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

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

3. In the evaluation of the Original Articles, the Selection Jury will analyze the following items:
   a. Relevance and originality;
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EDITORIAL

THE NEW HEALTH BASIC LAW - A PROCESS NOT YET FINISHED

A NOVA LEI DE BASES DA SAÚDE – UM PROCESSO AINDA NÃO TERMINADO

Pedro Lopes Ferreira[1,2]

A Health Basic Law aims to establish and frame the general principles that should preside over health policy and the organization of the health system, in particular the National Health Service (SNS).

On September 4, 2019, the Portuguese Parliament revoked the previous Law No. 48/90 of August 24 and approved the new Health Basic Law No. 95/2019.

The previous law, conceived almost 30 years earlier and passed during the government of Cavaco Silva, included aspects of considerable discussion by various sectors of society. Among these, we can highlight four aspects: (i) the state's obligation to support the private sector (...) in competition with the public sector; (ii) facilitating the mobility of SNS staff wishing to work in the private sector; (iii) the relationship between the SNS and the private sector; and (iv) the management of health units.

In fact, its XXXVII base of support to the private sector expressly stated that it was up to the State to support the "development of the private sector of health care, depending on the social advantages arising from the initiatives concerned and in competition with the public sector". More explicitly, examples of operationalization of this support were described, "in particular in facilitating the mobility of SNS staff wishing to work in the private sector, in creating incentives for the creation of private units and in the reserve of inpatient bed quotas in each health region". Finally, in the XXXIX base, it was stated that private hospitalization should act in conjunction with the SNS and that, in terms to be defined, it could "be authorized to deliver, through management contracts, hospitals or health centers of the SNS to other entities or, under convention, to groups of physicians (XXXVI base), envisaging, on this same base, the creation of health units with the nature of public limited societies of public capital. The first case of a public hospital run by a private economic group was the Dr. Fernando Fonseca (Amadora-Sintra) Hospital and dates from 1996.

To deal with this protectionism and incentive to promiscuity between public and private activities in health, in October 2017, a group of citizens led by Cipriano Justo launched a public petition, later presented and discussed in the Parliament by all the parties represented in it. The aim of this petition was to revise this Basic Law, focusing on the need for participation of all social actors in the community in accordance with the 2030 Sustainable Development Agenda, adopted by the UN in September 2015 and the 2010 Adelaide Declaration on Health in All Policies on the path to shared governance for health and well-being. In the same month of October is published the book "Save the SNS" authored by António Arnaut and João Semedo that was a fundamental impulse for change. The new Health Basic Law was considered a unique opportunity to rethink the SNS and adapt it to the demands and needs of the 21st century. A modern SNS must allow for better equity in the provision of care, regardless of the socio-economic situation of citizens.

At the same time, in order to densify the content of the petition, the same group of citizens draw a document entitled "Now, health... accessible, free, inclusive", later published on 19 December 2017. This document presents the principles and guidelines of health policy, including health promotion, disease prevention, public health, health in all policies and universal coverage. With regard to the health system, the principles reminded the Constitution when it established the decentralized and participatory management of the SNS.

Meanwhile, on January 31, 2018, Minister Adalberto Campos Fernandes, by Order No. 1222-A/2018, appoints the Committee for the Revision of Health Basic Law led by former Minister Maria de Belém Roseira. This Committee delivered a draft bill to the minister on September 3, 2018, but it was never discussed in the Council of Ministers. With the new Minister of Health Marta Temido, the

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Government sends to the Parliament the Proposal for Law No. 171/XIII, with substantial amendments relating to the Committee's Bill. Five political parties (Left Block [BE], Democratic Social Centre [CDS], Portuguese Communist Party [PCP], Socialist Party [PS] and Social Democratic Party [PSD]) submitted proposals and the discussion preceded the approval by the left wing of parliament of the new law.

One of the most discussed topics was the relationship between public and private hospitals, namely public-private partnerships (PPPs) regarding the management of these units. The PS, in its electoral program had already in 2015 started the discussion stating the need to "evaluate the existing hospital experiences under PPP regime explaining its advantages and disadvantages in order to introduce correcting or revising improvements". More specifically, and in relation to this subject, the position of parties during the discussion ranged from the position of CDS that defended the competition between the public, private and social sectors and that of the PSD, which agreed that, in general, the management of the SNS units was public, admitting, however, the possibility of being ensured by private and social entities, "provided that they show clear health gains for citizens and prove to be economically advantageous to the State", up to the position of the BE or the PCP that defended that the management should be exclusively public, and could not in any form be delivered to private or social entities, for profit or not for profit, and that the contracts already concluded in the meantime should be held, but only temporarily. The PS proposal, however, defended the public management of health units of the SNS, "and may be supplied and temporarily guaranteed by contract with private entities or the social sector".

Shortly before the approval in the Parliament, and considering the opinion of the President of the Republic that the new law should be the result of a broad consensus including the PSD, the parliamentary left agreed to withdraw the specific article concerning PPPs. The bill approved explicitly revokes Decree-law No. 185/2002 of August 20, which defined the legal regime of health partnerships with management and private financing. In addition, it is defined in paragraph 1 of base 6 that "the responsibility of the State for the realization of the right to health protection is effective primarily through the SNS and other public services, and in a supplementary and temporary way, agreements can be concluded with private entities and the social sector, as well as with professionals in an independent work regime, in case of justified need".

The new law, passed with votes against of the right-wing parties PSD and CDS, on its basis 1, reminds the right of all people to health protection and the guarantee given in the Constitution that this right is implemented by the State through the SNS, regional health services and other public, central, regional and local institutions. This protection of health, in addition to a right defined in the Constitution, is, first of all a form of investment of the country in its citizens. The new law, passed with votes against of the right-wing parties PSD and CDS, right on its basis 1, reminds the right of all people to health protection and the guarantee given in the Constitution that this right is implemented by the State through the SNS, regional health services and other public, central, regional and local institutions. This protection of health, in addition to a right defined in the Constitution, is, first of all, a form of investment of the country in its citizens.

Only on May 22, through Decree-Law No. 23/2020, are established the rules for the conclusion of management partnership contracts in the health area. According to this Decree-law "the conclusion of management partnership contracts in the health area assumes a supplementary and temporary character and depends, in addition to other legally applicable requirements, on the existence of a justified need" demonstrated in a study "to be carried out by the Central Administration of the Health System [ACSS] and the territorially competent Regional Health Authority [ARS]".

This new Health Basic Law is expected to be a legal instrument that will contribute to the alignment of health policy and the organization of the SNS, be the social contract that in the sector responds to the deficits that have accumulated and clarifies the role of the various actors with interests in health care. However, this law in point 3 of base 20 provides for the existence of a SNS statute with "regionalized organization and decentralized and participatory management".

Recently, the Minister of Health committed to the approval by the end of the first half of this year 2021 of the Statute of the SNS. If effective, as expected, this will be another extremely important step to recover values defined in the Constitution, clarifying the strategic direction guided by the mission of the SNS. Thus, it can continue to contribute to a better health status and quality of life of the populations, guided by the universality of care and the fight against determinants, especially socio-economic, that create inequalities between citizens.

Uma Lei de Bases da Saúde visa estabelecer e enquadrar os princípios gerais que devem presidir à política de saúde e à organização do sistema de saúde, em particular do Serviço Nacional de Saúde (SNS).

Em 4 de setembro de 2019, a Assembleia da República revogou a anterior lei nº 48/90 de 24 de agosto e aprovou a nova lei de bases da saúde nº 95/2019.

A anterior lei, concebida quase 30 anos antes e aprovada durante o governo de Cavaco Silva, incluía aspetos alvo de acesa discussão por vários setores da sociedade. Entre estes, podemos destacar quatro aspetos: (i) a obrigação do Estado de apoiar sector privado (...) em concorrência com o sector público; (ii) a facilitação da mobilidade do pessoal do SNS que desejasse trabalhar no sector privado; (iii) a relação entre o SNS e o setor privado; e (iv) a gestão de unidades de saúde.

De facto, na sua base XXXVII de apoio ao sector privado era expressamente dito que cabia ao Estado o apoio ao ”desenvolvimento do sector privado de prestação de cuidados de saúde, em função das vantagens sociais decorrentes das iniciativas em causa e em concorrência com o sector público”. De uma forma mais explícita,

descreviam-se exemplos de operacionalização deste apoio, "nomeadamente, na facilitação da mobilidade do pessoal do SNS que deseje trabalhar no sector privado, na criação de incentivos à criação de unidades privadas e na reserva de quotas de leitos de internamento em cada região de saúde". Por fim, na base XXXIX, afirmava-se que a hospitalização privada deveria atuar em articulação com o SNS e que, em termos a definir, poderia "ser autorizada a entrega, através de contratos de gestão, de hospitais ou centros de saúde do SNS a outras entidades ou, em regime de convenção, a grupos de médicos (base XXXVI), prevendo-se, nesta mesma base, a criação de unidades de saúde com a natureza de sociedades anónimas de capitais públicos. O primeiro caso de um hospital público gerido por um grupo económico privado foi o Hospital Dr. Fernando Fonseca (Amadora-Sintra) e data de 1996.

Face a este protecionismo e incentivo à promiscuidade entre as atividades pública e privada na saúde, em outubro de 2017, um grupo de cidadãos impulsionado por Cipriano Justo tomou então a iniciativa de lançar uma petição pública, mais tarde apresentada e discutida na Assembleia da República por todos os partidos nela representados. O objetivo desta petição era a revisão desta Lei de Bases, centrada na necessidade de participação de todos os atores sociais da comunidade de acordo com a Agenda de Desenvolvimento Sustentável para 2030, aprovada pela ONU em setembro de 2015 e a Declaração de Adelaide de 2010 sobre a Saúde em Todas as Políticas no caminho de uma governança compartilhada, em prol da saúde e do bem-estar. Ainda nesse outubro é publicado o livro "Salvar o SNS" de autoria de António Arnaut e João Semedo que foi um impulso fundamental para a mudança.

A nova Lei de Bases da Saúde foi considerada uma oportunidade única para repensar o SNS e adaptá-lo às exigências e necessidades do século XXI. Um SNS moderno tem de permitir uma melhor equidade na oferta de cuidados, independentemente da situação socioeconómica dos cidadãos.

Paralelamente, com o objetivo de densificar o conteúdo da petição, o mesmo grupo de cidadãos organizou um documento denominado "Agora, a saúde… acessível, gratuita, inclusiva", mais tarde publicado, a 19 de dezembro de 2017. Neste documento foram apresentados os princípios e orientações da política de saúde, nomeadamente a promoção da saúde, a prevenção da doença, a saúde pública, a saúde em todas as políticas e a cobertura universal. Relativamente ao sistema de saúde, os princípios lembraram a Constituição quando estabeleceu a gestão descentralizada e participada do SNS.

Entretanto, a 31 de janeiro de 2018, o ministro Adalberto Campos Fernandes, pelo Despacho n.º 1222-A/2018, nomeia a Comissão de Revisão da Lei de Bases da Saúde liderada pela ex-ministra Maria de Belém Roseira. Esta Comissão entregou ao ministro um projeto de proposta de Lei no dia 3 de setembro de 2018, que nunca foi apreciado em Conselho de Ministros. Já com a nova ministra da saúde Marta Temido, o Governo envia ao Parlamento a Proposta de Lei nº 171/XIII, com alterações substanciais relativamente à Proposta de Lei da Comissão. Cinco partidos políticos (BE, CDS, PCP, PS e PSD) apresentaram propostas e a discussão precedeu a aprovação pela ala esquerda do parlamento da nova lei.

Um dos temas mais discutidos foi a relação entre os hospitais públicos e privados, nomeadamente as parcerias público-privadas (PPP) no que respeita à gestão destas unidades. O PS, no seu programa eleitoral já tinha em 2015 iniciado a discussão afirmando a necessidade de "avaliar as experiências hospitalares existentes em regime de PPP explicitando as suas vantagens e inconvenientes de modo a introduzir melhorias corretoras ou revisoras". Mais concretamente, e em relação a este assunto, as posições partidárias tiveram durante a discussão uma amplitude desde a posição do CDS que defendia a competição entre os setores público, privado e social e a do PSD que concordava que, em geral, a gestão das unidades do SNS fosse pública, admitindo, no entanto, a possibilidade de ser assegurada por entidades privadas e sociais, "desde que estas revelem evidentes ganhos em saúde para os cidadãos e demonstrem ser economicamente vantajosas para o Estado", até à posição do BE ou do PCP que defendiam que a gestão deveria ser exclusivamente pública, não podendo sob qualquer forma ser entregue a entidades privadas ou sociais, com ou sem fins lucrativos e que os contratos entretanto já celebrados se deveriam manter, apenas transitoriamente. A proposta do PS, entretanto, defendia a gestão pública das unidades de saúde do SNS, "podendo ser supletiva e temporariamente assegurada por contrato com entidades privadas ou do sector social".

Pouco tempo antes da aprovação na Assembleia da República, e tendo em conta a opinião do Presidente da República de que a nova lei deveria ser resultado de um consenso alargado incluindo o PSD, a esquerda parlamentar aceitou retirar o artigo específico destinado às PPP. Entretanto, do articulado da lei aprovada é explícita revogação do decreto-lei nº 185/2002 de 20 de agosto que definia o regime jurídico das parcerias em saúde com gestão e financiamentos privados. Além disso, fica definido no nº 1 da base 6 que "a responsabilidade do Estado pela realização do direito à proteção da saúde efetiva-se primeiramente através do SNS e de outros serviços públicos, podendo, de forma supletiva e temporária, ser celebrados acordos com entidades privadas e do setor social, bem como com profissionais em regime de trabalho independente, em caso de necessidade fundamentada".

A nova lei, aprovada com votos contra dos partidos de direita PSD e CDS, logo na sua base 1, relembra o direito de todas as pessoas à proteção de saúde e a garantia dada na Constituição de que esse direito é efetivado pelo Estado através do SNS, dos Serviços Regionais de Saúde e de outras instituições públicas, centrais, regionais e locais. Esta proteção da saúde, para além de um direito definido na Constituição é, antes de mais, uma forma de investimento do país nos seus cidadãos.

Só em 22 de maio, através do decreto-lei nº 23/2020, é que são estabelecidas as regras para a celebração de contratos de parceria de gestão na área da saúde. Segundo este decreto-lei "a celebração de contratos de parceria de gestão na área da saúde assume caráter supletivo e temporário e depende, para além de outros

requisitos legalmente aplicáveis, da existência de necessidade fundamentada" demonstrada em estudo "a realizar pela ACSS e pela ARS territorialmente competente".

Espera-se que esta nova Lei de Bases da Saúde seja um instrumento jurídico que contribua para que a política de saúde e a organização do SNS estejam alinhados, sejam o contrato social que no sector responda aos défices que se foram acumulando e clarifique o papel dos vários atores com interesses nos cuidados de saúde. No entanto, esta lei no ponto 3 da base 20, prevê a existência de um estatuto próprio do SNS com "organização regionalizada e uma gestão descentralizada e participada".

Recentemente, a ministra da saúde comprometeu-se com a aprovação até ao fim do primeiro semestre deste ano de 2021 do Estatuto do Serviço Nacional de Saúde. A efetivar-se, como se espera, será mais um passo extremamente importante para recuperar valores definidos na Constituição, clarificando o sentido estratégico orientado pela missão do SNS. Assim, poderá continuar a contribuir para um melhor estado de saúde e qualidade de vida das populações, pautado pela universalidade dos cuidados e pelo combate aos determinantes, principalmente socioeconómicos, que criam desigualdades entre os cidadãos.

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ORIGINAL ARTICLE

PICA AND ATTENTION DEFICIT HYPERACTIVITY DISORDER: IS THERE A LINK?

COMORBIDITY AND TREATMENT OUTCOMES WITH METHYLPHENIDATE

PICA E PERTURBAÇÃO DE HIPERATIVIDADE E DÉFICE DE ATENÇÃO: EXISTE LIGAÇÃO?

COMORBILIDADE E RESULTADOS DO TRATAMENTO COM METILFENIDATO

Daniela Cardoso[1], Luísa Duarte[1], Vanessa Fonseca Pinto[1], Teresa Cartaxo[1]

ABSTRACT

Introduction: Pica is the persistent ingestion of non-nutritive substances. It is common during childhood and may be related to nutritional deficits, intellectual disability, stress, and psychosis. However, no causative biological condition is identified in most cases and there is limited evidence to support pharmacological intervention. As several authors describe pica as an impulse control disorder and impulsive symptoms are a core aspect of the diagnostic criteria of attention deficit hyperactivity disorder (ADHD), this study reviews literature data on pica, ADHD, and treatment response during childhood and adolescence and adds two case reports to this body of evidence.

Methods: Systematic literature review using the key terms "pica", "attention deficit", "hyperactivity", "child", and "adolescent". A retrospective analysis of clinical data of two patients with pica and ADHD followed at the Child and Adolescent Psychiatry Department of Hospital Pediátrico was also conducted.

Results: As far as the authors are aware, only three cases are currently reported in the literature describing comorbid pica and ADHD in children. Of these, two reported complete pica symptom remission after methylphenidate treatment. Two other cases of children with pica and ADHD observed at the Child and Adolescent Psychiatry Department of our institution were reported in this study, one of which had complete symptom remission after psychostimulant treatment optimization.

Discussion: The suggested association between pica and ADHD may have underlying etiology in poor impulse control and dopaminergic system dysfunctions. Therefore, a pharmacological approach capable of improving dopaminergic functioning may be an alternative treatment for pica. Psychostimulants may improve pica by eliciting an increase in brain dopamine levels and a decrease in impulsivity.

Keywords: attention deficit hyperactivity disorder; methylphenidate; pica; treatment

RESUMO

I**ntrodução:** Pica é uma condição caracterizada pela ingestão persistente de substâncias não nutritivas. É comum durante a infância e pode estar associada a défices nutricionais, perturbações do desenvolvimento intelectual, stress e psicose. No entanto, na maior parte dos casos não é possível identificar uma causa orgânica e existem poucas evidências que sustentem intervenção farmacológica. Dado que vários autores descrevem a pica como uma perturbação do controlo dos impulsos e os sintomas impulsivos fazem parte dos critérios chave da perturbação de hiperatividade e défice de atenção (PHDA), o presente estudo pretende rever os dados disponíveis na literatura sobre pica, PHDA e resposta ao tratamento durante a infância e adolescência.

