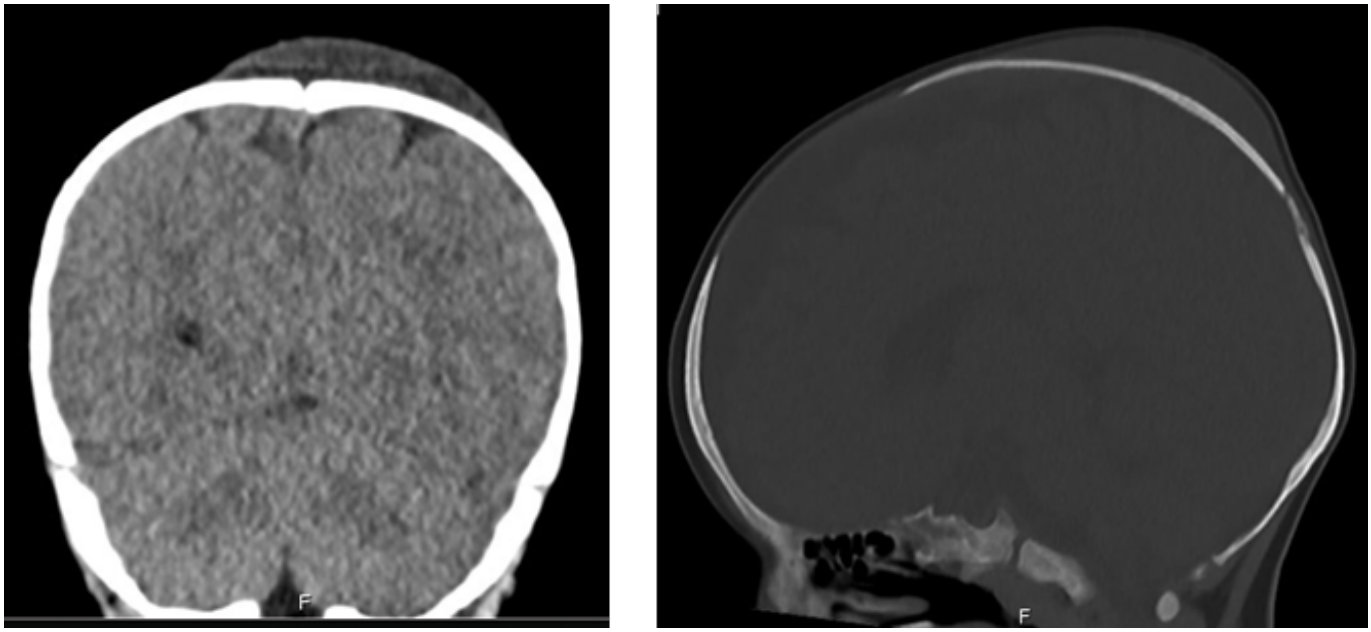

**Figure 2 -** Cranial CT scan in the coronal (left) and sagittal (right, bone window) planes showing the presence of a subaponeurotic fluid collection freely crossing the sagittal suture without evidence of skull fracture or intracranial abnormality

## DISCUSSION

DSFC is a rare disorder with no clear etiology.[3,5,10,11] It is characterized by the spontaneous development of a head swelling in early infancy in a healthy patient.[4,11] The literature identifies the typical age of onset at one to four months.[2-4,6,11,12] DSFC is described as a soft, ill-defined, mobile, and non-tender swelling that crosses the skull sutures lines.[3,4,6,10,12,13] Infants are well-appearing. The scalp area overlying DSFC has a normal appearance, without warmth, erythema, tenderness, or signs of trauma.[3,4,12] It is typically located over the superior occiput.[4]

The unexplained development of scalp swelling in infancy may raise suspicion of non-accidental injury or coagulopathy.[3,8] Although no published case has been linked to acute or non-accidental injury or other conditions, these causes should not be forgotten.[3,4,10,11,12]

The exact etiology of DSFC remains unknown.[3,6,9,11,12,14] However, prolonged or traumatic labor, instrumented delivery, or fetal scalp electrode monitoring have been identified as common features in affected infants.[3,5-8,11,12,14] In fact, most DSFC cases have a history of instrumented delivery or emergency cesarean section (mostly due to failure to progress).