Métodos: Revisão sistemática da literatura utilizando os termos chave "pica", "défice de atenção", "hiperatividade", "criança" e "adolescente". Foi também conduzida uma análise retrospetiva dos dados clínicos de dois doentes com pica e PHDA seguidos no Serviço de Pedopsiquiatria

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do Hospital Pediátrico.

Resultados: Existem atualmente na literatura apenas três relatos de casos de crianças com pica e PHDA. Destas, duas apresentaram remissão completa dos sintomas de pica após tratamento com metilfenidato. Os autores reportam outros dois casos de crianças com pica e PHDA observados no seu serviço hospitalar, uma das quais alcançou remissão completa dos sintomas após otimização do tratamento com psicoestimulante.

Discussão: A associação sugerida entre pica e PHDA pode ter por base um controlo inadequado dos impulsos e disfunção do sistema dopaminérgico. Consequentemente, uma abordagem farmacológica capaz de melhorar o funcionamento dopaminérgico pode ser um tratamento alternativo para a pica. Ao produzir um aumento dos níveis cerebrais de dopamina e diminuição da impulsividade, os psicoestimulantes podem associar-se a uma melhoria dos sintomas de pica.

Palavras-chave: metilfenidato; perturbação de hiperatividade e défice de atenção; pica; tratamento

INTRODUCTION

Pica refers to the persistent, compulsive craving for and ingestion of substances usually considered inedible. This behavior should be discordant with cultural practices and continue beyond the normal developmental phase of occasional indiscriminate and experimental mouthing and swallowing for at least one month (**Box 1**). An age cut-off of 24 months or more is suggested in the *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[1] The term originated from the Latin word for magpie, "*pica*", a bird famed for collecting and hoarding unusual objects.[2]

Pica is considered a common, dangerous, and potentially life-threatening behavior in children, as it can lead to multiple complications, like chocking, intestinal obstruction/perforation, mucosa damage, poisoning, and infection, among others.[2,3]

Although epidemiological data in the literature about the exact pica prevalence is scarce, it seems to be more common during childhood, mainly at the ages of two to three years.[3]. Pica may persist into adolescence when associated with intellectual disability or manifest during pregnancy.[3] Studies suggest that pica can be present in 5 to 25% of children with learning difficulties and its prevalence correlates with disability severity.[4]

Pica etiology is poorly understood and a wide range of explanatory mechanisms have been put forward. It has been conceptualized as a response to hunger or as oral gratification for anxiety and emotional stress relief in children.[5] Additionally, associations with micronutrient deficiency, including iron, calcium, and zinc, and with sickle cell anemia have been reported.[3,6]

Psychiatric comorbidities, such as obsessive-compulsive disorder, depression, and anorexia nervosa are often reported.[7] Several authors describe pica as an impulse control disorder and propose that it may appear in response to poor impulse control and within the obsessive-compulsive spectrum.[8]

Pica generally resolves in children of average intelligence after they have been trained to discriminate between edible and nonedible items and proper supervision has been provided.[2].Besides behavioral interventions, little is known regarding other therapeutic interventions, including pharmacological treatment. In some cases, vitaminic or mineral supplementation or treatment with selective serotonin reuptake inhibitors may be prescribed.[2,3]

Attention deficit hyperactivity disorder (ADHD) is characterized by patterns of inattention and/or hyperactivity/impulsivity. It

Box 1 - *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for the diagnosis of pica[1]

- The eating of non-nutritive, non-food substances is persistent for at least 1 month.
- The eating of such substances is inappropriate to the developmental level of the individual.
- The eating behavior is not part of a culturally supported or socially normative practice.
- If the behavior occurs within the context of another mental disorder or medical condition, it is sufficiently severe to warrant independent clinical attention.

is likely caused by a dopaminergic dysfunction and responds to psychostimulant treatment.[9] As impulsive symptoms are part of the diagnostic criteria for ADHD, which is identified as an inhibition and impulse control problem as described for pica, in this study the authors review the available literature on pica, ADHD, and treatment response during childhood and adolescence and present two case reports, with the aim of investigating the clinical overlap and treatment outcomes of these two disorders.[7,8]

METHODS

A systematic literature review was conducted on PubMed and Cochrane databases during November 2019 using the key terms "pica", "attention deficit", "hyperactivity", "child", and "adolescent". The search strategy included reviews and case reports and yielded 28 results. Abstracts of retrieved articles were screened and manual selection of papers was subsequently performed based on their relevance for the subject in matter. A total of 12 eligible records were identified. Six other records were additionally identified through referencing in those initially retrieved in the literature search. No restriction criteria were established regarding study design. Only articles written in English were considered.

Additionally, a retrospective analysis of two patients with pica and ADHD from the Child and Adolescent Psychiatry Department of Hospital Pediátrico was also conducted.

RESULTS

To date, only three cases have been reported in the literature describing children with diagnosis of pica and ADHD (or hyperkinetic disorder; **Table 1**). Of these, two were male, two had average intelligence quotient (IQ), and two had normal blood work. The only two case reports of children with pica and ADHD with no intellectual disability or blood deficit had complete pica symptom remission after methylphenidate treatment.

Gunes *et al*. reported the case of a six-year-old girl with pica and ADHD with complaints of eating substances with no nutritive value – like hair, fibre, slime, play dough, toothpaste, ice, paper, wood, and glue – since her toddlerhood.[10] This girl met DSM-IV criteria for ADHD. Physical and neurologic examinations and complete blood work revealed no abnormalities and she had an average IQ.[11] The girl was prescribed 10mg of methylphenidate twice daily, with improvement

Table 1 - Cases of Pica and ADHD reported in the literature

Article	Patient	Diagnosis	Psychometric evaluation	Tests	Treatment
Gunes *et al*. (2016)	six-year-old girl	Pica and ADHD	Average IQ level	Complete blood count and liver, kidney, and thyroid functioning tests revealed no signs of abnormalities; blood iron, lead, folic acid, zinc, and vitamin B 12 levels within normal range	Methylphenidate 20mg
Hergüner *et al*. (2010)	eight-year-old boy	Pica and ADHD	Normal IQ level	Complete blood count, serum ferritin, iron, zinc, vitamin B12, and folate levels, and liver, thyroid, and renal function tests within normal range	Methylphenidate 27mg
Gautam *et al*. (2014)	12-year-old boy	Moderate mental retardation, iron deficiency anemia, hyperkinetic disorder, pica, and nail biting	Low IQ level	Hemoglobin 8.1 g/dL Other tests within normal range	Fluoxetine 20mg; Iron supplements

ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient

in attention deficit, hyperactive, and impulsive behaviors and pica symptoms after four weeks and proper functioning during the following year.

Also Hergüner *et al*. described the case of an eight-year-old boy with pica and ADHD as comorbidity, both successfully treated with methylphenidate.[12] The boy presented with complaints of eating carpet and cloth fibres for more than three years and met DSM-IV criteria for ADHD. He described this habit as a strong, irresistible impulse, which he could not resist to. Although the boy did not like this feeling and did not want to eat, he was unable to overcome it. In psychiatric assessment, he showed inattention, hyperactivity, and impulsivity. He had aggressive behavior towards his parents and peers, concentration problems, poor school performance, and increased motor activity. Obsessive, compulsive, anxiety, and/or depressive symptoms were not identified. Psychometric testing revealed normal intelligence level and medical history was unremarkable. Full laboratory examinations were within normal limits. The boy was diagnosed with pica and ADHD (combined type) according to DSM-IV.[11] OROS methylphenidate 27mg daily was prescribed, with both ADHD and pica symptom improvement within three weeks. The boy remained symptom-free for six months.

Gautam *et al*. described a 12-year-old boy with hyperkinetic disorder and pica. According to the multiaxial International Classification of Diseases (ICD-10), the patient was also diagnosed with moderate mental retardation and iron deficiency anemia, both typically associated with pica symptoms.[13,14] He started on fluoxetine 20mg once daily due to nail-biting behavior and iron supplementation. Initial management of hyperactivity symptoms was conducted with behavioral modification techniques and special education was planned, with gradual improvement of pica behavior and nail biting habits on subsequent follow-ups.

Retrospective analysis of pica patients at the Child and Adolescent Psychiatry Department of our institution further identified two cases of children with pica and ADHD and average IQ (**Table 2**).

Case 1 was a ten-year-old girl referred to our outpatient clinic with complaints of difficulty in paying and keeping attention and focusing at school. She had difficulties in maintaining school activities for frequently talking with peers during class and presented poor school performance and increased motor activity. The girl had been diagnosed with ADHD at the age of eight years and was on methylphenidate short-acting formulation of 20mg + 10mg daily at the time of referral. The mother described nail-biting behavior and the recurrent habit of chewing and eating paper sheets since the first year of school and particularly during the last few months. The girl also frequently nibbled at some school materials, like pencils and pens. Psychometric tests revealed an IQ corresponding to average intelligence level. Growth and physical development were normal (weight and height between the 25thand the 50thpercentile). Laboratory examinations, including complete blood count, serum ferritin, iron, zinc, vitamin B12, and folate levels, and liver, thyroid, and renal function tests were within normal range. There was no history of pica or other psychiatric disorders among family members. Due to lack of adherence and response to previous treatment, the girl was stared on 27mg of OROS methylphenidate formulation, with improvements in school and no ingestion of non-nutritive materials within four weeks.

Table 2 - Pica and ADHD cases reported at the Child and Adolescent Psychiatry Department of Hospital Pediátrico

Patient	**Diagnosis**	**Psychometric evaluation**	**Tests**	**Treatment**
Case 1 ten-year-old girl	Pica and ADHD	Average IQ	Complete blood count, serum ferritin, iron, vitamin B12, and folate levels, and liver, thyroid, and renal function tests within normal range	Methylphenidate 27mg
Case 2 nine-year-old girl	Pica, ADHD, and Social Anxiety Disorder – performance specific	Average IQ	Complete blood count, serum ferritin, and C-reactive protein within normal range	Behavioral intervention Psychotherapy

ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient

Case 2 was a nine-year-old girl referred to our outpatient clinic by the family doctor due to habits of eating pens, crayons, pencils, glue sticks, and paper, as well as biting nails since infancy. However, she was only referred to specialty appointment when the mother noticed colored stools due to ingestion of wax crayons. The child described this habit as a strong impulse to which she could not resist and which worsened during school test period. She was ashamed of this behavior, which she felt unable to overcome. Parents and teachers also complained about her fidgeting behavior. In psychiatric assessment, the girl exhibited inattention, hyperactivity, and impulsivity symptoms and met ADHD criteria. She also feared being negatively judged by peers in school and met Social Anxiety Disorder criteria. Physical and neurologic examinations and complete blood work were normal and IQ was average. The girl started a multidisciplinary intervention based on behavioral training and psychotherapy to reduce pica and performance-related anxiety symptoms. Due to parental refusal, no pharmacological intervention directed at ADHD symptoms was initiated. Although she still reports difficulties in concentrating and behaving well in class and maintains some nail-biting behaviors, her pica and performance anxiety symptoms improved after behavioral intervention.

DISCUSSION

Little is yet known about pica etiology and treatment. Due to poor impulse control, several authors have conceptualized it as lying within the spectrum of compulsive-impulsive disorders. As in ADHD, impulsivity seems to be a cardinal pica feature.

There is a general impression among clinicians that children with ADHD often present comorbid pica at some point in their lives. However, pica is seldom diagnosed, possibly due to the generalized notion that its symptoms vanish with ADHD improvement through psychotherapeutic or, more frequently, psychopharmacologic interventions, namely methylphenidate.

Only single cases of comorbid pica and ADHD in young patients have been reported in the literature and, although a few authors have reported this association for over a decade, its prevalence is still largely unknown. Some children with comorbid pica and ADHD treated with methylphenidate have an excellent pharmacological response regarding both conditions, which seems to support the dopaminergic system dysfunction theory regarding pica etiology.

Some authors report the exacerbation of pica symptoms with thioridazine, which is well known for its anti-dopaminergic actions.[15] Also, one study reported a higher incidence of pica symptoms in patients receiving typical antipsychotic medication.[16] Other authors describe a reduction in pica symptoms with bupropion, an antidepressant acting as a norepinephrine and dopamine reuptake inhibitor, in developmentally disabled adults.[17] These data may also support the potential role of dopaminergic system dysfunction in the etiology of this condition.

In this study, the authors analysed clinical data and physiopathological cues available in the literature regarding pica and ADHD and added two clinical cases from their institution reporting a decrease in pica symptoms after ADHD assessment and treatment. Despite being independent clinical conditions, retrieved data suggests that pica and ADHD may share some neurobiological ground. Specifically, a subgroup of pica cases may be related to impulse control problems or dopaminergic system dysfunction and methylphenidate may be a reasonable treatment option for these patients.

Due to the still limited available evidence regarding pica and ADHD, it is necessary to increase the scientific and clinical body of evidence regarding this subject. Simultaneously, clinician's awareness about this association and reporting of cases identified is crucial to support further studies and research in this area.

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ORIGINAL ARTICLES

MINIMALLY INVASIVE SURFACTANT THERAPY IN PRETERM INFANTS: TOWARDS LESS INVASIVE MANAGEMENT

TERAPÊUTICA COM SURFACTANTE EM RECÉM-NASCIDOS PRÉ-TERMO: TENDÊNCIA PARA UMA ABORDAGEM MENOS INVASIVA

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ABSTRACT

Introduction: Minimally invasive surfactant therapy (MIST) is a surfactant administration procedure that intends to reduce intubations and associated risks. The aim of this study was to compare MIST with INtubation-SURfactant-Extubation (INSURE) technique.

Material and methods: Retrospective analysis (from January 2015 to June 2019) of preterm infants on nasal continuous positive airway pressure (nCPAP) treated with surfactant.

Results: Fifty-four preterm infants were included and divided in two groups: MIST (n=34) and INSURE (n=20). No significant differences were found between groups regarding gestational age (p=0.480), birth weight (p=0.299), fraction of inspired oxygen (FiO_2) prior to surfactant (p=0.220), oxygen therapy duration (p=0.306), progression to intubation (p=0.712), or length of Neonatal Intensive Care Unit stay (p=0.778). FiO_2 variation before and after surfactant administration was higher in MIST group (14% vs 9%, p=0.078). No significant complications were reported with either technique.

Conclusions: MIST is a safe technique in preterm infants on nCPAP. This study shows similar outcomes with MIST and INSURE procedures, with a greater reduction in FiO_2 requirements with MIST. Overall, MIST is less invasive and as effective as INSURE in preterm infants.

Keywords: INSURE; MIST; preterm; surfactant; ventilation

RESUMO

Introdução: A administração de surfactante por técnica minimamente invasiva (MIST) é um procedimento que visa reduzir o número de intubações e riscos associados. O objetivo deste estudo foi comparar a técnica MIST com a técnica INtubation-SURfactant-Extubation (INSURE).

Material e métodos: Análise retrospetiva (de janeiro 2015 a junho 2019) de recém-nascidos (RN) pré-termo sob ventilação não invasiva com pressão positiva contínua nas vias aéreas (nCPAP) tratados com surfactante.

Resultados: Foram incluídos 54 RN, que foram divididos em dois grupos: MIST (n=34) e INSURE (n=20). Não foram observadas diferenças significativas entre grupos relativamente à idade gestacional (p=0.480), peso ao nascer (p=0.299), fração inspirada de O_2 (FiO_2) prévia ao surfactante (p=0.220), duração da oxigenoterapia (p=0.306), progressão para intubação (p=0.712) ou tempo de permanência na unidade de cuidados intensivos neonatais (p=0.778). A variação de FiO_2 antes e após a administração de surfactante foi maior no grupo MIST (14% vs 9%, p=0.078). Nenhuma das técnicas registou complicações relevantes.

Conclusões: MIST é uma técnica segura em RN pré-termo em nCPAP. Este estudo evidencia resultados semelhantes entre as técnicas MIST e INSURE, com uma maior diminuição das necessidades de FiO_2 com a técnica MIST. Pode concluir-se que a técnica MIST é menos invasiva e tão eficaz como a INSURE.

Palavras-chave: INSURE; MIST; prematuridade; surfactante; ventilação

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INTRODUCTION

Respiratory distress syndrome (RDS) is a common morbidity and mortality cause in preterm infants.[1,2] Surfactant therapy is a hallmark in RDS treatment, being associated with an important decrease in preterm mortality.

For many years, surfactant therapy was administered to sedated and intubated patients, with the disadvantages of mechanical ventilation: volume and barotrauma, atelectrauma, and biotrauma. To reduce these complications, Victorin *et al* developed the INSURE technique in the 1990s.[3] The name INSURE is an abbreviation for INtubation-SURfactant-Extubation and refers to the procedure by which a patient on nasal continuous positive airway pressure (nCPAP) ventilation is intubated, receives surfactant through an endotracheal tube, and is extubated back to nCPAP. This procedure has advantages over the traditional surfactant administration, including mortality decrease, mainly due to a reduction in the use of invasive ventilation. Despite these advantages, INSURE also has disadvantages, such as frequently requiring sedation, with potential secondary effects, as bradycardia or hypotension, and extubation difficulty in a large number of patients.[4]

Several non-invasive or less invasive techniques for surfactant administration in non-intubated patients have been developed over time to avoid intubation-associated risks, namely administration via thin catheter (the most studied and employed method), aerosolized administration, laryngeal mask-guided administration, and pharyngeal administration.[1] This group of techniques has been inconsistently designated minimally invasive surfactant therapy (MIST) or less invasive surfactant administration (LISA). In this study, the first designation was adopted.

The most frequently described method for surfactant administration via thin catheter is through a feeding tube, known as the Cologne method. It was first described by Verder *et al*[5] and uses a 4- to 5-FG feeding tube and Magill forceps to introduce a thin catheter past the vocal cords. This technique allows surfactant administration while the patient is on non-invasive positive pressure ventilation.[4]

In recent years, several small trials have encouraged the use of MIST over the conventional INSURE technique[6-11] and larger studies (NINSAP and OPTIMIST-A) have also investigated the benefits of this procedure. In NINSAP trial, no difference was found between both methods regarding the primary outcome of death or progression to bronchopulmonary dysplasia (BPD) and some secondary outcomes, as intraventricular hemorrhage and pneumothorax, were significantly reduced with MIST. OPTIMIST-A is a large ongoing multicentre randomized controlled trial (RCT) that aims to investigate progression to BPD or death in a patient population with surfactant administration by MIST (Hobart method).[4]

A recent meta-analysis of three RCTs comparing MIST with INSURE showed that the minimally invasive technique reduced the need for mechanical ventilation, nCPAP duration, oxygen supplementation, and progression to BPD compared with INSURE.[12]

The aim of this study was to investigate the efficacy and feasibility of MIST compared with INSURE and assess short- and long-term effects, including intubation, oxygen supplementation, inward duration, and procedure complications.