*Schoberer et al.* reported that β2-transferrin and β-trace protein, which are specific markers of CSF, were found in the aspirated fluid of three affected infants.[9] Etiologic hypotheses generated from these findings suggest delayed CSF leakage into the subaponeurotic space through skull microfractures caused by traumatic birth or fetal scalp electrodes not detectable by imaging.[3,4,6,7,9-12,14] Another hypothesis is disruption of the emissary veins connecting the intracranial venous sinuses to the superficial scalp veins or disruption of scalp lymphatic drainage within the subaponeurotic connective tissue layer during traumatic labor.[3,5,7,9-12]

Traumatic delivery can cause three different types of scalp swelling in newborns: caput succedaneum, cephalohematoma, and subgaleal hematoma.[2,12] Scalp swelling is common in newborns, but uncommon after the perinatal period.[2,5,13]

Caput succedaneum is caused by fluid extravasation within the subcutaneous layer of the scalp due to excessive pressure on tissues in the presenting part of the fetal head during delivery.[5,10,12] The edematous tissue in patients with caput may extend across the suture lines and resolve over hours to days after delivery.[5,10,12,14] Cephalohematoma refers to bleeding in the subperiosteal space associated with traumatic birth and is easily distinguished from DSFC because it does not cross the suture lines.[3-5,10,12,14] These two types of scalp swelling occur in the immediate neonatal period, whereas DSFC has a delayed onset, occurring weeks to months after birth.[3,5,10,12] Finally, subgaleal hemorrhage is caused by bleeding into the same anatomic space as DSFC, crosses the suture lines, and may have a similar fluctuant, boggy mass on physical examination.[4,5,10,12,14] Blood from a subgaleal hemorrhage may travel down the head or neck, producing the Battle sign, whereas DSFC tends to remain localized at the top of the head or occiput.[5,10,12] The subaponeurotic layer between the aponeurosis and connective tissue is highly vascular, increasing the risk of massive bleeding in this large space, which can lead to life-threatening hypovolemic shock in young infants.[1,3-5,10,12,13] Although most subgaleal hemorrhages develop in the immediate neonatal period in association with birth trauma, they may also occur in older infants after head injury, sometimes in association with coagulopathy, vascular abnormalities, or non-accidental trauma (shaken baby syndrome), and may present acutely with hemorrhagic shock.[3,5,10,12-14] Conversely, infants with DSFC are usually well-appearing and do not experience adverse impact on their health, feeding, or behavior.[10,12]

The diagnosis of DSFC is primarily clinical, based on history and physical examination.[3-5,7,12] The classic presentation is a well-appearing infant with an acute, large, soft, fluctuant subcranial fluid collection that freely crosses suture lines, without report or evidence of associated head injury, and with a history of difficult or instrumented delivery.[12] Laboratory tests or head imaging study (US, CT scan, or magnetic resonance imaging [MRI] scan) may be considered in the differential diagnosis to confirm the anatomic location of the fluid collection and screen for skull fracture or associated intracranial injury.[3-5,7,8,10,12,14] Aspiration and analysis of fluid contents are not recommended and may lead to infection or injury.[1,6-8,10,12] Usually, cranial US shows a mobile and hypoechoic fluid collection within the subgaleal space that crosses suture lines, and CT or MRI do not reveal skull fracture or intracranial pathology.[4,8,11-13] If trauma, child abuse, or coagulopathy disorders are of concern, further assessment should be performed.[3,10,13]

The literature unanimously recommends a conservative approach to DSFC, as it usually resolves spontaneously within two weeks to five months of diagnosis without sequelae or recurrence.[2-4,6,7,11,12] Lesion drainage has invariably resulted in fluid re-accumulation.[5,6,8,10,11,14]

Follow-up consists of assessment of clinical evolution and should be performed by primary care providers.[8,12]

In conclusion, the authors presented a case of DSFC, a rare condition in which the clinical history, scalp swelling, and delivery outcome were similar to the few cases described in the literature. Spontaneous resolution was achieved with conservative management.

DSFC should always be considered in the differential diagnosis of scalp swelling in infants. The increasing awareness of this benign and rare entity will help physicians (pediatricians, emergency room physicians, and neurosurgeons) and parents in the diagnosis and management of the condition.

## AUTHORSHIP

Catarina Cristina - Writing – original draft; Writing – review & editing
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# IMAGING CASES

## Dermatology clinical case

### Caso clínico dermatológico

Ana Sofia Figueiredo[1], Carolina Quintela[1], Susana Machado[2], Glória Velho[2], Jorge França Santos[3]

A ten-year-old boyobserved during a routine pediatric visit presented withnail changes onthe hands and toes and a concomitantskinlesion on the sole of the foot. Fever, pain, or direct contact with similar lesions were denied. Family history revealed that the mother was followed in rheumatology for suspected autoimmune disease and thegrandmother had rheumatoid arthritis.

On physical examination, the boy presented with yellow and thickened proximal and lateral nail folds onthe right hallux andfourth toe of the left foot (**Figure 1**) and an erythematous squamous plaque on the sole of the right foot (**Figure 2**). Ten months later, the boy presented with multiple yellowish, scaly, and thickened finger and toe nails (**Figure 3**).