MATERIAL AND METHODS

Patients

This was a retrospective observational study conducted in the Neonatal Intensive Care Unit (NICU) of Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, between January 1st 2015 and June 30th 2019.

Inclusion criteria comprised preterm infants admitted to NICU who received nCPAP support and surfactant (Curosurf®, Chiesi Farmaceutici, Parma, Italy) either by INSURE or MIST technique.

MIST procedure

MIST was performed in patients on nCPAP with a fraction of inspired oxygen (FiO_2) equal or above 0.3. Direct laryngoscopy was performed and a 5-FG feeding tube was inserted into the trachea with Magyll forceps. Surfactant was instilled through the feeding tube at standard dose (200 mg/Kg) as a slow bolus and the catheter immediately removed. Analgesia with sucrose and/or morphine was frequently administered before the procedure. Positive pressure inflation was provided in cases of apnea and/or bradycardia.

INSURE procedure

INSURE was performed via elective intubation and surfactant was given via endotracheal tube (ET) while on positive pressure ventilation without target volume. After administration, ET was promptly removed and the patient returned to nCPAP. Patients who did not respond started invasive ventilation.

Statistical analysis

Patient data analysed included gender, gestational age, birth weight, prenatal corticosteroid administration, and pre- and post-surfactant FiO_2. Complications, oxygen therapy duration, respiratory support (nCPAP and/or invasive ventilation), and NICU length of stay were also recorded.

Sociodemographic data were expressed as medians. Discrete variables were analyzed with Chi-square test. Depending on data distribution, Student's t or Mann-Whitney U test were performed to compare continuous variables. Statistical analysis was performed using IBM® SPSS® Statistics, version 25.0 (SPSS, Chicago, IL, USA).

RESULTS

During the study period, 167 neonatal preterm infants required surfactant therapy in NICU. A total of 113 patients were excluded from

the study for having received surfactant under invasive ventilation. Overall, 54 patients were treated with nCPAP, 34 of which by MIST (Group 1) and 20 by INSURE (Group 2; **Figure 1**). Both techniques were performed by NICU neonatologists.

Group 1 included 15 female and 19 male patients versus 6 and 14 in Group 2, respectively. Demographics and general characteristics, as gestational age (p=0.480), birth weight (p=0.299), and median maternal age (p=0.129), were balanced between groups, as were prenatal corticosteroid administration (p=0.395), intrauterine growth restriction incidence (p=0.147), delivery mode (p=1.000), and median Apgar Score in first and fifth minutes (p=0.705 and p=0.902, respectively). Birthweight class analysis also showed no relevant between-group differences (**Table 1**).

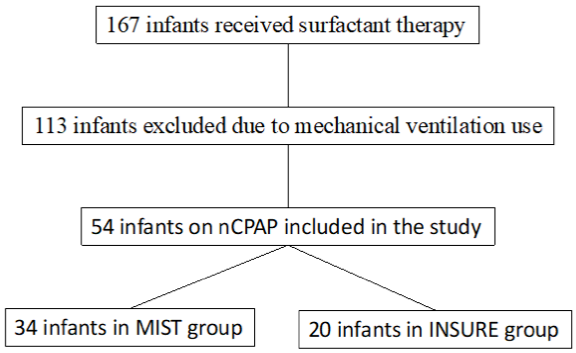

Figure 1 - Study flowchart

Table 1- General characteristics of the study population

	MIST (N = 34)	**INSURE (N = 20)**	***P value***
Gender			0.391*
Female	15 (44%)	6 (30%)	
Male	19 (56%)	14 (70%)	
Gestational Age (weeks)			
Median (IQR)	30 (3)	31 (4)	0.480**
< 32 weeks – n (%)	23 (68%)	13 (65%)	
≥ 32 weeks – n (%)	11 (32%)	7 (35%)	
Weight (grams)			
Median (IQR)	1345 (786)	1370 (653)	0.299**
< 1000 gr – n (%)	7 (21%)	2 (10%)	
≥ 1000 gr to < 1500 gr – n (%)	13 (38%)	10 (50%)	
≥ 1500 gr to < 2500 gr – n (%)	12 (35%)	7 (35%)	
≥ 2500 gr – n (%)	2 (6%)	1 (5%)	
Maternal age – median (IQR)	30.5 (8.5)	32 (11.5)	0.129**
Antenatal corticosteroids – n	29	19	0.395*
IUGR – n (%)	4 (12%)	6 (30%)	0.147*
Delivery mode – n (%)			1.000*
Vaginal	10 (29%)	5 (25%)	
C-section	24 (71%)	15 (75%)	
Apgar Score – median			
1st minute	7	7	0.705**
5th minute	8	9	0.902**

IQR, interquartile range; IUGR, intrauterine growth restriction; ST, surfactant therapy

** Fisher's Exact test*

*** Mann-Whitney U test*

According to medical records, 14 patients received premedication, all from MIST group. Five patients received morphine (0.05 to 0.1mg/Kg) and atropine (0.01 to 0.02mg/Kg), seven only morphine, one morphine and midazolam, and one only atropine.

Table 2 depicts FiO_2 values before surfactant administration and respective variation before and after the procedure. No significant differences were found between Group 1 and 2 regarding FiO_2 before surfactant (p=0.220) and FiO_2 variation before and after the procedure (p=0.078).

Pneumothorax was reported in two MIST patients (6%), but deemed to be unrelated to the procedure. Regarding complications directly related to the procedure, gastric surfactant deposition was reported in three MIST patients (9%). MIST was repeated in four patients (12%) and INSURE in three (15%). Five MIST patients (15%) compared to four INSURE patients (20%) required mechanical ventilation within the first 72 hours after surfactant administration. General characteristics were balanced and not significantly different between both cohorts (**Table 2**). Among MIST patients, one was intubated three hours after surfactant administration due to apnea with bradycardia episodes. Information about reasons for intubation was lacking in the medical records of the remaining MIST patients. In INSURE group, one patient was intubated due to pneumothorax and another due to apnea with bradycardia. In the latter, surfactant was observed in gastric aspirate. Data was lacking for the remaining two INSURE patients.

Median oxygen therapy duration was 7.5 days (interquartile range [IQR] 33) in Group 1 and 25 days (IQR 34) in Group 2 and median NICU length of stay was 15 days (IQR 23) and 13 days (IQR 23), respectively. No statistically significant differences were found between groups regarding oxygen therapy duration (p=0.778) and NICU length of stay (p=0.942).

Prevalence of bronchopulmonary dysplasia was similar with both techniques, with 12 cases reported in MIST and seven reported in INSURE group (both 35%). Other clinical complications are described in **Table 3**. Prevalence of hemodynamically significant patent *ductus arteriosus* (HS-PDA) (five in MIST *vs* four in INSURE) and severe intraventricular hemorrhage and cystic periventricular leukomalacia (three in MIST *vs* two in INSURE) was similar between groups. Retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC) were only found in Group-1 patients (three and one cases, respectively).

One MIST patient died of reasons unrelated to the procedure.

An increased interest in surfactant administration via catheter has been observed in NICU since the beginning of MIST use, with a total of 15% surfactant administrations in 2015 and 100% in the first half of 2019 (**Figure 2)**.

Table 2- Clinical characteristics of the study population

	MIST (N = 34)	**INSURE (N = 20)**	***P value***
F_iO_2 before ST – median (IQR)	0.40 (9)	0.36 (14)	0.220**
F_iO_2 after ST – median (IQR)	0.23 (6)	0.25 (11)	0.307**
F_iO_2 variation – median (IQR)	0.14 (10)	0.09 (10)	0.078**
Intubation < 72h – n (%)	5 (15%)	4 (20%)	0.712*
Oxygen therapy duration (days) – median (IQR)	7.5 (33)	25 (34)	0.306**
Length of NICU stay (days) – median (IQR)	15 (23)	13 (23)	0.778**
Clinical complications – n, %			
Bronchopulmonary dysplasia	12 (35%)	7 (35%)	1.000*
HS-PDA	5 (15%)	4 (20%)	
Severe IVH/cPVL	3 (9%)	2 (10%)	
ROP	3 (9%)	0	
NEC	1 (3%)	0	
Pulmonary hemorrhage	0	0	
Non-survival – n	1 (3%)	0	1.000*

cPVL, cystic periventricular leukomalacia; F_iO_2, fraction of inspired oxygen; HS-PDA, hemodynamically significant patent ductus arteriosus; IQR, interquartile range; IVG, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; ST, surfactant therapy

* Fisher's Exact test

** Mann-Whitney U test

Table 3 - General characteristics of patients intubated within the first 72 hours

	MIST (N = 5)	INSURE (N = 4)
Gender		
Female/male – n	3/2	1/3
Gestational Age (weeks)		
Median (IQR)	31 (7.5)	32 (6)
Weight (grams)		
Median (IQR)	1585 (1285)	2000 (1481)
Maternal age – median (IQR)	31 (14)	34 (13.5)
Antenatal corticosteroids – n	4	3
IUGR – n (%)	1 (12%)	1 (%)
Delivery mode – n (%)		
Vaginal	1 (%)	1 (%)
C-section	4 (%)	3 (%)
Apgar Score – median		
1st minute	7	8
5th minute	8	9

IQR, interquartile range; IUGR, intrauterine growth restriction; ST, surfactant therapy

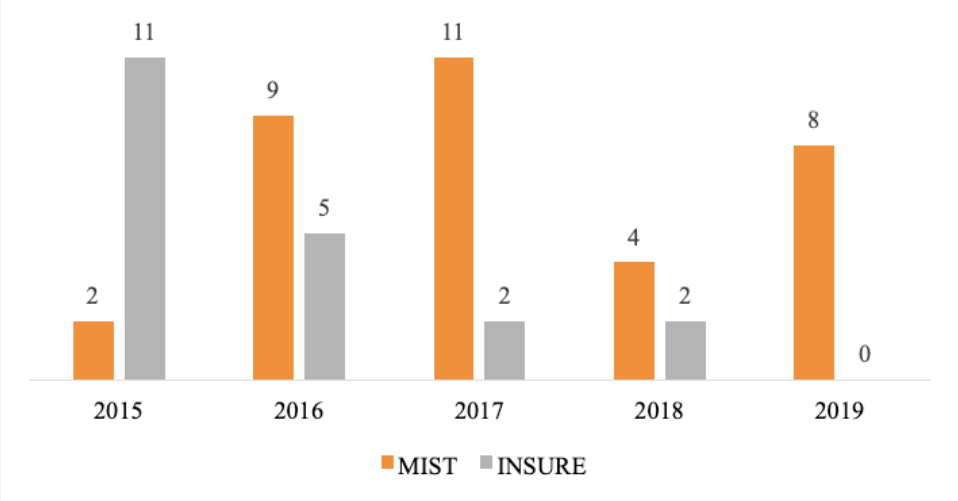

Figure 2 - Total MIST and INSURE procedures performed per year

DISCUSSION

Avoiding mechanical ventilation has been the clinical focus in RDS preterm neonates in recent years. Several large clinical trials (COIN, SUPPORT, and VON-DRM) reported no benefit with INSURE over only nCPAP support.[13-15] This may be explained by adverse effects associated with intubation and invasive ventilation, which may increase acute lung injury in preterm patients. Other disadvantages are related to the need for sedative medication (with associated secondary effects, as bradycardia and hypotension) and extubation difficulty.[4] Patients submitted to INSURE often fail to be extubated after surfactant administration, resulting in longer mechanical ventilation support. In a 2014 cohort study, 60% of patients treated with this technique failed to be extubated in the first two hours after surfactant administration.[16]

Additionally, not all preterm infants are effectively managed with nCPAP only. For some neonates with moderate-to-severe RDS, nCPAP support seems insufficient, and more aggressive respiratory management is required.[4] In this setting, minimally invasive surfactant therapy techniques emerged as a strategy for avoiding invasive ventilation in these patients.

MIST enables surfactant administration while the patient is on noninvasive CPAP. Four different MIST methods have been described: intrapharyngeal surfactant instillation (first used by Enhoerning

and Robertson in 1972 in a rabbit model); surfactant nebulization (a promising procedure also known as noninvasive surfactant therapy, but with several physical limitations related to aerosol size and nebulizer type); surfactant instillation via laryngeal mask; and surfactant administration via thin catheter.[16-18]

Surfactant administration via thin catheter can be performed by four different methods, with the Cologne method being the most widely used. It was first described by Verder *et al* and published by Kribs *et al* in 2007.[19] Hobart method is an alternative procedure described in 2011 which obviates the need for Magill forceps and is currently being investigated in the large OPTIMIST-A trial.[20] This multicentre RCT is enrolling preterm infants with 25–28 weeks of gestation with six hours of life treated with nCPAP and with FiO_2 ≥0.30 and aims to compare surfactant administration via Hobart method (intervention group) versus via nCPAP (control group).

No study has been conducted to date comparing MIST methods, which results in great clinical practice heterogeneity within NICUs worldwide.

INSURE remains the most commonly used surfactant administration method in several Portuguese NICUs. In our NICU, INSURE is the chosen method when there is the possibility of patients requiring invasive ventilation.

In the present study, both INSURE and MIST patient populations displayed similar general demographic characteristics and median FiO_2 before surfactant administration. Progression to mechanical ventilation, oxygen therapy duration, and length of NICU stay were also similar between groups. Although data was lacking for some patients, reasons for intubation in the first 72 hours were similar between groups, with one apnea and bradycardia episode reported in one patient in each group. Although not statistically significant, the most relevant between-group difference was the greater decrease in FiO_2 requirements after surfactant administration with MIST compared with INSURE (0.14 vs. 0.09, p=0.078).

MIST also has associated issues. Preterm infants with mild RDS probably improve with nCPAP and do not benefit from MIST. MIST comprises several methods and techniques and successful outcomes are directly related to staff experience and training. In our NICU, method success has progressively increased over the last four years due to staff-acquired skills.

Premedication is another issue to take into consideration. Premedications may include oral sucrose, atropine, ketamine, caffeine, morphine, lidocaine, among others. A 2017 European survey reported that 52% of neonatologists used no premedication in MIST. Use of narcotic agents is common in INSURE, but their absence does not seem to be associated with short-term deleterious effects. Since spontaneous breathing plays a major role in surfactant pulmonary distribution in MIST, breathing effort reduction with narcotics may be disadvantageous in preterm infants.[21] In our NICU, sucrose, low morphine doses, and in some cases atropine are usually used in MIST. However, information regarding premedication is lacking in our database, what constitutes a study limitation; this information was only available for 14 of the total enrolled patients.

As surfactant reflux is a common complication, the effective dose administered is difficult to determine.[22] In this study, this complication was reported in three cases, but its importance is difficult to discuss due to limitations associated with the study's retrospective design. Other complications associated with the technique, like unilateral surfactant deposition, mucosal bleeding, or airway obstruction, were not observed.

Although no side effects were observed with MIST in this study, the procedure may pose technical challenges, like using a laryngoscope to visualize vocal cords, what can be difficult and sometimes traumatic.[23]

Due to the retrospective nature of this study, information gaps in clinical records preclude conclusions regarding aspects as the effective surfactant dose, premedication, and minor technique complications.

Previous Australian and European studies have shown a growing interest of neonatologists in MIST methods.[24] In the 2019 European Consensus Guidelines on RDS management, less invasive surfactant administration is recommended as the preferred surfactant administration method for spontaneously breathing infants on nCPAP, provided that clinicians are experienced with the technique (B2).[25] This study supports these results, with MIST being the preferred technique by most neonatologists in our NICU.

CONCLUSIONS

In the literature, MIST is associated with a significant reduction in mechanical ventilation requirement and duration, supplemental oxygen, and nCPAP. This means that surfactant administration via thin catheter may have a role in the future care of preterm infants.[12]

This study confirms some of the potential advantages of minimally invasive surfactant administration reported in literature.

MIST via catheter is a gentle, feasible, and effective technique in preterm RDS infants. This technique is preferred over surfactant administration via INSURE due to inherent intubation disadvantages in preterm neonates with moderate-to-severe RDS.

Some MIST-associated problems should be emphasized, as method variability (with potential result discrepancy), uncertainty about the effective surfactant dose, premedication use, and patient selection. Overall, MIST seems to be as effective as INSURE, but the best minimally invasive method remains to be determined. Further studies are required to standardise indications and procedures, namely comparing the four different MIST techniques.

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REVIEW ARTICLES

FINDINGS IN PHYSICAL EXAMINATION OF THE EXTERNAL GENITALIA IN PEDIATRIC AGE – DIFFERENT IS NOT ALWAYS PATHOLOGICAL – PART I (MALE)

ALTERAÇÕES AO EXAME FÍSICO DO APARELHO GENITAL EM IDADE PEDIÁTRICA - O QUE É DIFERENTE NEM SEMPRE É PATOLÓGICO – PARTE I (MASCULINO)

Diana Morais Costa[1], Nuno Teles Pinto[2], Ana Sofia Marinho[3], João Moreira Pinto[3,4]

ABSTRACT

Introduction: Findings in the physical examination of the external genitalia in children are often a source of concern for parents and caregivers, not only for the emotional significance that people unconsciously attribute to these structures (partly due to their reproductive function), but also for the physical and psychological impact in the child.

Due to the child's close monitoring and periodic surveillance, the family physician has a key role in the identification and initial guidance of these cases.

Objectives: To review the evidence about main variations and anomalies of the external male genitalia in pediatric age regarding diagnosis and clinical approach in primary health care.

Results: In most cases, anomalies in the external male genitalia represent variants of normal and/or do not significantly affect function, thus only requiring clinical surveillance and no intervention. However, some cases – as epispadias, hypospadias, and urethral duplication – require surgical intervention and early action is crucial for the success of implemented measures.