**What is your diagnosis?**

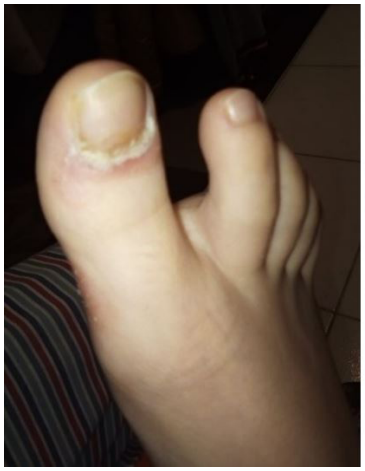

**Figure 1**

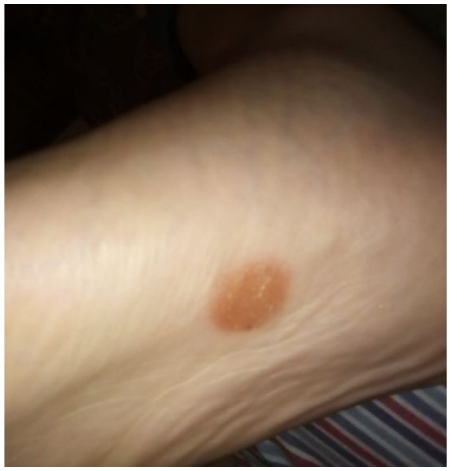

**Figure 2**

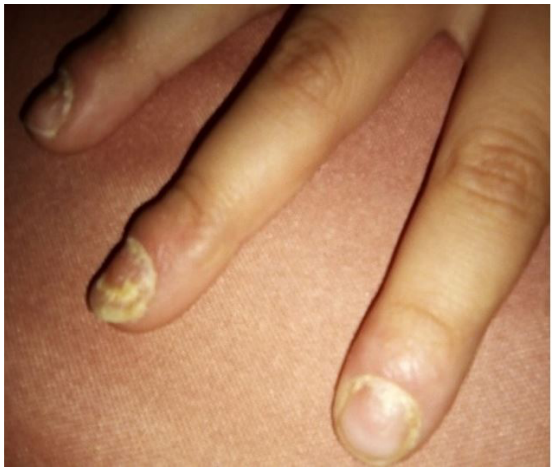

**Figure 3**

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## DIAGNOSIS

Nailpsoriasis

## DISCUSSION

Psoriasis is a systemic inflammatory disease that affects the skin, mucous membranes, phanera (nails and scalp), and joints, with variable presentationand severity. The average age of onsetis 7-10 years, meaning that one third of adults with psoriasis have their first symptoms before the age of 20.[1,2]A positive first-degree family history is reported in 17% of children and adolescents with psoriasis, possibly predicting more severe disease.[1,3]

Similar to adults, the most commontype of psoriasis in childrenis plaque psoriasis, which presents as erythematous plaques with a silvery-white scale typicallyaffecting thelimbs, scalp,postauricular region, elbows, knees, and umbilicus. Children may have thinner plaques with irregular borders and morefacial and anogenital involvement than adults, with facial psoriasis being the sole manifestation in 4-5% of cases and anogenital psoriasis being the most common manifestation under two years of age.[1,4]Anogenital involvement, possibly related to the Koebner phenomenon (appearance of skin lesions on previously unaffected skin secondary to trauma), presents as alarge area of confluent erythema or salmon-colored patches or plaques.[1,2] Guttate psoriasis and psoriatic arthritis are also more common in children. The former manifests as drop-like, erythematous, scaly, small papules on the trunk and extremities, often preceded by group A beta-hemolytic streptococcus infection, and the latter is characterized by joint pain, most commonly affecting the fingers and toes.[4]

Childhood psoriasis has a widespectrum of physical manifestations,with nail involvement occurring in 12-32% of cases.Nail psoriasis maymanifest as plate dystrophy, leukonychia, hyperkeratosis, and nail fold involvement, as described in the presentpatient. Other nail lesions described in the literature may include pitting, splinter hemorrhages, oil droplets,andsalmon spots, among others.[1,5]

Because most patients with nail psoriasis have concomitant cutaneous psoriasis or psoriatic arthritis, the patient history should include an assessment of personal history for signs or symptoms of these conditions. A strong family history of psoriasis may also raise suspicion of nail psoriasis in a patient with no other manifestations. A complete skin examination, including nails, scalp, and anogenital skin,should also be performedto evaluate forother psoriasis-related changes.[1]

The diagnosisof nail psoriasis is clinical. Differential diagnosis withonychomycosis canbe challenging due to overlapping clinical features. In addition, psoriatic nail involvement may predispose to secondary fungal infection, most commonly caused by *Candida parapsilosis* and dermatophytes, in up to 1/3 of patients. Consequently, treatment of psoriasis with systemic agents without treatment ofthe concomitant fungal infection may lead to an unsatisfactory therapeutic outcome.[6]

In addition to onychomycosis, seborrheic dermatitisshould also be considered in thedifferential diagnosis of nail psoriasis. The condition is characterized by pink-yellow to reddish-brown patches with greasy scales, but psoriasis plaques tend to be thicker, silverywhite, and unrelated to seborrhea. Lichen planus also presents with a pruritic papulosquamous eruption, usually on the extremities, and with nail inflammation, which rarely results in permanent destruction of the nail matrix. Pityriasis rosea is the less likelydiagnosis, affecting the trunk and producing the classic “Christmas tree” pattern.[7]

Data on themanagement of psoriasis in children are limited, so treatment should be individualized based on scientific evidenceand clinical experience. Most patients have mild to moderate disease with good therapeutic response to topical agents. In these cases, the first-line treatment is topical corticosteroids with vitamin D analogues, which optimizes theclinical response and reduces the risk of corticosteroid-inducedside effects (skin atrophy and stretching, acne).[1] Narrow-band UVB phototherapy is safe and effective,but less attractive because it requires two to three sessions per week inthe hospital.[1]A few patients with moderate to severe psoriasis or refractory to topical treatment/phototherapy are treated with systemic agents. Methotrexate is the most commonoption, followed by acitretin and cyclosporine, which requireregular analytical and clinical control.Recently, etanercept (>4years of age), adalimumab (>4years of age), and ustekinumab (>12 years of age) have been indicated as preferred therapeutic options in children due to theirtargeted action with less toxicity and less frequent laboratory monitoring.[8]

In the present case, the boy was initially treated with topical antifungal agents, with poor response. Later, during clinical follow-up, he presented with two erythematous squamous lesions on the foot and trunk, as well as erythema and penile skin plaquesconfirming the diagnosis of psoriasismadein collaboration with dermatology specialists. Excellent results were achieved after treatment with topical betamethasone/calcipotriol and a period of oral acitretin, with no side effects.

The complexity of nail psoriasis requires the involvement of a multidisciplinary team with psychosocial support. Indeed, several factors need to be considered before treatment, including age, disease extent and location, previous treatment and results, andpresence of comorbidities.[2,4] Patients with psoriasis have an increasedcardiovascular risk (3-4 times increased risk of hypertension, diabetes, dyslipidemia) and a higher prevalence of mental disorders such as depression, anxiety, and alcohol or drug abuse, which are associatedwith significant impact on quality of life.[9]

In conclusion, this case highlights the importance of differential diagnosis and work-up andregular follow-up in a less common presentation of a known disease.

## ABSTRACT

Psoriasis is a systemic disease that commonly affects the skin, scalp, and nails. Occasionally, nail psoriasis may be the only manifestation at the time of clinical presentation. The authors present the case of a 10-year-old boy with nail involvement as the main featureat presentation, initially treated with antifungal agents. The emergence of skin lesions allowedthe diagnosis of nail psoriasis and appropriatetreatment. Differential diagnosis with onychomycosis canbe difficult due to overlapping clinical features of the nails. Therapeutic options for psoriasis includetopical agents formoderate to mild disease, systemic agents formoderate to severe disease, and biologic agents forsevere or refractory disease. This case reviews the diagnosis and treatment of a well-known conditionwith a less common presentation.

**Keywords:** nail; psoriasis; treatment

## RESUMO

A psoríase é uma doença sistémica que envolve frequentemente a pele, o couro cabeludo e as unhas. Em alguns casos, as alterações ungueais podem ser a única manifestação naapresentação. Os autores relatam o caso clínico de um rapazde 10 anos com envolvimento ungueal como principal manifestação. O rapaz foi inicialmentetratadocom antifúngicos, mas o aparecimento de lesões cutâneas permitiu o diagnóstico e tratamento adequados. O diagnóstico diferencial com onicomicose pode ser difícil, uma vez que as alterações a nível ungueal se sobrepõem. As hipóteses terapêuticas na psoríase podem ser divididas em agentes tópicos na doença ligeira a moderada, agentes sistémicos na doença moderada a grave e agentes biológicos na doença grave ou refratária. Este caso clínico revisita o diagnóstico e tratamento de uma doença conhecida com uma apresentação menos comum.

**Palavras-chave:** psoríase; tratamento; unha

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# IMAGING CASES

## Severe multifocal alopecia areata – An imaging case report

### Alopecia areata multifocal grave – Um caso imagiológico

Susana Correia de Oliveira[1], Patrícia Sousa[1], Cecília Pereira[1], Carla Meireles[1]

A previously healthy eight-year-old boy was referred to the pediatric consultation with a chief complaint of asymptomatic, non-scarring scalp hair loss with seven months of evolution. The hair loss had started as circular patches in the frontal region only, later spreading to the occipital region and then to the parietal and frontal regions (**Figure 1 and 2**). There was no scalp erythema, desquamation, or edema; no involvement of eyelashes, nasal hair, or nails; and no other clinical manifestations. No similar cases in family members, systemic diseases, history of drug use, or trauma were reported, and no contact with pets was mentioned. Hair examination with potassium hydroxide showed no fungal elements, and fungal culture was negative. Physical examination was otherwise unremarkable. The condition had a significant impact on the patient's life, causing him to wear a hat to cover his scalp at all times.