Conclusion: Physical examination is a key aspect of child assessment. Although changes in physical examination of the external male genitalia mostly represent normality variants, clinicians should be able to recognize pathological changes and properly refer those cases without overloading health services or causing unnecessary anxiety to children and caregivers.

Keywords: anomaly; children; external genitalia, male; physical examination

RESUMO

Introdução: Os achados no exame físico da genitália externa em crianças são frequentemente uma fonte de preocupação para pais e cuidadores, não só pelo significado emocional que inconscientemente é atribuído a essas estruturas devido à sua função reprodutiva, como, também, pelo impacto físico e psicológico na criança.

Devido ao acompanhamento próximo e vigilância periódica da criança, o médico de família tem um papel fundamental na identificação e orientação inicial destes casos.

Objetivos: Rever a evidência sobre as principais variações e anomalias da genitália masculina em idade pediátrica no que se refere ao diagnóstico e abordagem clínica nos cuidados de saúde primários.

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Resultados: Na maior parte dos casos, as anomalias da genitália externa masculina são apenas variantes da normalidade e/ou não afetam significativamente a função, necessitando apenas de vigilância clínica e não requerendo intervenção. No entanto, alguns casos – como epispádias, hipospádias e duplicação uretral – necessitam de intervenção cirúrgica e a ação precoce é essencial para o sucesso das medidas implementadas.

Conclusão: O exame físico é uma parte fundamental da avaliação da criança. As alterações no exame físico da genitália externa são, na maior parte dos casos, apenas variantes da normalidade. No entanto, os médicos devem ser capazes de reconhecer alterações patológicas e referenciá-las adequadamente, não sobrecarregando os serviços de saúde ou causando ansiedade desnecessária às crianças e cuidadores.

Palavras-chave: anomalia; criança; exame físico; genitália externa; masculino

INTRODUCTION

Physical examination is a fundamental part of children's regular clinical evaluation and often one of the most useful and effective tools for establishing a specific diagnosis. Findings in physical examination of the external genitalia in children are often a source of concern for parents and caregivers, not only for the emotional significance attributed to these structures (partly due to their reproductive function), but also for the physical and psychological impact in the child.

In most cases, anomalies in the external genitalia are only normality variants and/or do not significantly affect function, therefore requiring only clinical surveillance and no intervention. However, some cases require medical intervention, either from a therapeutic or specialized point of view, and early intervention is key for the success of implemented measures.

Due to to the child's close monitoring and periodic surveillance, the family physician has a crucial role in identifying and initially guiding these cases. By often being the first person to diagnose these anomalies and the first line of support for parents and caregivers, the family physician should acknowledge the specific guidelines regarding each case, not only for reassuring parents in cases without pathological significance, but also for properly referring the child to secondary health care when necessary.

OBJECTIVES

The aim of this work was to review available evidence on the main male external genitalia anomalies in pediatric age and discuss their accurate diagnosis, approach, and follow-up in primary health care. For being a more uncommon entity spectrum with highly variable, specific, and complex multidisciplinary approach, anomalies related to sexual differentiation (intersex) disorders are beyond the scope of this article.

CHANGES IN PHYSICAL EXAMINATION OF THE MALE GENITAL TRACT

Balanopreputial adhesions

Balanopreputial adhesions consist of physiological adhesions between the inner face of the foreskin and the outer face of the glans, being present in most newborns.[1] Contrarily to what happens in phimosis, in balanopreputial adhesions there is no stenotic ring when the foreskin is retracted. They usually do not require treatment, spontaneous resolving with age. Natural detachment of adhesions and gradual preputial ring increase occur with smegma production and spontaneous erections.[2-4] Foreskin retraction should be gradually and delicately performed to avoid excessive and forced detachment that may elicit continuity lesions, with consequent cicatricial phimosis risk.[3]

Smegma Pearls

Smegma is a physiological substance produced by the foreskin and glans mucosa, composed of desquamating epithelial cells and sebaceous substance.[2] It should not to be confused with purulent exudate, usually associated with pain and local inflammatory signs.[2] Smegma pearls consist of a benign collection of smegma in the subpreputial space, being common in uncircumcised boys with partial balanopreputial adhesions.[28,29] It is a benign finding with spontaneous resolution.[28,29]

Phimosis

Phimosis is defined as the inability to completely retract the foreskin due to a constrictive preputial ring, hindering the total exposure of the glans.[2] It is present in most newborns, gradually decreasing with age.[4] Phimosis is classified into two types: physiological and pathological.[3,4] During the diaper period, until around two years of age, physiological phimosis is believed to have a protective role of the glans and no additional care is required beyond normal hygiene.[5-7] Pathological phimosis occurs as a consequence of aggressive and precocious prepuce manipulation, with anomalous preputial meatus scarring. It may also be secondary to inflammatory and infectious

processes.[8]

Medical treatment can be started at the age of three years, when there are important adhesions with little probability of spontaneous resolution, or in presence of repetitive balanitis (**Figure 1**).[9] Application of a topical corticosteroid – as 0.05% betamethasone cream – twice daily for four to six weeks, associated with non-traumatic retraction of the foreskin and hygiene care, are usually effective.[8-10]

The Portuguese General Health Board recommends surgical treatment after the age of five years, with circumcision being the most commonly used technique.[11] Referral to pediatric surgery should occur early in cases of history of urinary tract infection (UTI), congenital malformation of the excretory system, repetitive balanitis, or urinary retention, since phimosis resolution decreases bacterial colonization of the glans and foreskin, thus reducing the probability of subsequent infections.[2]

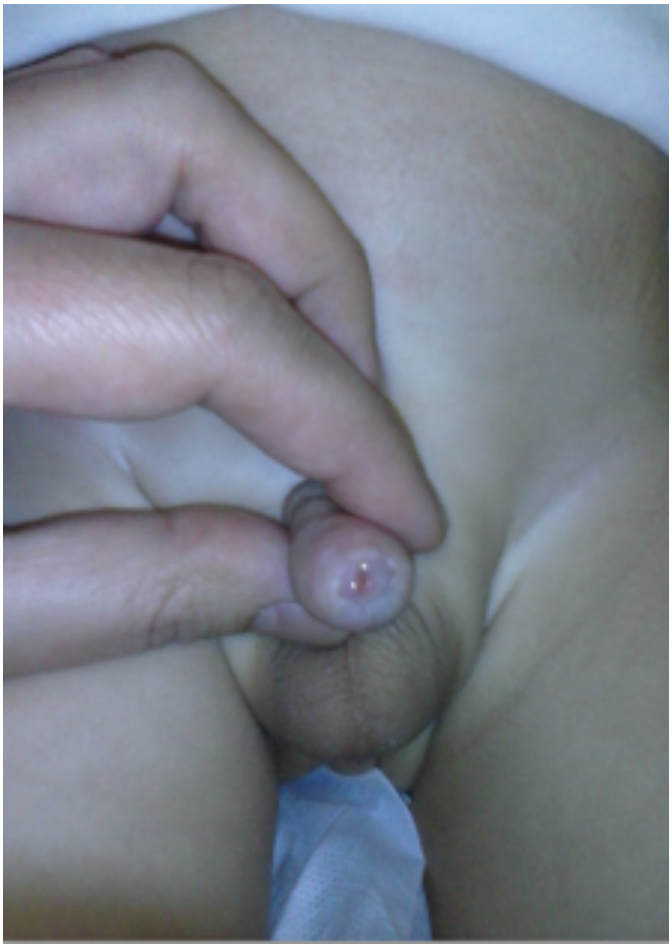


Figure 1 - Pathological phimosis after recurrent balanitis

Paraphimosis

Paraphimosis results from excessive retraction of the foreskin beyond the coronal groove without its replacement on the glans, causing a stenotic ring that decreases venous return and arterial supply to the glans.[12] This vascular compromise causes edema, redness, intense pain and, in extreme cases, ischemia and necrosis, and represents a surgical emergency requiring immediate treatment.[12] Diagnosis is clinical and treatment consists of immediate manual reduction.[13] A topical anesthetic may be applied during the procedure for pain relief.[12,13] If manual reduction is not effective, the subsequent treatment is surgical, aiming at dorsal venous discharge.[13] Circumcision is usually not a therapeutic option in the acute phase, due to significant tissue edema with potential impact on subsequent healing and suture dehiscence risk. Nevertheless, it should be performed at a later phase to prevent recurrent episodes.[12]

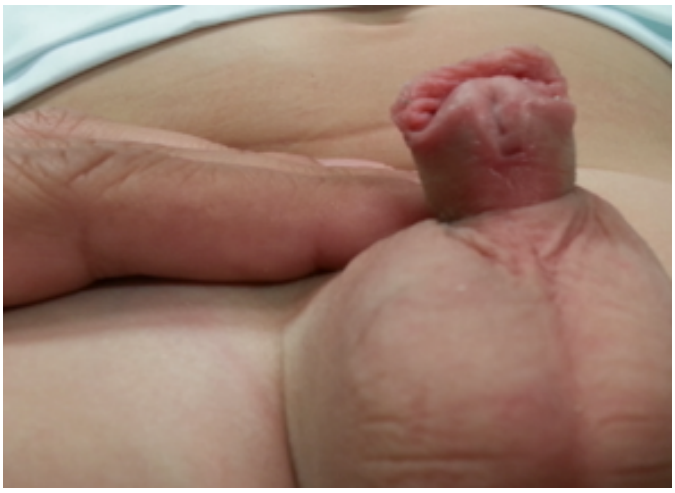
Epispadias

Epispadias is a rare genital malformation in which the urethral meatus is located on the dorsal surface of the penis.[14,15] It most frequently occurs in association with bladder exstrophy (exstrophy-epispadias complex) [15,16], with urinary incontinence being one of the main complications.[14,17] Treatment is surgical and should be considered in view of the condition's severity and associated complications.[17]

Hypospadias

Hypospadias is a congenital malformation in which the urethral meatus is located anywhere on the ventral surface of the penis, from the glans (40–50% of cases) to a more proximal position (**Figure 2**).[2,18] As a general rule, the more proximal the meatus position is, the more severe the hypospadias degree, and this evaluation should be considered to decide on the surgical correction.[2,19,20] Diagnosis is clinical and other physical findings are usually associated, as ventral curvature of the penis and emergence of a dorsal hooded prepuce (preputial skin over the dorsal surface of the penis) .[18,19] Presence of other congenital anomalies, such as unilateral or bilateral cryptorchidism, should raise suspicion of a sexual development disorder.[21]

Surgical treatment consists of urethroplasty. It is indicated in cases of functional impairment and should be considered from the age of six months onwards, taking into account the specific features of each individual case .[19,22] Prognosis is usually favorable from an esthetic and functional point of view, being always necessary to explain caregivers the potential postoperative complications, which can motivate future corrective surgical interventions.[20, 21]



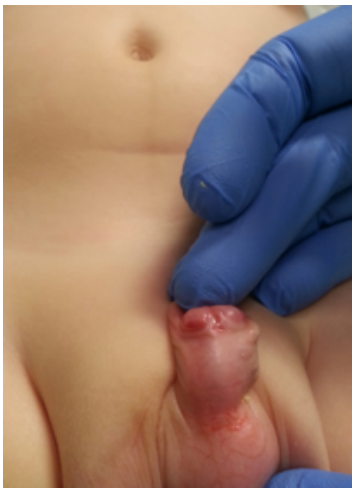


Figure 2 - A - Midshaft hypospadias. B - Subcoronal hypospadias

Hypospadias is a very rare congenital malformation consisting of two "true" urethral openings, in which the ectopic meatus corresponds to the functional urethra.[18,23] Urethral duplication includes a wide spectrum of anatomical variants in which the urethra can be partially or completely duplicated.[24] Likewise, the clinical presentation is also variable: patients may be completely asymptomatic or have associated abnormalities, such as double-flow, urinary incontinence, outflow obstruction, or recurrent urinary infections.[24,25] Treatment is surgical and depends on the type of duplication, clinical manifestations, and coexistence of other associated abnormalities.[24,25]

Short Frenulum (Frenulum Breve of the Penis)

Short frenulum causes a ventral curvature of the penis and may cause pain during preputial retraction or erection.[26] If symptomatic, it requires surgical correction (frenuloplasty).[27]

Cryptorchidism

Cryptorchidism refers to the absence of one or both testicles from the scrotal sac and represents the most common congenital abnormality of the genitourinary tract.[30,31] Cryptorchidism includes different clinical entities, as undescended testicles (most common), retractile testicles, testicular ectopy, and absent testicles.[32] Clinical history is crucial to guide the subsequent therapeutic approach, being important information whether testicles were palpable during the neonatal period and whether there is a history of inguinal surgery or relevant family history, among other aspects.[32] Clinical examination is equally important. An empty scrotal sac, hypoplastic and poorly rugated, may indicate that the testicle was never in the scrotum.[32] It is crucial to know whether cryptorchidism is uni or bilateral, if there are other associated genital tract anomalies (as hypospadias, often suggestive of a sexual development disorder), and if there are findings suggestive of endocrinologic, metabolic, or genetic pathology.[33,34] Cryptorchidism diagnostic and therapeutic approach depends on whether the testis is palpable or not.[30,35] Usually, undescended testicles complete their descent into the scrotal sac in the first four months of life, with spontaneous descent rarely occurring after this period.[31] Imaging tests, as ultrasound, are usually not necessary, since they do not obviate the need for exploratory surgery.[30,32] Regardless of whether testicles are palpable or not, cryptorchidism management holds better prognosis when carried out in the first year of life.[36,37] Therefore, referral should occur as early as possible after the age of four months.[32]

Undescended testicles

Condition in which the testicles do not complete the normal descent into the scrotal sac, being more often unilateral than bilateral.[36,38] Undescended testicles can be palpable or nonpalpable. Unilaterally nonpalpable testicles are predominantly left-sided.[32] Nonpalpable testicles always require laparoscopic exploration to confirm presence of the gonad and attempt orchidopexy. If not feasible, orchidectomy is mandatory. Testicular location in the inguinal canal or abdominal cavity exposes the testicles to higher temperatures, conditioning an increased risk of infertility and testicular malignancy.[30,35,38,39] Undescended testicles are associated with an increased risk of torsion, trauma, and psychological disturbance[31,35,36,40] and have a high percentage of spontaneous resolution during the first six months of life.[36] After this age, spontaneous resolution is uncommon and surgical treatment may be required. Surgical treatment (orchidopexy) is currently recommended between the age of six and 18 months.[36] Orchidopexy is able to reduce but not prevent potential long-term complications, particularly testicular cancer, reason why ongoing clinical follow-up is essential.

Retractile testicles

Non-pathological, often bilateral condition, in which the normally descended testicles temporarily rise to a suprascrotal position due to cremasteric reflex.[35] The differential diagnosis from undescended testicles is established by pulling the testicle to the scrotal position and confirming that it holds the position when loose. In most cases, spontaneous resolution occurs until puberty onset and only clinical annual surveillance is required.[31,36] Annual follow-up until puberty is necessary, since this entity occasionally evolves to acquired undescended testicles, requiring corrective orchidopexy.

Ectopic testicles

In this condition, testicles are absent from the scrotal sac and located outside their normal descent path.[32,36] Potential complications include blunt trauma from compression against the pubic bone and diminished spermatogenesis.[32] Association with malignant transformation is not consensual[32] and surgical exploration is usually required for diagnosis and treatment.[41]

Anorchia (congenital absence of testicles)

Anorchia may result from testicular agenesis or atrophy secondary to intrauterine vascular compromise (due to prenatal testicular torsion – "vanishing testis syndrome").[32,36] Exploratory laparoscopy is mandatory for diagnostic confirmation.[36]

Hydrocele

Hydrocele is a very frequent condition in newborns in which fluid accumulation occurs between the visceral and parietal layers of the vaginal tunic of the testicles, being perceptible by transillumination of the testicular sac.[42] Resolution is spontaneous and considered physiological until the age of two years.[42] Hydrocele can be classified as communicating or non-communicating. In the first (**Figure 3**), peritoneal fluid accumulation around the testicles occurs as a consequence of late *processus vaginalis* closure and is usually characterized by volume variation throughout the day: in the morning, hydrocele is smaller, becoming progressively larger by the end of the day.[42,43] In non-communicating hydrocele, *processus vaginalis* has already closed or narrowed. Sometimes there is no communication with the peritoneum and fluid accumulation may be idiopathic or secondary to testicular inflammatory/pathological processes (reactive hydrocele). In these cases, there is usually associated pain.[42,43]

Diagnosis is clinical. However, in an acute setting, particularly with associated pain, scrotal ultrasound may be useful in the differential diagnosis with inguinal hernia or testicular torsion. Due to the high probability of spontaneous resolution within the first 24 months of age, surgical treatment is not indicated before this period, except in cases in which an inguinal hernia is also present or suspected (such as in communicating hydroceles), which require earlier intervention.[42]

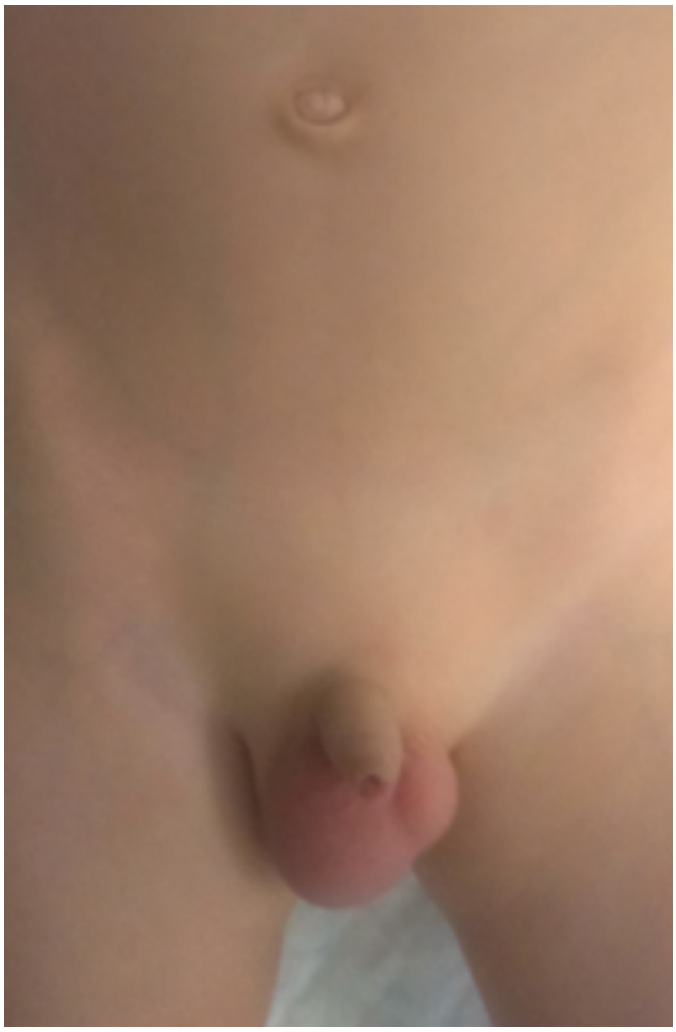


Figure 3 - Right communicating hydrocele

Varicocele

Varicocele is an abnormal and tortuous dilation of the pampiniform plexus veins, more common on the left (around 85–95% of cases).[42,44] It is due to the anatomical difference between left and right testicular veins, the first entering the left renal vein at a 90 degree angle, and the second draining at a more obtuse angle directly into the inferior vena cava, facilitating more continuous flow.[42] Varicocele can be subdivided into primary and secondary type. Primary/idiopathic varicocele, the most common, occurs spontaneously by incompetence of the venous valves, being more prominent in orthostatism and with the Valsalva maneuver and reducing in dorsal decubitus position.[42,43] Secondary varicocele results from extrinsic compression and obstruction of the inferior vena cava, is generally of acute onset, and persists in the dorsal decubitus position.[42,43] Clinically, varicoceles may present as asymptomatic findings or be associated with a sense of weight and scrotal pain that aggravate with orthostatism.[42] If there is clinical suspicion of secondary varicocele (in cases that varicocele persists

in the supine position, has an acute onset, or is located on the right side or bilaterally), ultrasound and abdominal computed tomography should be performed to exclude obstruction from a retroperitoneal mass compressing the vascular structures.[45]

Grade I varicocele is not visible and only palpable with Valsalva maneuver, grade II varicocele is visible in orthostatism only with Valsalva, and grade III varicocele is always visible in orthostatic position, even without Valsalva maneuver.