**What is your diagnosis?**

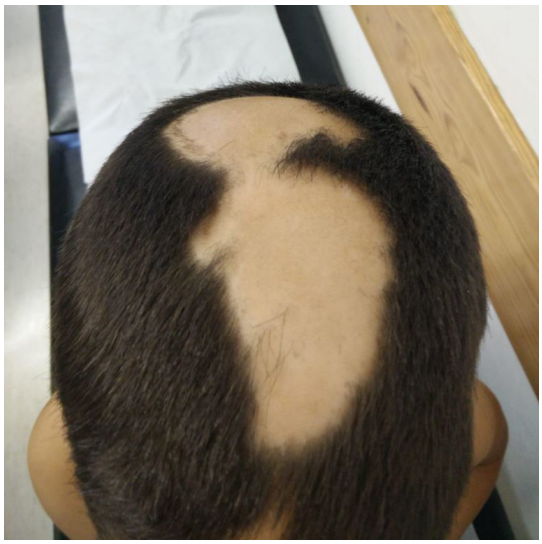

**Figure 1 -** Patches of alopecia at the time of diagnosis resembling ophiasis pattern

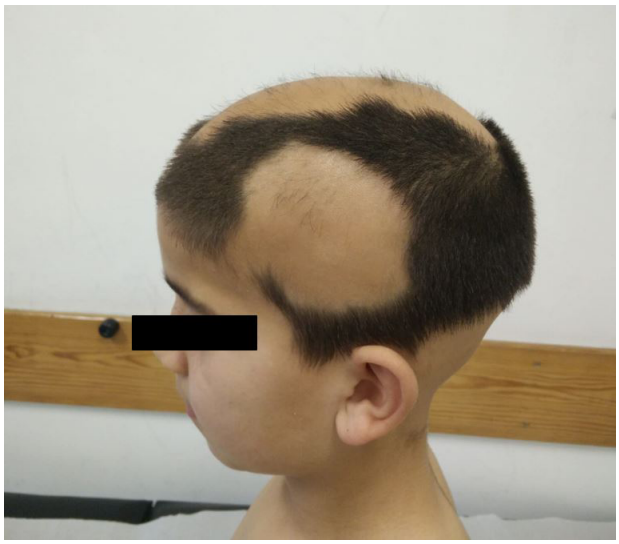

**Figure 2 -** Evolution of the condition seven months after the initial treatment, showing persistent patches of alopecia in the parietal, occipital and frontal areas of the skull

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## DIAGNOSIS

Multifocal alopecia areata

## DISCUSSION

The diagnosis of alopecia areata was easily established in this clinical case due to the progressive hair loss. Alopecia areata is an autoimmune disease that targets the hair follicles, causing nonscarring hair loss through inflammation of the hair follicles. Treatment is often challenging. Several off-label options are available for children.[1] In this case, the child was initially treated with topical minoxidil 2% once daily and the dietary supplement Ecophane®, with no significant improvement after a few months of treatment. Due to lack of response, he was referred to the Dermatology consultation and started on topical tacrolimus 0.1% ointment twice daily and topical hydrocortisone 1 mg/mL ointment every morning.

Because of the significant impact on daily life and because alopecia areata is often associated with psychiatric disorders, the patient was also referred to a child and adolescent mental health clinic. Although he had never exhibited psychiatric symptoms before, the development of alopecia patches led to oppositional behavior, agitation, and initial insomnia. He also began to have difficulty relating to peers, isolating himself from others, becoming disobedient, with disruptive behavior and poor concentration that ultimately affected his school performance. He confided that he was being bullied at school, with kids calling him bald. The child's mother was overly protective and admitted to a difficult family background, with both parents unemployed and the father spending a lot of money on cigarettes. The boy underwent a Conners evaluation with a diagnosis of attention deficit hyperactivity disorder and was started on methylphenidate. He was also diagnosed with depression as a result of the physical impact of the disease on his self-image and was medicated with fluvoxamine.

The patient was reevaluated seven months after treatment initiation, still with no hair growth, and started on a stronger topical corticosteroid, clobetasol proprionate 0.5 mg/g ointment, and increased minoxidil to the 5% formulation once daily, while maintaining tacrolimus 0.1% twice daily (**Figure 2**). It was only after this very aggressive treatment and significant mood improvement with intensive psychotherapy that hair growth was observed in the parietal region. After four years of intensive treatment, the boy achieved complete hair regrowth and all treatments were discontinued (**Figure 3**). His mood improved significantly and he stopped wearing a hat.

Because alopecia areata is a chronic, immune-mediated, inflammatory disease that is often associated with other autoimmune disorders, such as vitiligo, thyroid abnormalities, and diabetes, the patient was screened for other autoimmune diseases at diagnosis and was positive for antithyroid antibodies and anti-neutrophil cytoplasmic antibodies (ANCA), despite the absence of clinical manifestations or changes in thyroid function.[1] Currently, the boy has now been followed for five years with no changes in thyroid function, although he remains positive for antithyroid antibodies and negative for ANCA several months after starting treatment.

The authors raise awareness that alopecia areata may be an early sign of an autoimmune disease that may later manifest with other symptoms, and thus follow-up is warranted.[1,2] Although most patients experience spontaneous hair regrowth within one year, the present patient required four years of treatment to achieve complete regrowth. Duration of disease and onset in childhood are poor prognostic factors.[3] Thyroid dysfunction may be present at diagnosis or develop later in life, so reassessment is warranted if symptoms recur.[4]

Despite a variety of treatment options, alopecia areata remains difficult to treat and relapse is often difficult to prevent.[1] The authors emphasize the importance of psychotherapy in these cases, as the condition can have a significant impact on children's mental health, with several studies linking alopecia areata in adolescents to an increased rate of psychiatric symptoms.[6] The present patient experienced a negative impact of the disease on his self-image, which likely affected his recovery.

**Figure 3 -** Full hair growth after four years of treatment

## ABSTRACT

The authors report a severe case of a common disorder in a healthy

eight-year-old male child. The boy was observed for asymptomatic hair loss with seven months of evolution that greatly disrupted his life and caused him to wear a hat at all times. Alopecia areata was diagnosed, and the boy underwent four years of multiple treatments before achieving full hair regrowth. It should be noted that alopecia areata can be an early sign of an autoimmune disease that may manifest later with other symptoms.

**Keywords:** alopecia areata; multifocal alopecia

## RESUMO

É descrito o caso grave de uma patologia comum num rapaz saudável de oito anos de idade. O rapaz foi observado em consulta devido a queda de cabelo com sete meses de evolução sem outros sintomas associados, que condicionou grandemente a sua qualidade de vida, fazendo-o utilizar chapéu em todas as situações. Foi estabelecido o diagnóstico de alopecia areata e o rapaz foi submetido a diversos tratamentos ao longo de quatro anos antes de alcançar crescimento capilar completo. Os autores relembram que a alopecia areata pode ser um sinal precoce de uma doença autoimune que poderá manifestar-se apenas anos mais tarde.

**Palavras-chave:** alopecia areata; alopecia multifocal

## AUTHORSHIP

Susana Correia de Oliveira – Writing – original draft; Writing – review & editing
Patrícia Sousa - Writing – original draft; Writing – review & editing
Cecília Pereira - Supervision
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# IMAGING CASES

## Imaging clinical case

### Caso clínico imagiológico

André Morais[1], Ana Luísa de Carvalho[1], Catarina Barroso[2], Maria João Magalhães[3], Vera Baptista[3], Liliana Abreu[3], Margarida Reis Morais[1]

A previously healthy three-year-old girl presented to the Emergency Department with acute severe abdominal pain refractory to oral analgesia and persistent vomiting with one hour of evolution. She also had anorexia and reported no bowel movements for the past two days.

No fever, dyspnea, or other relevant symptoms were reported.

On admission, the girl complained of persistent severe pain and was agitated and pale. Vitals were stable. On physical examination, she had no signs of respiratory distress. Vesicular breath sounds were decreased on the left inferior pulmonary field, the abdomen was flat, and there was no pain on palpation.

Laboratory studies, including complete blood count, chemistry panel, and urinalysis, were normal. Abdominal and thoracic radiographs were performed (**Figures 1a** and **b**). Abdominal ultrasound showed no abnormalities.