Varicocele is a common pathology in adolescence (10–15%), frequently associated with infertility in adulthood. Most varicoceles require no specific treatment, with only clinical follow-up and symptomatic treatment recommended. Surgical correction in adolescence is not unanimous. Open or laparoscopic surgical treatment with ligation of spermatic vessels is indicated in cases of grade II or III varicocele associated with more than 2 mL or 10% decreased testicular volume or evident symptoms of pain and discomfort that alleviate in supine position and bilateral varicocele.[42, 44]

Spermatocele (epididymal cyst)

Spermatocele consists of a cyst of variable dimensions located in the epididymis head with a liquid, painless content that may contain nonviable sperm.[42] On physical examination, a cystic mass adjacent to the testicular structures is palpable.[42] This entity is sometimes accidentally diagnosed during testicular ultrasound, considering that when a scrotal lump is found during clinical examination this radiological exam can be useful to confirm diagnosis. Spermatocele is not a cause of infertility and surgical treatment is only indicated for symptom relief.[42]

CONCLUSION

Physical examination is a crucial part of child assessment. Alterations in the physical examination of the external genitalia are frequently not pathological, having favorable prognosis and requiring no more than clinical surveillance. Conversely, some situations require specialized evaluation and sometimes surgical correction, and should therefore be referred to hospital consultation and follow-up.

The family physician, as a primary element of the child's clinical follow-up, is often the first to diagnose these abnormalities and should be able to recognize those that are benign from pathological and requiring formal secondary care referral.

The anxiety that many of these changes elicit in caregivers should also deserve attention from the family physician, who should reassure that clinical issues are being properly addressed.

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REVIEW ARTICLES

FINDINGS IN PHYSICAL EXAMINATION OF THE EXTERNAL GENITALIA IN PEDIATRIC AGE – DIFFERENT IS NOT ALWAYS PATHOLOGICAL - PART II (FEMALE)

ALTERAÇÕES AO EXAME FÍSICO DO APARELHO GENITAL EM IDADE PEDIÁTRICA - O QUE É DIFERENTE NEM SEMPRE É PATOLÓGICO – PARTE II (FEMININO)

Nuno Teles Pinto[1], Diana Morais Costa[2], Ana Sofia Marinho[3], João Moreira Pinto[3,4]

ABSTRACT

Introduction: Findings in the physical examination of the external genitalia in children are often a source of concern and anxiety for parents and caregivers. Due to the proximity and role in child's periodic surveillance, the family physician is in a privileged position to identify and initially provide guidance on these situations, key for the success of future interventions.

Objectives: To review available evidence on the main variations and anomalies of the external female genitalia in pediatric age, focusing on diagnosis and clinical approach in primary health care.

Results: In most cases, anomalies of the prepubertal female external genitalia are only variants of normal and/or do not significantly affect function, hence not requiring intervention other than clinical surveillance – e.g., fusion of labia minora. However, others require referral to secondary health care − like congenital vaginal obstruction or clitoral hypertrophy –, with early intervention being crucial for the success of implemented measures in some cases.

Conclusion: Genital pathology in prepubertal children is most often diagnosed by systematic and careful physical examination and usually has a favorable outcome. It is important to distinguish variants of normal from situations requiring more specialized assessment, in order to optimize health care system resources without overloading it and decrease parental anxiety.

Keywords: child; female; genitalia; urogenital abnormality

RESUMO

Introdução: Os achados no exame físico da genitália externa em crianças são frequentemente uma fonte de preocupação e ansiedade para pais e cuidadores. Devido à proximidade e papel na vigilância periódica da criança, o médico de família encontra-se numa posição privilegiada para a identificação e orientação inicial destas situações, chave para o sucesso das intervenções.

Objetivos: Rever a evidência disponível sobre as principais variações e anomalias da genitália externa do sexo feminino em idade pediátrica, com foco no diagnóstico e abordagem clínica nos cuidados de saúde primários.

Resultados: Na maioria dos casos, as anomalias prepubertais da genitália externa feminina são apenas variantes do normal e/ou não afetam significativamente a função, não necessitando de outras intervenções para além de vigilância clínica, como é o caso da fusão dos pequenos lábios. No entanto, existem outras situações que requerem referenciação para os cuidados de saúde secundários, como é o caso

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da obstrução vaginal congénita ou hipertrofia do clitóris, sendo que em alguns casos a intervenção precoce é essencial para o sucesso das medidas implementadas.

Conclusão: A patologia genital na criança pré-púbere é mais frequentemente diagnosticada através de um exame físico sistemático e cuidadoso e, na maioria dos casos, tem um resultado final favorável. É importante distinguir variantes do normal de situações que requerem avaliação mais especializada, de modo a otimizar os recursos do sistema de saúde sem o sobrecarregar e diminuir a ansiedade dos pais.

Palavras-chave: anomalia urogenital; criança; feminino; genitália

INTRODUCTION

Findings in the physical examination of the external genitalia in children are often a source of concern for parents and caregivers, not only due to the emotional significance people attribute to these structures – in part for their role in the reproductive function –, but also to the potential physical and psychological impact on the child.

Due to the role in the child's close monitoring and periodic surveillance, the family physician has a crucial role in identifying and initially guiding these situations. Physical examination is a fundamental part of the child's regular clinical evaluation and usually the most useful and effective tool for establishing a specific diagnosis. Variants of normal with maintenance of normal physiological function are the most frequent cases, not requiring intervention other than clinical surveillance and reassurance. However, some cases require medical intervention, frequently in the secondary health care setting, with early intervention being key for success of implemented measures.

As the family physician is often responsible for diagnosing these anomalies, he/she should be informed about guidelines for each particular situation, not only for reassuring parents in cases without pathological significance, but also for properly and timely referring the child to secondary health care, when necessary.

OBJECTIVES

To review available evidence and discuss the diagnosis, medical approach, and guidance at primary health care of the principal anomalies of the female external genitalia in pediatric age. Discussion of anomalies related to sexual differentiation disorders is beyond the scope of this article, since they are frequently diagnosed in hospital setting and have a highly specific approach.

CHANGES IN PHYSICAL EXAMINATION OF THE FEMALE GENITAL TRACT

Fusion/coalescence of labia minora

Fusion of labia minora, also designated labial adhesions or labial coalescence, refers to adhesion of the small vaginal labia on the midline, often in upward direction.[1] Physical examination often reveals a thin semitransparent pale membrane between the labia minora, sometimes obstructing the vaginal introitus (**Figure 1**).[2] The condition has an incidence of 1.8–3.3% at two years of age and a peak between 13 and 23 months.[3] However, several minor cases are likely to go unnoticed in regular observations, with some authors pointing real incidence rates as high as 40%.[4] Tissue hypoestrogenism, more pronounced between the age of three months and six years, seems to be the most determining factor for development of this alteration, even though studies have not yet found a clear link between hypoestrogenism and incidence of this pathology. [3]

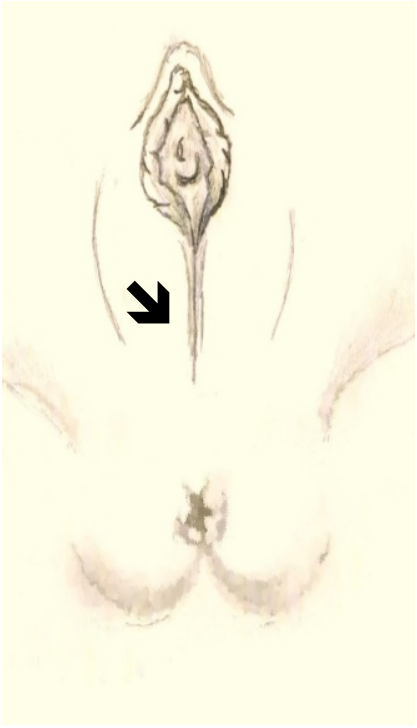

Figure 1 - Inferior labial fusion (black arrow)

Chronic vulvar inflammation, poor hygiene habits, infection, or genital trauma (including sexual abuse and female circumcision) may contribute to this alteration by acting on a hormonally propitious terrain.[5]

Diagnosis is clinical and usually asymptomatic. In some cases, the child may report local itching, pain, or genital discharge.[6]

Although rare, recurrent urinary and vulvovaginal infections are possible complications. Coalescence of labia minora may also interfere with genital hygiene.[2,3,7] Urinary changes, as vaginal reflux, have been reported in most severe cases, although urinary retention is uncommon, since urine stream passage prevents labia adhesion in the urinary meatus area.

An expectant attitude should be adopted in most cases, especially if asymptomatic and involving a small labia portion, thus not interfering with urine flux. High rate of spontaneous healing (about 80% in one year) is usually observed.[8]

In case of symptoms or complications, first-line treatment consists of application of topical estrogen 0.01% cream three times daily, applied in the fusion line with a small and downward traction massage, until adhesion resolution (usually two to four weeks).[6] Efficacy of this treatment is however debatable and probably higher in relapse prevention. Treatment is generally well tolerated and with mild side effects, such as local hyperpigmentation, vaginal bleeding, and rarely breast augmentation, which resolve with treatment discontinuation.[9] Topical betamethasone 0.05% applied in two to three cycles for four to six weeks is an effective and well tolerated treatment, with some studies reporting at least identical efficacy to local estrogen therapy.[10-11] Manual lysis is commonly performed under sedation, to avoid pain and psychological trauma, although it can be done with topical anesthesia if the child accepts and cooperates. Vaseline, estrogen cream, or local emollient application is recommended after mechanical adhesion resolution to reduce recurrence, which occurs in around 14% of cases.[12]

Hypertrophy/asymmetry of vaginal labia

Despite parents' concern, in most cases this situation is a variant of normal.

It is usually a transient finding in the newborn (edema of the labia majora), resulting from fluid accumulation in tissues.

Hypertrophy of the labia minora can be associated with difficulties in genital hygiene, pain, or use of tight clothing. Reduction labiaplasty may be indicated in some cases, due to its important impact on quality of life, comfort, and self-image, but always after menarche.[13]

Clitoris hypertrophy

Clitoral hypertrophy may be related to fetal exposure to androgens, usually resulting from congenital deficiency of cortisol synthesis enzymes in the adrenals, such as 21-alpha-hydroxylase deficiency (adrenal hyperplasia) or tumor testosterone producer. Suspected cases should first rule out sexual differentiation disturbances,[14] which require referral to specialized consultation for hormonal study.

Depending on hypertrophy degree, reduction clitoroplasty may be indicated.[15]

Congenital vaginal obstruction

Congenital vaginal obstruction is often caused by imperforate hymen (0.5:1000) or more rarely by transverse vaginal septum (1:30000 to 1:80000) (**Figure 2**), in which case is frequently associated with Mullerian anomalies.[16] Hemivagina obstruction by a longitudinal septum may also be present, a situation that may be associated with di-delphic uterus and unilateral renal agenesis (Herlyn-Werner-Wunderlich Syndrome).[17]

Diagnosis is difficult in the newborn, since an asymptomatic pattern due to mucus reabsorption is often the rule, and frequently goes unnoticed on physical examination of external genitalia.

This condition may present as interlabial cysts, especially if the obstruction is caused by an imperforate hymen, causing lower abdominal swelling.

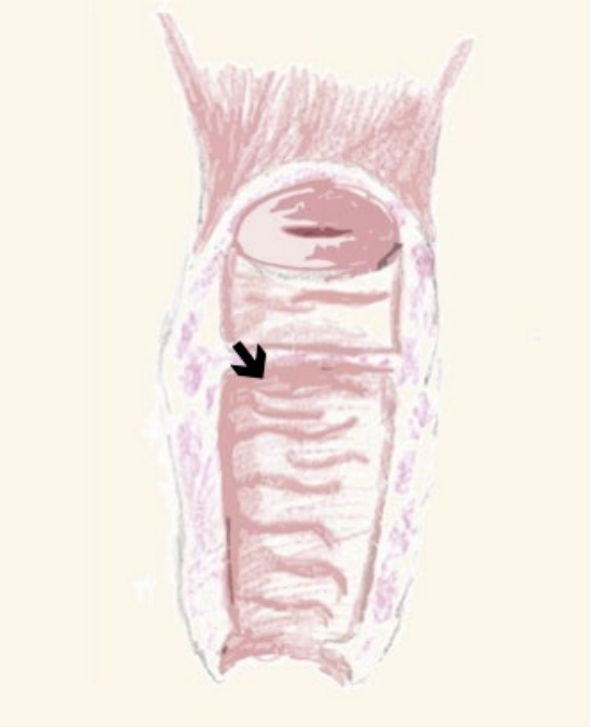

Figure 2 - Transverse vaginal septum in upper vagina (black arrow)

Ultrasound is the exam of choice and diagnosis is often established at the time of menarche. By this time, blood accumulation is present in the vagina (hematocolpos) and/or uterus (hematometra), depending on the obstruction type and location. Primary amenorrhea occurs, as well as cyclic or continuous pelvic pain, and it is often possible to see an interlabial swelling or transverse septum on gynecological examination.[18] CT or preferably MRI may be useful to characterize

the vaginal septum and associated structural abnormalities of the reproductive and urinary systems.[18,19]

Excision or incision of the hymen or transverse septum is ideally performed prior to hematocolpos or hematometra development, but preferably after tissue estrogenization.[20,21]

Genital polyps

Vaginal and hymenial polyps are rarely observed.

This condition is characterized by growth of "fingerlike" fleshy fibroepithelial tissue in the vagina or hymen, sometimes accompanied by genital discharge, being rare in newborns.[22] Without immediate indication for surgical correction, lesion biopsy or excision should be considered to exclude malignancy, namely rhabdomyosarcoma.[23]

Urethral eversion

Urethral eversion is a rare entity in girls and more frequently reported in the black race. It consists in eversion of a portion of the distal urethral mucosa through the external meatus, with a cleavage plane between the internal longitudinal and external circular-oblique smooth muscle layers of the urethra.[24,25]

Urethral eversion can occur with perineal hemorrhage due to vascular congestion of the spongy body and dysuria, and with eversion of the urethral mucosa on physical examination.

Topical estrogen twice daily for three to four weeks and two-week sitz baths may be effective in mild cases.[26,27]

Excision of prolapsed urethral mucosa and suturing of the remaining mucosa into vestibule is an option in more severe or nonresponsive cases.[28]

Vulvar cysts

Vulvar cysts are rare in pre-pubertal children and often require pediatric gynecology evaluation.

Skene cysts (para-urethral cysts) are retention cysts secondary to inflammatory obstruction of the Skene ducts (usually asymptomatic and regressing between the 4th and 8th weeks).[29,30]

Gartner cyst is a remnant of the Wolff duct, being most common in the lateral and posterior portion of the vagina.[31]

Bartholin gland cyst occurs when drainage from this gland is blocked, with subsequent inflammation.

Cysts are usually identified in physical examination and present as inter-labial masses.

Treatment is conservative in asymptomatic cases, requiring antibiotics in case of infection. Drainage/marsupialization/surgical excision may be indicated.[32]

Botryoid sarcoma

Botryoid sarcoma corresponds to an embryonal rhabdomyosarcoma subtype and is the most frequent neoplasia of the female genital tract in childhood, accounting for approximately 5% of all children malignancies.[33]

It presents as polypoid and multilobular, smooth-surface tumors often resembling a bunch of grapes, which protrude through the vagina and lead to abnormal vaginal bleeding and leucorrhea.[34]

The most common metastatic sites are the lungs, liver, and bone marrow.

Referral for biopsy and histological examination is paramount in this type of lesion, and treatment is individualized and consists of a combination of surgery, radiotherapy, and chemotherapy.[35]

Prolapse of ectopic ureterocele

Ureterocele is a cystic dilation of the terminal ureter that can dictate varying degrees of ureteral obstruction, being more frequent in girls. It is termed ectopic ureterocele when prolapse extends from the bladder neck to the urethra.

Diagnosis is often established in prenatal ultrasound and can be associated with ureteral duplication, with frequent drainage of the superior renal pole.

Ectopic ureterocele may rarely cause bilateral urinary obstruction and may insinuate through the urethral meatus, thus becoming visible on physical examination of female pediatric patients.[36,37]

Treatment is surgical, with presence of lower ureteral reflux representing an important factor determining the approach.[38-40]

CONCLUSION

Anatomic genital pathology in prepubertal children is most often diagnosed by systematic and careful physical examination and in most cases has a very favorable outcome. Although these situations cause increased anxiety in parents due to their meaning, it is the physician's role to reassure parents and clarify the condition's meaning. When necessary, implementing simple and feasible therapeutic measures in primary health care is often enough to solve the problem, which in many cases is self-limited.