**What is your diagnosis?**

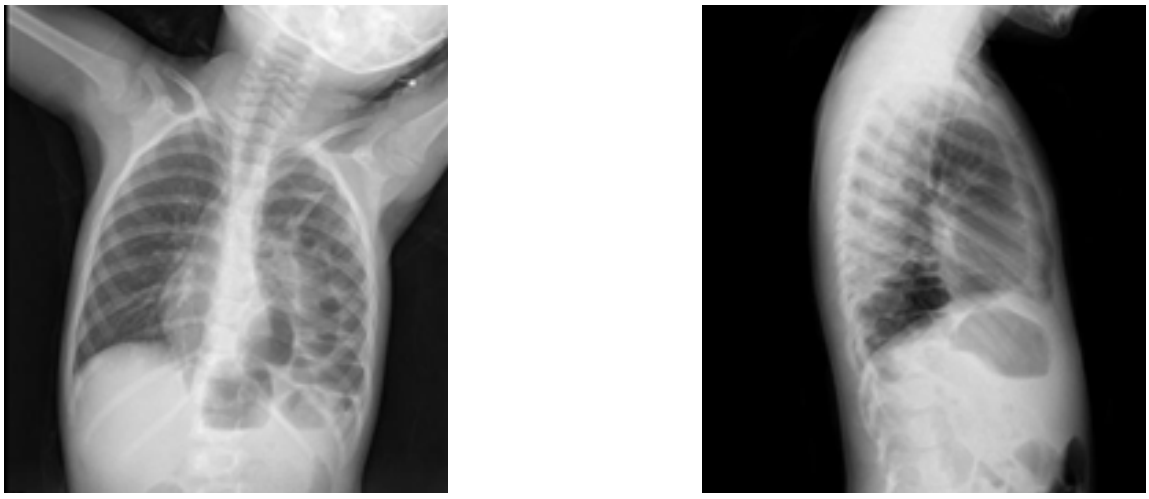

**Figure 1 -** Thoracic and abdominal radiograph showing bowel loops in the left hemithorax in a) anteroposterior view and b) lateral view.

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## DIAGNOSIS

Left posterolateral congenital diaphragmatic hernia

## DISCUSSION

Congenital diaphragmatic hernia (CDH) results from incomplete closure of the pleuroperitoneal canal during fetal development, allowing herniation of abdominal contents into the thoracic cavity.[1] The condition has a prevalence of 1 in 3000-5000 children. Currently, CDH is diagnosed prenatally by ultrasound and only a minority of small and mostly right-sided hernias are missed.[2,3]

CDH usually presents in the neonatal period with respiratory distress, but in 5-25% of cases it manifests later in life. The wide clinical spectrum of late-onset CDH seems to be influenced by the timing of the intrathoracic herniation and the type of displaced viscera.[4,5] Failure to thrive is the most common manifestation, with gastrointestinal and respiratory symptoms, or a mixture of both, potentially also present. In some cases, the diagnosis is made incidentally through analysis of radiographic images obtained for other reasons.

The left hemithorax is the most commonly affected side and often determines a more acute presentation in older children where abdominal symptoms predominate. Presentation on the right side is more common in younger patients and typically has an insidious pattern in which respiratory symptoms predominate. The most important factor responsible for chronic or acute presentation seems to be related to the type of herniated viscera.[4]

Early surgical correction of the diaphragmatic defect is crucial to prevent possible passage or strangulation of abdominal viscera and severe respiratory problems.[6]

This case represents a typical late-onset CDH with acute onset of gastrointestinal symptoms including abdominal pain and vomiting.

The patient underwent thoracoscopic repair, with reduction of the abdominal contents (small bowel and colon) and suturing of the posterior diaphragmatic defect. No intraoperative complications occurred. Postoperative care was uneventful, and the child was discharged home three days later.

She currently remains on outpatient pediatric surgery follow-up, without any symptoms or imagiological recurrence of the hernia.

The overall prognosis of late-onset CDH is better than that of CDH diagnosed prenatally or in the early postnatal period. There is a lower risk of pulmonary hypoplasia and pulmonary hypertension and an also a lower association with malformations.[7] However, misdiagnosis is much more common in late-presenting CDH and may result in increased morbidity and mortality.[6]

In summary, the diagnosis of late-onset CDH should be kept in mind in the differential diagnosis of children with acute or recurrent non-specific symptoms, namely respiratory or gastrointestinal symptoms or both. Clinical suspicion and plain radiography remain key to diagnosis. Early accurate diagnosis and timely surgical repair are crucial to prevent life-threatening complications.[5]

## ABSTRACT

Congenital diaphragmatic hernia (CDH) results from incomplete closure of the pleuroperitoneal canal during fetal development, allowing herniation of abdominal contents into the thoracic cavity. It usually presents in the neonatal period with respiratory distress, but can also manifest later in life.

The diagnosis of late-onset CDH should be kept in mind in the differential diagnosis of children with acute or recurrent nonspecific symptoms, especially respiratory or gastrointestinal symptoms or both. Clinical suspicion and plain radiography remain the key to diagnosis. Early surgical correction of the diaphragmatic defect is crucial to prevent possible passage or strangulation of abdominal viscera and severe respiratory problems.

In the present report, the authors present a typical case of late-onset CDH with acute presentation of gastrointestinal symptoms (e.g., abdominal pain and vomiting). Thoracoscopic repair was performed, with reduction of the abdominal contents (small bowel and colon) and suturing of the posterior diaphragmatic defect.

**Keywords:** abdominal pain; children; congenital diaphragmatic hernia; late-presentation

## RESUMO

A hérnia diafragmática congénita (HDC) resulta do encerramento incompleto do canal pleuroperitoneal durante o desenvolvimento fetal, permitindo a herniação do conteúdo abdominal para a cavidade torácica. Apresenta-se tipicamente durante o período neonatal sob a forma de dificuldade respiratória, podendo no entanto manifestar-se mais tarde na vida.