It is also the responsibility of the family physician to identify situations which, due to their less favorable evolution, complexity, or potential functional or emotional impairment, require timely referral for specific diagnostic study, implementation of therapeutic measures, or even specialized surveillance.

In most cases, with implementation of the correct measures, prognosis of genital pathologies in the pre-pubertal child is favorable.

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REVIEW ARTICLES

SHARED DECISIONS IN NEONATAL INTENSIVE CARE – BIOETHICAL APPROACH

DECISÕES PARTILHADAS EM CUIDADOS INTENSIVOS NEONATAIS – ABORDAGEM BIOÉTICA

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ABSTRACT

Technological and therapeutic advances in neonatal intensive care have led to a decrease in neonatal morbidity and mortality in recent decades. Along with technical and scientific expertise, it is important to provide a holistic and comprehensive approach to the care of the newborn and family. The purpose of this review is to describe and analyze strategies to improve decision-making within a shared process between health professionals and caregivers at neonatal intensive care setting.

The decision-making process is not linear or immutable over time and there is no consensus on the definition of 'shared decision'. More unanimous is the role of communication as a atherapeutic relationship pillar. Professional ethics, bioethics, and narrative medicine should be used as tools to address the vulnerabilities of families and professionals and as a way to consolidate and structure the human relational dimension intrinsic to medical practice.

Keywords: bioethics; decision-making; narrative medicine; neonatal intensive care; newborn

RESUMO

Os avanços tecnológicos e terapêuticos em cuidados intensivos neonatais levaram a uma diminuição da morbimortalidade neonatal nas últimas décadas. A par do conhecimento técnico e científico, é importante concentrar o cuidado do recém-nascido e sua família numa abordagem holística e abrangente. O objetivo desta revisão é descrever e analisar estratégias para melhorar a tomada de decisão através de um processo partilhado entre profissionais de saúde e cuidadores no contexto dos cuidados intensivos neonatais. O processo de tomada de decisão não é linear ou imutável no tempo e ainda não existe consenso na definição de 'decisão partilhada'. Mais consensual é o papel da comunicação enquanto pilar da relação terapêutica. A ética profissional, bioética e medicina narrativa devem ser usadas como ferramentas para lidar com as vulnerabilidades de famílias e profissionais e como forma de consolidar e estruturar a dimensão relacional humana inerente à prática médica.

Palavras-chave: bioética; tomada de decisão; medicina narrativa; cuidados intensivos neonatais; recém-nascido

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INTRODUCTION

Extraordinary progress has been achieved in neonatal intensive care in recent decades, mainly due to huge technological and therapeutic advances, with consequent neonatal morbidity and mortality reduction. All this progress requires adaptation, specific training, technical skills, permanent knowledge update, protocol adjustments, and use of clinical guidelines and standards of care based on international meta-analyses and evidence-based medicine. Along with all this technical and scientific progress, it is particularly relevant to integrate and focus the care on the newborn and the family. Efforts must be made towards a more holistic and comprehensive care, greater space humanization, and improved relationship and communication between professionals and families, addressing the various (bio)ethical questions involved.

Hospitalization of a newborn in a neonatal intensive care unit (NICU) constitutes a disruptive life event with great impact on family health.[1] During this period, parents need to assume new and unknown roles under adverse conditions, such as physical separation from their baby and constraints in contact opportunities, either due to the clinical severity of the baby's condition or to maternal illness. Moreover, parents fear for the present and future life of their child, while also experiencing feelings of guilt, hope, love, and happiness.[2-4]

In Neonatology, there is often uncertainty regarding prognosis, time urgency, and two instead of one patient (the critically ill infant and the mother).[5] These circumstances raise ethical issues mainly related to withdrawing and withholding treatments during the neonatologist clinical practice. Not less relevant are health professionals' doubts, uncertainties, and emotions when exercising a highly demanding clinical activity, not only from a technical-scientific, but also emotional, relational, and psycho-social perspective.[5-8]

According to Rita Charon, skills conferred by narrative medicine, through reading, reflective writing, and decoding writing experiences, enable professionals to become more powerful readers, conscientious and attentive to their patients' narratives. These skills allow doctors to recognize suffering and to interpret and be sensitized by the story of those who suffer and people who care for them.[9,10]

OBJECTIVES

The purpose of this article is to describe and analyze strategies for improving the process of shared decisions between doctors and parents in NICU.

DEVELOPMENT

Throughout the history of medicine, physicians have taken responsibility for their patient decisions. Over the last few decades, studies have shown that patients differ in their willingness to take control of the decision and many prefer to delegate it to doctors. Decision-making in Neonatology should follow the same general principles applied to patients who cannot make decisions for themselves. Changes have occurred in Neonatology decision-making since the 1960s, when some decisions were scrutinized by government intervention and courts, as exemplified by the cases of Hopkins Baby, Baby Doe, or Baby K, among others.[8,11,12]

Nowadays, neonatologists, nurses, and parents rely on moral cumulative past experiences. Decision-making is more transparent and shared among clinicians and parents, despite its potential difficulties, especially when cultural beliefs collide. Bioethical principles help to maintain moral insight and balance in difficult decisions.[7,12] Respect for autonomy as a bioethical principle has provided the foundation for a different relationship between physicians and patients, moving from a paternalistic approach that denied patients the opportunity to take part in healthcare decisions to a dialogical one that allows for shared decision-making. This approach aligns with the concept of ethical deliberation by Diego Gracia.[13] "A procedure that aims to reach wise and prudent decisions, obliging us to take others into account, respecting their different beliefs and values, and prompting them to give reasons for their own points of view".

Several ethical guidelines recognize the importance of parental involvement in decision-making. Still, many studies based on parents' and professionals´ opinions show that it is far from being unanimous. Some professionals prefer to exclude parents from explicit participation to protect them from potential guilt feelings. Others believe parents should make the final decisions. On the other hand, some parents claim that they have to live with the consequences of decisions taken unilaterally by professionals. Most of the times, parents do not want to be excluded. Instead, due to the difficulties in decision-making, they often want to participate but not decide. Nevertheless, the type of parental involvement is influenced by their own cultural setting.[14-16]

A mother of twins suffering from twin anemia-polycythemia syndrome (TAPS) wrote: "After a routine ultrasound, when there was nothing to predict it, doctors told me that an urgent C-section had to be done. It was the worst nightmare of my life, I did not understand the reason for that decision, I did not have any pain, I did not feel bad and I did not have any signs of childbirth. I was told that one of the twins was in distress and at life risk (…) I did not know if M. would survive. The names of the exams were complicate and difficult to understand (...) sometimes doctors used a weird language. Other parents helped me understand what they were talking about."[17]

"I froze my heart and I promised that it would only restart beating when I would be able to take my baby home ... Every day I arrived at the hospital and my legs trembled. News rarely were cheerful, he had several complications due to extreme prematurity. Sometimes the silence of the doctors almost killed me. Nurses told me happy stories of little heroes and I got stronger." - narrative of a 25-week preterm mother.[17]

These narratives emphasize the importance of recognizing

the family´s understanding level and the relevance of good communication.

The American Academy of Paediatrics (AAP) indicates three key factors of good communication: the quality and quantity of information provided; the interpersonal dimension (active listening and real interest in parent´s feelings and concerns); and the bond between doctors and parents/children.[18] In the neonatal area, communication is not linear (doctors and patients). Neonatologists care for the baby and a significant part of the communicative and relational work is directed at parents - this is known as the "neonatal triangle" (doctors, newborns, parents).[19] Communication is therefore crucial to build a trusted relationship between parents and health professionals.[20] This is particularly relevant in the case of distressing news, since coping strategies can only be promoted if skillful communication takes place.[21]

The newborn's best interest has been central to decision-making. However, "best interest" definitions are ambiguous when it comes to seriously compromised newborns. In general, neonatologists are guided by bioethical principles: beneficence (do good), non-maleficence (do no harm), autonomy (respect for the right of own´s decision or, in this context, respect for parental decision), and justice (treatment equity).[7,22-24]

Each baby is unique, as each family is different and each course of life private, so there can be no absolute and rigid rules. However, to make good decisions, updated and correct data are required, as well as the ability to communicate it the best possible way. Some authors consider communication the most common "procedure" in medicine. Communication is the therapeutic relationship cornerstone, the basis of Ethics, and a physician´s fiduciary obligation to patients and their families.[21-23]

A 34-year-old vascular surgeon, mother of 30-week-preterm twins, wrote: "one Friday afternoon the doctors came and talked to me. I heard what they said and called my husband. I can´t say what I felt at that moment. My little L. had multiple brain abscesses. My husband and I had no doubts that it would be preferable for her to die ... Well, I had some (...) for a moment I thought that if they could have been wrong ... I had a bit of hope (…) my brother, a psychiatrist, came to see the baby and the ultrasound. I was not able to do it. My doubts disappeared when my husband and my brother came to see me after seeing the cerebral ultrasound. I was afraid she would survive with cerebral palsy. We baptized my baby L. and I stayed with her all afternoon in my arms while the milk flowed through me. We all stayed together, me and my husband, the doctor, and the nurse (…) I was always calm, I was there for my baby, my little one. We went home after his death, it was already night. The shift was over, but no one left".[17]

Medical decisions regarding severely ill newborns affect caregivers in an intense and profound way. There are no simple answers to help guide doctors in the difficult decisions they must make, especially when family and medical staff disagree. Adopting the shared decision model will relieve parents from the full decision responsibility and may encourage them to participate in the discussion.

There are several strategies to promote parental involvement: listening carefully (i.e., actively and intensely), using open-ended questions, sharing relevant information, giving parents time to think and reflect, and establishing a relationship of trust. The shared decision process involves at least two parties and bidirectional information. When the process is well conducted, it allows a balanced involvement of all parties, supporting both the family/baby and professionals.[11,16]

Finding balance between the respect for parental autonomy and doctor´s role and responsibility in the shared decision process requires insight, empathy, and enormous analytical and communication skills. This process has barriers and facilitators, which can be divided into knowledge, attitude, agreement, lack of expectations/hope, and behavior categories. Barriers include family characteristics, health system constrains (time, lack of medical care continuity, inadequate environmental conditions), inadequate relationships, linguistic barriers, lack of evidence to support the decision, biased attitudes, poor medical knowledge, and lack of applicability. The most common decision-making facilitators include caregivers' motivation, positive impact on the clinical process, and a correct patient prognosis definition.[11]

This process generally implies tough decisions and should hence be done in a phased manner and led by the treating doctor, who has established a trusted relationship with the family.

Narrative medicine skills could help in shared decision-making by improving communication and understanding of parents' feelings, doubts, and uncertainties, empowering parents and also helping health professionals dealing with difficult situations and dilemmas.[25,26]

Some practical aspects to consider include acknowledging the decision-making process, identifying key stakeholders, disclosing various therapeutic options in an unbiased way, recognizing the family's level of understanding and their expectations, identifying parties´ priorities and preferences, and negotiating the "non-consensual issues" in a calm and sensitive way, scheduling follow-up or revisiting the decision until the end of the process.

Decision-making is a multifaceted process. Understanding risk information depends on relationships, trust, cognitive and affective balance, life experiences, subjective outcome interpretations, risk/uncertainty tolerance, and other personal factors. Doctors will need to learn new skills to help parents understand the choices they face, clarify their own values, and make good decisions.

CONCLUSIONS

The process of shared decision-making in Neonatology setting is not straightforward. The very own definition of 'shared decision' is not yet consensual. The deliberative process requires in-depth knowledge of bioethical issues, and therefore acquiring communication skills is vital. The vulnerability of those involved (newborns, parents/family,

and health professionals) demands commitment with professional ethics, bioethics, and narrative medicine, as a way of structuring and consolidating relational and human dimensions, inherent to a medical practice of excellence.

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CASE REPORTS

SUSPECTING CLASSICAL HOMOCYSTINURIA IN AN ADOLESCENT BORN BEFORE THE NEWBORN SCREENING PROGRAM

SUSPEITA DE HOMOCISTINÚRIA CLÁSSICA NUMA ADOLESCENTE NASCIDA ANTES DO RASTREIO NEONATAL PRECOCE

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ABSTRACT

Introduction: Classical homocystinuria (HCU) is an autosomal recessive disorder caused by a deficiency in the cystathionine beta-synthase enzyme and associated with a high probability of vascular complications. Herein is presented the case of an adolescent diagnosed with HCU during cerebral venous sinus thrombosis (CVST) study.

Case Report: A 14-year-old girl presented with thrombophilia screening tests suggestive of HCU during CVST study. After referral to an Inherited Metabolic Diseases Unit, she started supplementation with pyridoxine, folic acid, vitamin B12, betaine anhydrous, and cysteine and was advised to restrict natural proteins and methionine from diet. Genetic analysis revealed a homozygous *CBS* mutation (c.572C>T (p.T191M) with c.699C>T (p.Y233Y) polymorphism.

Discussion: In adolescents born before 2004 (year of implementation of the Portuguese newborn screening program), HCU should be considered when studying hypercoagulability syndromes, as it is a treatable condition and treatment can prevent major morbidity and mortality causes.

Keywords: homocystinuria; neonatal screening; sinus thrombosis

RESUMO

Introdução: A homocistinúria clássica (HCU) é uma doença autossómica recessiva caracterizada por um défice na enzima cistationina beta-sintase, com probabilidade de ocorrência de complicações vasculares associadas. É apresentado o caso de uma adolescente diagnosticada com HCU no decorrer do estudo etiológico de trombose dos seios venosos (TSV).

Descrição do caso: Uma adolescente de 14 anos apresentou um resultado de teste de trombofilia sugestivo de HCU durante o estudo de TSV. A doente foi orientada para uma Unidade de Doenças Hereditárias do Metabolismo, onde iniciou suplementação com piridoxina, ácido fólico, vitamina B12, betaína e cisteína e foi aconselhada a restringir proteínas naturais e metionina na dieta. O estudo genético revelou uma mutação homozigótica do gene CBS (c.572C> T (p.T191M) e o polimorfismo c.699C> T (p.Y233Y).

Discussão: Os autores salientam a importância de considerar a HCU no estudo etiológico da trombofilia, principalmente em adolescentes

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nascidos antes de 2004 (ano de inclusão da HCU no rastreio neonatal), uma vez que se trata de uma doença tratável e o tratamento é capaz de prevenir as principais causas de morbimortalidade associadas.

Palavras-chave: homocistinúria; rastreio neonatal precoce; trombose dos seios venosos

INTRODUCTION

Classical homocystinuria (HCU-OMIM 236200) is a rare autosomal recessive disorder caused by a deficiency in the cystathionine beta-synthase (CBS) enzyme.[1,2] Its real worldwide prevalence is unknown but estimated to range from 1:1,800 to 1:900,000 since the condition was included in newborn screening (NBS) programs.[1]

The wide severity spectrum explains why some patients remain asymptomatic until adolescence and adulthood. Main clinical features include eye, skeleton, nervous system, and vascular system abnormalities.[1,3,4] The latter represents the major cause of morbidity and early death in untreated or poorly controlled HCU patients, with the probability of suffering from a vascular event being as high as 30% before the age of 20 and 50% before the age of 30 years.[2,3,5] Vascular complications more commonly affect the venous territory and include deep venous thrombosis, pulmonary embolism, stroke, and cerebral venous sinus thrombosis (CVST).[1] Since it may present with non-specific clinical manifestations, CVST requires a high suspicion index.

CASE REPORT

A 14-year-old girl with irrelevant past medical and familial history, normal school development, 48.8 kg of weight (P25-50), and 166.5 cm of height (P75) presented to the Emergency Department with severe frontal pulsatile headache with six days of evolution associated with occasional vomiting, neck pain, sleepiness, loss of appetite, and earache. On day one of illness, the girl was observed at the hospital and discharged 24h later after complaint resolution. On day three, she was readmitted and diagnosed with acute otitis media and discharged with antibiotics. The patient returned to the Emergency Department at day six of illness due to complaint aggravation with neck pain over the last 12h and episodes of paresthesia and loss of muscular strength in the left arm and hypovision at left.

Clinical course and investigation

On admission, physical examination (including neurologic) revealed no alterations except for left-eye blurred vision, papillary edema on both eyes, and mild neck rigidity.

Brain computed tomography angiography was performed, revealing increased density of the left transverse, superior sagittal, and straight sinus and some cortical veins with filling defect suggesting venous sinus thrombosis, associated with white matter attenuation on both sides and discrete edema of the frontal lobe.

Coagulation profile revealed normal prothrombin time and activated partial prothrombin time and markedly elevated D-dimer test (1883 ng/mL).

Anticoagulation therapy with intravenous heparin was started and the patient continued to be monitored at the High Dependency Care Unit (HDCU).

On the fourth day at HDCU, she experienced another paresthesia episode in the left arm and face, with deviation of the labial commissure to the left, which spontaneously regressed within one minute. Severe headache persisted for seven days. Brain magnetic resonance imaging (MRI) was performed on the fifth day at HDCU, showing extensive CVST affecting the superior longitudinal, straight, and left transverse sinuses and the left internal cerebral vein, with acute leukoencephalopathy signs. It also showed involvement of the right optic nerve, prompting decision to start oral acetazolamide. The heparin dosage was titrated according to coagulation profile and warfarin was initiated on day 14 to maintain an International Normalized Ratio of 2–2.5 times normal. At discharge (day 20), the patient maintained acetazolamide and warfarin. Results of thrombophilia screening tests revealed increased total homocysteine (tHcy >500 µmol/L; normal: 4–12 µmol/L) and methionine (Met; 841 µmol/L; normal: 4–44 µmol/L) and low levels of cystine (Cys; 9 µmol/L; normal: 18–122 µmol/L). Initial serum folate levels were within the normal range and vitamin B12 levels were decreased.

Due to HCU suspicion, the patient was referred to the Inherited Metabolic Diseases (IMD) consultation.

Management and outcome

At the IMD Unit, the patient initiated supplementation with cofactors involved in Met metabolism: pyridoxine (B6) 450 mg once daily, folic acid 2.5 mg daily, and intramuscular administration of vitamin B12 2.5 mg. She also received supplementation with betaine anhydrous and cystine and was advised to start a diet with restriction of natural proteins and 500 mg daily Met intake. One week later, a decrease in tHcy (206.5 µmol/L) and Met (438 µmol/L) and an increase in Cys (13 µmol/L) were observed. Supplementation with synthetic Met-free and Cys-supplemented amino acid mix was prescribed, together with caloric supplements to prevent catabolism and minimize hyperhomocysteinemia, since the patient had lost weight

and referred starvation. Genetic analysis revealed a homozygous *CBS* mutation non-responsive to pyridoxine (c.572C>T (p.T191M), with c.699C>T (p.Y233Y) polymorphism, and pyridoxine supplementation was reduced to avoid neuropathic side effects. Subsequent analytic evaluations showed a consistent tHcy decrease (<50 µmol/L) and adequate Met and Cys control.

Ten months after diagnosis, the patient remains hypocoagulated with warfarin and is gradually reducing acetazolamide, after control MRI showing edema improvement and intact optic nerve. Cardiac evaluation showed no alterations and ophthalmologic assessment revealed improvement and no evidence of *ectopia lentis*. The girl maintains periodic evaluation and compliance to dietary and pharmacologic treatment.

DISCUSSION

To the best of our knowledge, only a few reports in the literature refer to patients diagnosed with HCU during CVST study.

CVST is a rare condition most often affecting young adults, which may be secondary to head injury, infection, pregnancy, and prothrombotic conditions, as HCU. An HCU predisposing event can be identified in about 85% of CVST patients.[6] The most common clinical manifestation is headache, identified in more than 90% of patients, which is also a very common symptom in the pediatric Emergency Department, especially in adolescent girls. Therefore, the pediatrician must be aware of red flags suggesting an underlying secondary pathology that can be treatable if timely diagnosed.[6,7] In the present case, there were other signs suggestive of CVST, such as visual impairment, loss of muscular strength, and paresthesia.[6]

HCU is a multisystemic disorder characterized by eye, skeleton, central nervous system, and vascular system involvement.[1,4,8] The most prevalent associated disorders are dislocation of the optic lenses, osteoporosis and 'marfanoid' habitus, learning difficulties, and thromboembolism predisposition.[5] Although rare, HCU is the second most common treatable aminoacidopathy, with well-described natural history and prolonged asymptomatic phase. Several studies suggest that patients benefit from early treatment, reasoning its eligibility for NBS programs.[9,10] Most NBS programs use only Met concentration measurements in dried blood spot samples through tandem mass spectrometry, which is a low-specific method that identifies several benign MAT I/III deficiency forms usually requiring no specific treatment.[11] Use of a second-tier test (tHcy) enhances the specificity and positive predictive value of HCU screening and has been adopted in several NBS programs.[9,11] In Portugal, HCU was first included in NBS program in 2004 and the second-tier test in 2014 and, until the last annual report in 2018, the condition's birth prevalence was 1:624,588. All newborns were asymptomatic, started treatment, and remained asymptomatic until now. There are no known HCU missing case reports since NBS implementation, although more prospective studies are required to confirm that.[11]

HCU can present two phenotypes, defined according to pyridoxine responsiveness. In Portugal, the most prevalent CBS gene mutation is p.T191M, characterized for being B6-non-responsive.[11,12] The main treatment goal is to prevent vascular events by reducing tHcy to levels below 50 µmol/L, and in B6-nonresponsive homocystinuria compliance to dietary treatment is even more important and should be lifelong.[1]

The present patient was born shortly before the inclusion of HCU in Portuguese NBS program[13] and remained asymptomatic until the referred episode. This case highlights the importance of considering HCU diagnosis in adolescents and adults with hypercoagulability syndrome born before the inclusion of HCU in Portuguese NBS, since it is a treatable condition and early identification prevents morbidity and mortality.

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CASE REPORTS

CONGENITAL CANDIDIASIS – A DIAGNOSTIC CHALLENGE

CANDIDÍASE CONGÉNITA – UM DESAFIO DIAGNÓSTICO

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ABSTRACT

Introduction: Congenital candidiasis is a rare intrauterine infection characterized by vesicular and pustular skin lesions appearing in the first six days of life.

Clinical case: The authors describe the case of a full-term infant presenting erythematous macules, vesicles and pustules involving the trunk and extremities and cervical burn-like dermatitis at birth. Mycological skin lesion culture was positive for *Candida albicans.* Blood culture was positive for methicillin-sensitive *Staphylococcus aureus*. After systemic antifungal and antibiotic therapy was started, the newborn remained asymptomatic with lesion improvement.

Discussion/ Conclusion: Herein is reported a case of congenital candidiasis in a full-term infant, with a successful recovery. The rarity of congenital candidiasis can lead to delayed diagnosis and unnecessary treatment. This case shows that fungal infection should be considered in the differential diagnosis of vesiculopustular skin lesions in neonates. Systemic therapy should be initiated if invasive candidiasis is suspected.

Keywords: candidiasis; invasive fungal diseases; neonate

RESUMO

Introdução: A candidíase congénita é uma infeção intrauterina rara caracterizada por lesões cutâneas vesiculares e pustulares que aparecem nos primeiros seis dias de vida.

Caso clínico: Os autores reportam o caso de um recém-nascido de termo que se apresentou com máculas, vesiculas e pústulas envolvendo o tronco e extremidades e dermatite cervical de tipo queimadura ao nascimento. A cultura micológica das lesões cutâneas foi positiva para *Candida albicans* e a hemocultura foi positiva para *Staphylococcus aureus* sensível à meticilina. Após início de tratamento sistémico antifúngico e antibiótico, o recém-nascido manteve-se assintomático, com resolução das lesões.

Discussão/ Conclusão: É descrito um caso de candidíase congénita num recém-nascido de termo, que evoluiu favoravelmente. A raridade desta entidade pode levar a atrasos no diagnóstico e tratamento desnecessário. Este caso pretende alertar para a infeção fúngica no diagnóstico diferencial de exantema vesiculo-pustular em recém-nascidos. O tratamento sistémico deve ser iniciado perante candidíase invasiva.

Palavras-chave: candidíase; doenças fúngicas invasivas; recém-nascido

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INTRODUCTION

Pustular eruptions are common in the neonatal period. The differential diagnosis is varied and includes infections, benign self-limited conditions, hereditary disorders, and other diseases.[1] Differentiating between benign and transitory eruptions and severe and potentially fatal cases is crucial. Congenital candidiasis is a rare disorder included in this differential diagnosis.

Candida infection in the newborn can be divided in two forms: congenital and neonatal. Congenital cutaneous candidiasis (CCC) is an intrauterine infection and neonatal candidiasis is acquired when the baby goes through a contaminated vaginal canal. In both forms, the etiological agent is the *Candida* species, a pathogen found in the vaginal canal of at least 20% of women, rising to 30% in pregnancy.[2] Despite this, congenital candidiasis seems to be an extremely rare condition of the term or preterm newborn.[3]

Invasive candidiasis describes all disseminated *Candida* infections, including candidemia (*Candida* isolation in blood cultures) and single-organ infections. Newborns with invasive candidiasis are most often extremely premature and immunocompromised.[4] Congenital cutaneous candidiasis diagnosis is established through microscopic examination of skin scrapings and confirmed by fungal culture of lesions, umbilical cord, and/or placenta if available.[5-7]

CCC treatment remains controversial and is largely based on case reports.[4,6] The condition is topically treated with azole agents, as miconazole or clotrimazole. Lesions peel off and disappear without residue, lasting approximately two weeks. Invasive candidiasis recognition treatment initiation are crucial for prognosis. Intravenous amphotericin B is the recommended drug.[7,8]

CASE REPORT

A 3200-g term female infant was born with vacuum extraction to a 32-year-old primigravida. The mother was diagnosed with *Candida* vulvovaginitis during pregnancy and received antifungal topical treatment, without symptom resolution. Maternal serological tests and viral markers, including hepatitis B virus surface antigen (HBsAg), human immunodeficiency virus (HIV), venereal disease research laboratory test (VDRL), rubella virus and toxoplasmosis in the third trimester showed no evidence of acute infection. Maternal group B streptococcus screening was negative. Membranes ruptured four hours before delivery and amniotic fluid was reported as having foul smell. Apgar scores were 9 and 10 at 1st and 5th minutes, respectively.

At birth, the newborn had a foul smell but was otherwise well-appearing, vigorous, afebrile, and without respiratory distress. Her skin showed erythematous macules, vesicles and pustules involving the trunk and extremities, including the palms and soles. An exfoliating burn-like dermatitis was evident around the neck (**Figure 1**), with mucous membranes and skin folds being spared. The remainder physical examination was normal. After birth, the newborn was admitted to the Neonatal Care Unit for investigation and treatment. The placenta could not be recovered for macroscopic examination and culture.

Laboratory workup and serological tests were performed, viral markers were investigated, and skin, blood, and urine cultures were collected and the newborn was started on empiric treatment with ampicillin, gentamicin, and acyclovir.

Complete blood count revealed 31,580 white blood cells/µL (50.3% neutrophils and 31.9% lymphocytes). Serum C-reactive protein concentration was normal (0.10 mg/dL) and liver transaminases were also normal.

On the third day of life mycological culture of skin lesions was positive for *Candida albicans*, prompting systemic intravenous fluconazole and topical clotrimazole administration. As blood culture was positive for methicillin-sensitive *Staphylococcus aureus*, ampicillin and gentamicin were maintained for ten days. Urine Cultures were sterile. Acyclovir was suspended on the fifth day of life following negative serological tests and viral markers, including HIV, cytomegalovirus, and herpes simplex virus (HSV).

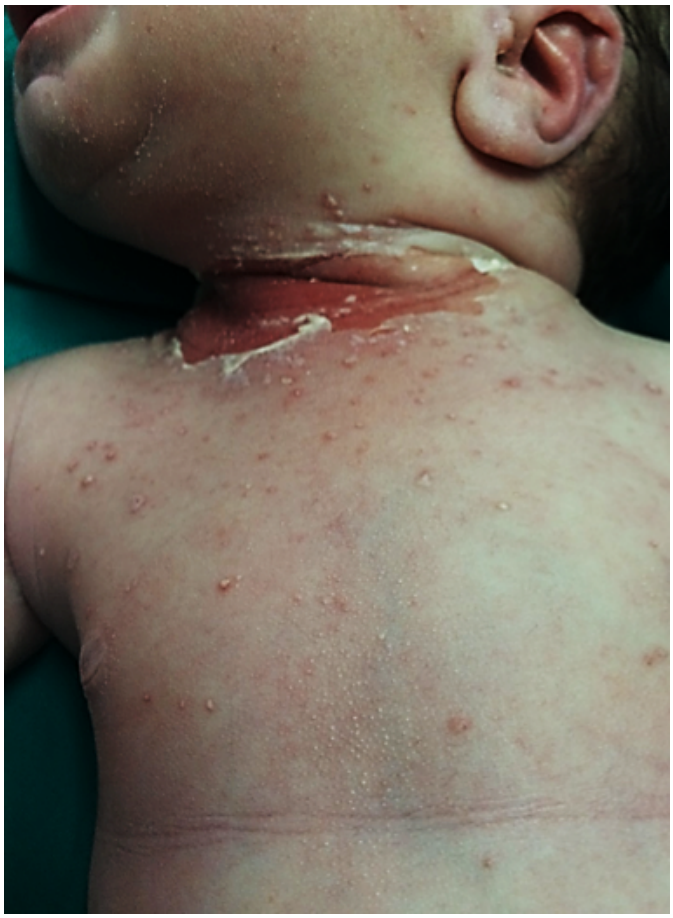

Figure 1 - Erythematous macules, vesicles and pustules involving the trunk and cervical exfoliating burn-like dermatitis

The newborn remained well and thrived. At discharge, on the 12th day of life, lesion desquamation and absence of pustules or vesicles were evident and only slight erythema was present in the cervical region (**Figure 2**). Serial laboratory workup revealed a progressive WBC count decrease (13,940/µL at discharge).

Systemic fluconazole and topical clotrimazole were maintained for a total of 21 days. On the first follow-up visit, one month after discharge, no rash or skin lesions were observed. The newborn was well, with normal growth and neurodevelopment.

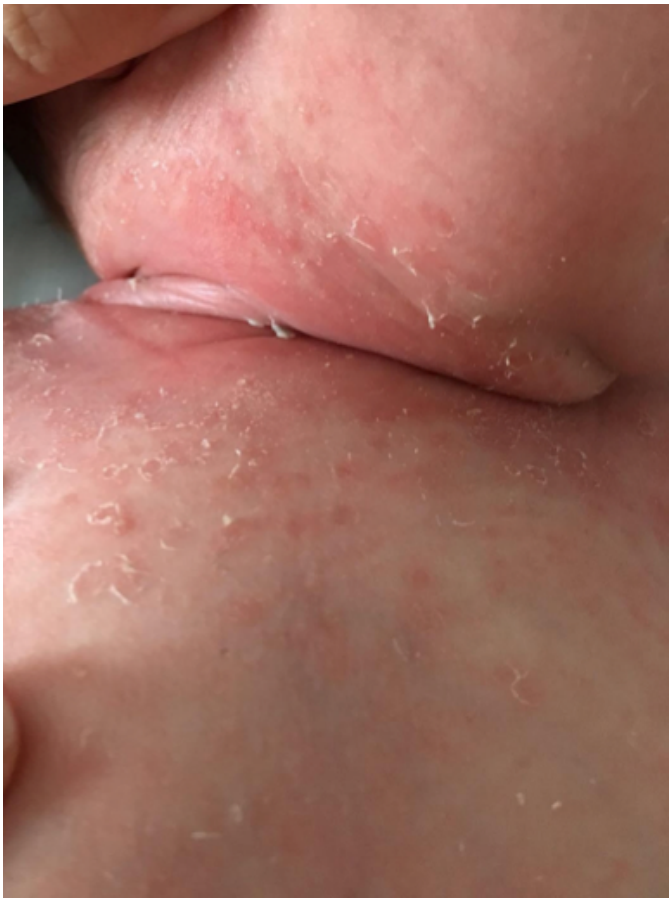

Figure 2 - Lesion desquamation and absence of pustules or vesicles at the time of discharge

DISCUSSION

Congenital cutaneous candidiasis is a rare intrauterine infection that may occur due to rise of *Candida* in the vagina, by penetrating the broken or intact pouch. Main risk factors include presence of foreign intrauterine bodies, such as intrauterine devices, or cervical cerclage.[3] *Candida* chorioamnionitis and peripheral funisitis with microabscesses are generally present.[6] Lesions are present at birth or appear in the first 12 hours to six days after delivery.[1,5] The rash generally spreads throughout the body, namely to the face, chest, back, extremities, and palms and soles, usually without oral or perineal region involvement. Lesions usually begin as macules and erythematous papules, which rapidly develop into pustules and vesicles. Rash may also develop as a bright red "burn-like" dermatitis, usually associated with positive cerebrospinal fluid, blood, and urine culture.[4] Marked peeling with crusty exfoliations follows the acute phase.[1]

This type of candidiasis should be considered in the differential diagnosis of generalized neonatal maculopapular or pustular skin eruptions, along with other disorders such as *Listeria monocytogenes* infection, impetigo, varicella, herpes virus infection, syphilis and epidermolysis bullosa.[1] For this reason, an extensive workup including laboratory and serology tests and cultures should be performed.

Although in this newborn skin lesions and maternal history of *Candida* vulvovaginitis were suggestive of congenital candidiasis, empiric treatment with antibiotic and antiviral agents was immediately started for other more common conditions, that can become severe when left untreated, including infectious causes of vesiculopustular skin lesions, as impetigo, group B streptococcal infection, varicella, and primary herpes virus infection. Additionally, foul smell at birth in an asymptomatic newborn and high WBC count (31,580/ µL) raised suspicion of an infectious cause. Because the newborn remained asymptomatic and there were multiple vesicles at the puncture site, lumbar puncture was not attempted in this case.

Cutaneous congenital candidiasis was confirmed after positive skin scraping culture for *Candida albicans*. Unfortunately the placenta could not be recovered for examination and culture to corroborate diagnosis.

It is acknowledged that the clinical course in full-term infants with congenital candidiasis and skin involvement only is often benign and the optimal treatment choice remains controversial.[5] Systemic involvement is rare and more likely in extremely- and very-low-birth-weight (ELBW and VLBW) infants. An estimated 5 – 20% of ELBW newborns develop invasive candidiasis.[7] Other factors that increase the risk of systemic disease include extensive instrumentation in the delivery room, invasive procedures on the neonate, and an altered immune response.[5] Candidemia cannot be distinguished from bacteremia presentation easily, because signs and symptoms are often nonspecific and subtle and may include fever, lethargy, apnea, hypotension, respiratory distress, abdominal distension, hypertension, and poor feeding. [4] Definitive invasive candidiasis diagnosis requires organism isolation from a typically sterile body fluid or tissue (e.g., blood, cerebrospinal fluid, bone marrow, or biopsy specimen). However as blood culture is only 50% sensitive in some settings, a negative *Candida* species culture result does not exclude invasive infection.[7]

Systemic antifungal therapy should be considered in preterm newborns with VLBW and in all infants with respiratory distress and/or laboratory signs of sepsis, such as elevated WBC count with increase of immature forms or persistent hyperglycemia and

glycosuria. *Candida* isolation from blood, urine, and/or cerebrospinal fluid cultures and/or presence of burn-like dermatitis should prompt systemic treatment.[4,5]

In the present case, a high WBC count, burn-like dermatitis, and instrumentation in the delivery room (vacuum suction) raised suspicion of invasive candidiasis. For this reason, systemic fluconazole in association with topical clotrimazole was started, even though the neonate was asymptomatic and blood and urine cultures were negative for *Candida*. Because the clinical course was benign and laboratory workup showed disease improvement, no other investigations, such as imaging exams, were performed. Nevertheless, target organ damage should be investigated in invasive candidiasis, namely through ophthalmologic examination and head, renal, and hepatic ultrasound. [4]

Ampicillin and gentamycin were maintained, as blood culture for methicillin-sensitive *Staphylococcus aureus* was positive. *Staphylococcus aureus* infection can also present as vesicle-pustular skin lesions or bullae that rupture easily, commonly found in areas of trauma, such as the diaper area and skin folds.[1]

Amphotericin B deoxycholate (d-AMB) is the drug of choice for the treatment of neonates with systemic candidiasis, including meningitis. In candidemia, fluconazole is an alternative to d-AMB, provided the species is susceptible. The recommended treatment duration for uncomplicated candidemia is two weeks.[6-8] In the present case, the benign disease presentation in a full-term newborn, led to the choice for fluconazole, which does not require prolonged venous access.