O diagnóstico de HDC tardia deve ser considerado no diagnóstico diferencial de crianças com sintomas agudos ou recorrentes inespecíficos, principalmente respiratórios ou gastrointestinais, ou ambos. A clínica e a radiografia simples continuam a ser os elementos-chave para o diagnóstico. A correção cirúrgica precoce do defeito diafragmático é crucial para prevenir uma possível passagem ou estrangulamento das vísceras abdominais e problemas respiratórios graves.

Neste artigo, os autores apresentam o caso de uma HDC de apresentação tardia, caracterizada pelo início agudo de sintomas gastrointestinais, como dor abdominal e vómitos. Foi realizada correção toracoscópica com redução do conteúdo abdominal (intestino delgado e cólon) e sutura do defeito diafragmático posterior.

**Palavras-chave:** apresentação tardia; criança; dor abdominal; hérnia diafragmática congénita

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Catarina Barroso - Conceptualization; Investigation; Writting – original draft; Writing review & editing

Maria João Magalhães - Writing review & editing

Vera Baptista - Writing review & editing

Liliana Abreu - Writing review & editing

Margarida Reis Morais - Writing review & editing

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# AUTHOR GUIDELINES

## AIMS AND SCOPE

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

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

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

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

The journal charges no fees to authors or readers.

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

## AUTHORSHIP AND RESPONSIBILITY CRITERIA

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

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

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

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

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

## Ethics in publishing

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

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

A conflict of interest and funding statement is mandatory.

# PUBLICATION GUIDELINES

## SUBMISSION

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

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

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

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

### First page

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

### Second page

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

### TEXT

**Editorials**

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

**Original Articles**

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

**Review Articles**

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

**Clinical Cases**

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

**Imaging Cases**

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

**Letters to the Editor**

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

**Current Perspectives**

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

**General Guidelines**

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

**REFERENCES**

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

Examples:

a. Medical journal: list the six first authors followed by et al. (in italic) in the case of six or more authors, followed by article title, journal name, publication year, volume, number, and pages. : Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, et al. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-65. https://doi: 10.1097/00006454-198611000-00004.
b. Book chapter: author(s), chapter title, name(s) of the Editor(s), book title, edition number, city and name of the publisher, publication year, first and last page number of the chapter. Ex.: Phillips SJ, Whisnant Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.
c. Book: author(s), book title, edition number, city and name of the publisher, publication year, and page numbers. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on 2nd. London: Taylor & Francis; 2013. p. 120.
d. Electronic reference: journal article in electronic format. Ex.: Jeha G, Kirkland Etiology of hypocalcemia in infants and children. January, 2010. (Assessed May 8, 2013). Available at: http://www.uptodate.com.

**FIGURES AND TABLES**

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

**ACKNOWLEDGMENTS AND DECLARATIONS**

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

## ARTICLE STRUCTURE – AUTHOR GUIDELINES

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

**REVISION PROCESS**

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

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

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

**PROOFS**

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

**INFORMATION AND CLAIMS**

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

# INSTRUÇÕES AOS AUTORES

## OBJETIVOS E ÂMBITO

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

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

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

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

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

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

## CRITÉRIOS DE AUTORIA E RESPONSABILIDADE

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

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

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

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

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

### Questões éticas

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

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

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

# NORMAS DE PUBLICAÇÃO

## SUBMISSÃO

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

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

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

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

### Na primeira página

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

### Na segunda página

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

## TEXTO

### Editoriais

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

### Artigos Originais

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

### Artigos de Revisão

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

### Casos clínicos

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

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

**Casos de imagem**

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

**Cartas ao Editor**

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

**Perspetivas Atuais**

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

**Normas gerais**

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

**REFERÊNCIAS BIBLIOGRÁFICAS**

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

Seguem-se alguns exemplos:

a. Revista médica: listar os primeiros seis autores, seguidos de et al (em itálico) se ultrapassar seis, título do artigo, nome da revista, ano, volume, número e páginas. Ex.: Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, et al. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-5. https://doi: 10.1097/00006454-198611000-00004.
b. Capítulo em livro: autor(es), título do capítulo, nome(s) do(s) Editor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação, primeira e última páginas do capítulo. Ex.: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.
c. Livro: autor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação e número de páginas. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on guide. 2nd edition. London: Taylor & Francis; 2013. p. 120.
d. Referência eletrónica: artigo de revista em formato eletrónico. Ex.: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. Janeiro, 2010. (Acedido em 8 de maio de 2013). Disponível em: http://www.uptodate.com.

**FIGURAS E QUADROS**

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

**AGRADECIMENTOS E ESCLARECIMENTOS**

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

## ESTRUTURA DOS ARTIGOS - NORMAS DE PUBLICAÇÃO

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

### PROCESSO DE REVISÃO

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

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

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

### PROVAS DE ARTIGOS ACEITES

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

### INFORMAÇÕES E RECLAMAÇÕES

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