Most newborns, particularly full-term, follow a benign course and recover without long-term sequelae. On the other hand, invasive candidiasis is associated with prolonged hospitalization and neurodevelopmental impairment or death in almost 75% of affected ELBW infants.[7]

This report describes a case of congenital cutaneous candidiasis and *Staphylococcus aureus* bacteremia in a full-term infant, with successful recovery after treatment initiation. CCC rarity can lead to delayed diagnosis and unnecessary treatment and this report highlights that fungal infection should be considered in the differential diagnosis of vesiculopustular skin lesions in neonates. Due to the condition's poor prognosis, systemic treatment should be initiated if invasive candidiasis is suspected.

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CASE REPORTS

CASTLEMAN DISEASE. A RARE DIAGNOSIS IN CHILDHOOD

DOENÇA DE CASTLEMAN. UM DIAGNÓSTICO RARO NA INFÂNCIA

Sara Monteiro Cunha[1], Sofia Vasconcelos[1], Cláudia Neto[1], Tereza Oliva[2], Miguel Salgado[1]

ABSTRACT

Introduction: Castleman Disease (CD) is a rare polyclonal lymphoproliferative disorder characterized by massive growth of lymphoid tissue. The most common sites of disease are the chest, abdomen, neck, and axilla. Excisional biopsy is mandatory for diagnosis, and complete surgical resection the gold-standard treatment in unicentric CD.

Case report: A ten-year-old girl was observed at the Emergency Department with sore throat and fever. Oropharynx examination revealed inflamed tonsils, with no exudates. Enlarged lymphadenopathy was palpable in the right supraclavicular fossa. Ultrasound revealed right supraclavicular lymphadenopathy with loss of adipose hilum and histopathologic assessment established CD diagnosis.

Discussion/Conclusion: Lymphadenopathy is a common presentation in children, usually benign and self-limited. But it may also be a sign of underlying malignancy. Any lymphadenopathy in the supraclavicular fossa is worrisome and requires prompt investigation. CD diagnosis may be challenging, due its rare nature in childhood and nonspecific symptoms.

Keywords: Castleman disease; childhood; lymphadenopathy

RESUMO

Introdução: A doença de Castleman (DC) é um distúrbio linfoproliferativo policlonal raro caracterizado por crescimento anormal de tecido linfóide. Os locais mais comummente afetados são o tórax, abdómen, pescoço e axila. A biópsia excisional é mandatória para o diagnóstico e a resseção cirúrgica é o tratamento de eleição na forma unicêntrica.

Caso clínico: Uma criança de dez anos de idade, do sexo feminino, foi observada no Serviço de Urgência por odinofagia e febre. Ao exame físico, apresentava rubor amigdalino sem exsudados e adenomegalia palpável na região supraclavicular direita. A ecografia cervical confirmou linfoadenopatia com perda do centro adiposo e o exame histopatológico foi compatível com DC.

Discussão/Conclusão: As adenomegalias são uma apresentação comum na infância e geralmente benignas e auto-limitadas. Contudo, poderão ser um sinal de neoplasia. Uma adenopatia na região supraclavicular é preocupante e requer investigação atempada. O diagnóstico de DC é desafiante, devido à sua raridade em idade pediátrica e sintomas inespecíficos.

Palavras-chave: adenopatia; doença de Castleman; infância

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INTRODUCTION

First described in 1954 and better classified by Benjamin Castleman in 1956, Castleman Disease (CD) is a polyclonal lymphoproliferative disorder characterized by massive growth of lymphoid tissue, with several different characteristic histopathologic variants.[1,2] Although rare in the pediatric population, its exact prevalence remains unknown.[3] The pathogenesis of CD is poorly understood, although reaction to a chronic viral antigenic stimulation has been proposed as possible underlying etiology.[3,4] Talat *et al* reported a slightly increased incidence of CD in female patients in the early decades of life and in male patients in the second half of life.[5] However, Rabinowitz *et al* showed that, in pediatric populations, the male-to-female ratio was approximately 1:1.[3] Early literature on CD was based on a very limited number of cases and the condition was traditionally classified by its centricity as unicentric CD (UCD) – usually one lymph node or a single lymph node region affected – or multicentric CD – two or more lymph nodal groups affected.[2,5] However, the more recent classification system categorizes CD based on histopathologic findings in hyaline vascular CD, plasma cell CD, mixed variant (with features of both previous variants), and plasmablastic variant (with plasma cell features and plasmablasts).[2,3] Recently, three entities emerged in CD classification, with multicentric CD further subdivided in human herpesvirus-8 (HHV8)-positive or HHV8-negative according to presence or absence of HHV8 infection, and UCD remaining a single entity.[2] Patients diagnosed with UCD are commonly asymptomatic or display signs or symptoms related to compression of adjacent structures.[4] CD may occur anywhere in the lymphatic system, but in pediatric age the most commonly affected sites are the chest, followed by the abdomen, neck, and axilla.[3] The outcome is not influenced by location of the affected lymphadenopathy.[1] Although useful for excluding other diagnoses far more common in childhood, blood analyses and imaging findings are not helpful for diagnosing CD.[3] An excisional biopsy of the most abnormal lymph node is mandatory to diagnose CD by histopathologic review.[4] Complete surgical resection of the affected lymph node is considered the gold-standard treatment in UCD, with recurrences occasionally reported.[4] Some case reports document gradual spontaneous improvement to even complete remission without treatment.[1] In the pediatric population, CD often holds favorable prognosis, particularly in cases of hyaline-vascular CD subtype.[3]

CASE REPORT

A ten-year-old Caucasian girl was observed at the pediatric Emergency Department (ED) with complaints of recent-onset sore throat and fever. Medical history was unremarkable, except for recurrent tonsillitis and a history of suspected penicillin allergy. Her two-year-old sibling had been diagnosed with acute viral tonsillitis three days earlier. The girl's general appearance was good. Oropharynx examination revealed inflamed tonsils with no exudate. The girl presented five lymph nodes bilaterally on the neck (the largest with 2–2.5 cm), with no tenderness on palpation or overlying erythema. Additionally, an enlarged lymph node with rubbery consistency measuring 2 cm in diameter was palpable in the right supraclavicular fossa. No other significant lymphadenopathy was identified. The girl had no respiratory distress and pulmonary auscultation was normal. The abdomen was soft, with normal bowel sounds, non-palpable liver and spleen, and no abdominal masses. No recent travel abroad, previous medication history, animal exposure (namely cats), or tuberculosis contact were reported. The girl had complete routine immunisation vaccine schedule. Initial laboratory data included complete blood count, with white cell count of 12.500/µL (68.3% neutrophils, 22.4% lymphocytes, and 8.8% monocytes), hemoglobin of 13.1 g/dL, hematocrit of 37.5%, and platelet count of 184.000/µL. Erythrocyte sedimentation rate was 22 mm/h, C-reactive protein was 33.5 mg/L, and lactate dehydrogenase and uric acid levels were normal for age. Rapid antigen test in the oropharynx to detect group A streptococcal infection was negative. Serological tests for Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* were negative for IgM antibodies, and human immunodeficiency virus was also negative. No mediastinal enlargement was detected in chest radiograph. Cervical ultrasound showed numerous lymph nodes in the anterior cervical area bilaterally (the largest with 45x13 mm in diameter) and a right supraclavicular lymphadenopathy (with 18x9 mm in diameter), suggestive of reactive lymph node. Abdominal ultrasound revealed splenomegaly with 12.2 cm of diameter (normal range, 6.8–11.4 cm).

Considering bacterial lymphadenitis as the most probable diagnosis, an empiric course with azithromycin (10 mg/kg once daily, 7 days) was prescribed. One week later, the patient was afebrile and asymptomatic, but still maintained a palpable supraclavicular lymph node with similar size. A new cervical ultrasound showed persistent adenopathy with loss of adipose hilum. The patient was referred to the pediatric Oncology Unit for lymph node fine-needle aspiration (FNA) biopsy. Smears showed a polymorphic population of lymphocytes, immunoblasts, and lymphohistiocytic aggregates, suggestive of reactive lymphadenitis. Four weeks later, as no lymph node size regression was observed, an excisional biopsy was performed. Histopathologic assessment showed occasional vascular proliferation and hyalinization of vessel walls and germinal centres traversed by penetrating vessels, and expansion of the mantle zones with lymphocytes arranged in layers. The lymphatic follicle contained more than one germinal centre (2 to 3) and immunohistochemistry study (CD20, CD3, CD10, Bcl-2, CD21, Kappa, and Lambda) was not compatible with malignancy. These features confirmed CD hyaline-vascular subtype diagnosis. Whole-body 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) scan excluded other hypermetabolic lesions. The child was diagnosed with UCD and, after six months of follow-up, she was asymptomatic, with no palpable lymphadenopathies, and normal abdominal ultrasound.

DISCUSSION/CONCLUSIONS

The lymphatic system is an important component of the immune system and lymphadenopathy is a common presentation in children seeking medical support. In the pediatric population, lymphadenopathies are usually secondary to a benign and self-limiting infection.[9] Either viral or bacterial infections may lead to localized lymphocyte and macrophage responses, causing lymph node swelling.[6] However, they may occasionally indicate presence of more serious underlying conditions.[10] A palpable lymph node in the supraclavicular fossa is worrisome and requires further investigation, as it is often associated with malignancy in children. Right supraclavicular adenopathy is linked to mediastinal cancer, whereas left supraclavicular suggests intra-abdominal cancer.[11] Castleman disease, or angiofollicular lymph node hyperplasia, comprises a diverse group of lymphoproliferative disorders.[4] CD diagnosis is challenging, as patients are commonly asymptomatic and therefore underdiagnosed or misdiagnosed. Although rarely, these patients may develop systemic symptoms or signs – including night sweats, fever, weight loss, fatigue, enlarged liver or spleen, or skin findings as violaceous papules – or symptoms related to compression of adjacent structures (as the airway or vessels) by the enlarging mass.[4] Laboratory tests are often unremarkable in UCD patients, although they may occasionally exhibit blood workup abnormalities, such as elevated inflammatory parameters, anemia, thrombocytopenia or thrombocytosis, renal dysfunction, or polyclonal hypergammaglobulinemia.[4] Nonspecific lymphoid hyperplasia is a common finding in FNA biopsy. While useful in excluding other diagnoses, FNA unlikely establishes CD diagnosis.[3]

Excisional biopsy of the lymph node is the gold-standard procedure, since it is both diagnostic and therapeutic and complete surgical resection is the only significant predictor of survival.[4] Lymphadenopathy location may prevent a safe surgical procedure if the mass is adjacent to a main bronchus or major blood vessels. In these cases, as removal might be life threatening, some authors recommend embolization or using rituximab to convert the lymph node into a resectable mass.[4] Usually, death due to UCD is a rare event and life expectancy after CD diagnosis remains unchanged.

In the present case, the patient sought medical support due to fever and sore throat. Recent symptom onset and oropharynx examination findings suggested viral infection as the most likely diagnosis, enhanced by a history of contact with viral tonsillitis of the sibling. However, detailed physical examination enabled detection of a lymph node in the supraclavicular fossa. Presence of fever and characteristics of this adenopathy prompted further investigation. Initial findings in neck ultrasound and chest radiograph suggested a benign disorder. Laboratory tests showed elevated inflammatory parameters, common in the setting of tonsillitis infection. Considering a possible bacterial lymphadenitis, the child was discharged from the ED with antibiotic prescription. Since the most common organisms implicated are *Staphylococcus aureus* and group A streptococcus, first-line empiric treatment should be an association of penicillin-like antibiotic and beta-lactamase inhibitor or first- or second-generation cephalosporin. However, due to suspicion of penicillin allergy, a macrolide was prescribed. Despite general condition recovery and symptom resolution, persistence of the abnormal lymph node in the supraclavicular fossa, combined with new ultrasound findings, prompted referral for biopsy in the Oncology Unit. FNA results suggested reactive lymphoid hyperplasia, a common and inconclusive finding, and reasoned for a wait-and-see approach. The observation of stable findings one month later argued in favor of excisional biopsy, and histopathologic assessment established CD diagnosis.

After complete lymphadenopathy surgical removal, the child was assessed for systemic involvement. 18F-FDG PET scan excluded additionally affected lymph nodes, confirming the surgical procedure effectiveness. Although complete removal of affected lymphadenopathies is associated with low recurrence rates, long term follow-up of these patients is still mandatory.

Because CD is an uncommon entity in childhood and may be associated with nonspecific symptoms, it is often underdiagnosed or misdiagnosed as infectious or inflammatory disease, a more common entity in pediatric age.[3]

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CASE REPORTS

PRECONCEPTIONAL IMMUNITY AND CONGENITAL CYTOMEGALOVIRUS INFECTION – A SEROLOGIC PITFALL

IMUNIDADE PRÉ-CONCECIONAL E INFEÇÃO CONGÉNITA POR CITOMEGALOVÍRUS – UMA ARMADILHA SEROLÓGICA

Joana da Silva Ferreira[1], José Luís Fonseca[2], Maria João Vieira[2]

ABSTRACT

Congenital cytomegalovirus infections are the most prevalent intrauterine infections worldwide and result from maternal primary or non-primary infections. Diagnosis of primary cytomegalovirus infection during pregnancy is considered reliable and mainly relies on maternal serology. However, diagnosis of non-primary cytomegalovirus infection is more questionable. Herein is reported the case of a 34-week-old male newborn with congenital cytomegalovirus infection of a mother with preconceptional immunity. The organism was identified in urine by polymerase chain reaction in the first week of life. Maternal peripartum serology was the same as prior to conception. This case highlights the pitfalls of cytomegalovirus serology interpretation in non-primary infection during pregnancy. Clinicians should be aware of this and consider congenital cytomegalovirus infection, particularly when suggestive signs are present.

Keywords: cytomegalovirus; congenital cytomegalovirus infection; serology

RESUMO

As infeções congénitas por citomegalovírus são as infeções intrauterinas mais prevalentes em todo o mundo e resultam de infeções primárias ou secundárias. O diagnóstico de infeção primária por citomegalovírus durante a gravidez assenta na serologia materna, sendo considerado um método fiável. No entanto, o diagnóstico de infeção secundária é mais complexo. É apresentado o caso de um recém-nascido prematuro de 34 semanas, do sexo masculino, com infeção congénita por citomegalovírus, cuja mãe apresentava imunidade pré-concecional. O diagnóstico no recém-nascido foi confirmado por deteção do vírus na urina através da técnica de PCR (*polymerase chain reaction*) na primeira semana de vida. A serologia materna periparto foi semelhante à pré-concecional. Este caso alerta para possíveis armadilhas na interpretação da serologia de citomegalovírus na infeção secundária durante a gravidez. Os clínicos devem estar alerta para esta situação e considerar o respetivo diagnóstico, particularmente perante sinais sugestivos de infeção.

Palavras-chave: citomegalovírus; infeção congénita por citomegalovírus; serologia

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INTRODUCTION

Cytomegalovirus (CMV) has been identified as an important viral pathogen in humans for more than a century. CMV histopathology was first described in 1904, but it was not until 1957 that the virus was isolated by Craig *et al*.[1] CMV is a member of the human herpesvirus family and infects multiple human cell types, including fibroblasts, epithelial cells, endothelial cells, macrophages, and myocytes. Over the last several decades, the prevalence and relevance of CMV as a human pathogen became more apparent. Congenital CMV (cCMV) infection occurs frequently. Birth prevalence is around 1% and 11% of infants are symptomatic at birth.[1,2] CMV infection is the most common cause of nonhereditary sensorineural hearing loss. In addition to congenital and perinatal infection, CMV is associated with significant morbidity in immunocompromised patients, including chorioretinitis, pneumonia, colitis, and neuropathy.[1] During pregnancy, CMV transmission can occur due to maternal primary infection in previously seronegative women or after a non-primary infection (reactivation or reinfection by a new viral strain) in women with preconceptional immunity.[3] In proven cases of CMV non-primary infection (NPI) very different serologic and molecular patterns may be observed and routine serologic testing may fail to assist in diagnosis.[4,5] This case report illustrates pitfalls of serologic analysis in CMV NPI and discusses the respective underlying rationale.

CASE REPORT

A 37-year-old mother delivered a male infant after 34 weeks by cesarean section. Maternal CMV serology prior to conception showed positive immunoglobulin (Ig) G (15.3 AU/mL; reference value <1.1) and negative IgM (0.438 index; reference value <1.1), indicating CMV infection in the past. Other serology tests, including hepatitis B virus surface antigen, human immunodeficiency virus, venereal disease research laboratory, rubella virus, and toxoplasmosis in all trimesters showed no evidence of acute infection. Routine ultrasound (US) screening revealed fetal echogenic bowel at 20 weeks of gestation (WG) and fetal growth restriction with absent diastolic flow in the umbilical artery at 33+5 WG. At that time, the mother was admitted for observation and administration of antenatal corticosteroids for fetal lung maturation. The boy was born four days later, with Apgar scores of 6 and 9 at 1 and 5 min, respectively, with a birth weight of 1780 g in the 10th percentile (P10), 42 cm of length (P10), and 31 cm of head circumference (P50). He was admitted to the Neonatal Intensive Care Unit with respiratory distress and initially treated with nasal continuous positive airway pressure (nCPAP) during the first six hours of life, receiving a mean airway pressure of 6 cm H_2O and with an oxygen requirement of 21%. On day one of life, diffuse jaundice, petechiae on trunk and limbs, and hepatosplenomegaly were observed on physical examination. Laboratory studies showed decreased platelet count (105,000/µL) and hyperbilirubinemia (total bilirubin level at 9.7 mg/L). Based on physical and laboratory findings, cCMV infection was suspected. At this time, due to risk of CMV transmission through breast milk, the mother was advised to stop breastfeeding. A preterm infant formula was started and maintained until peripartum maternal serology results were known. Abdominal US performed on the second day of life confirmed hepatosplenomegaly and cranial US revealed enlargement of lateral ventricles (right ventricle = 13.3 mm; left ventricle = 11.3 mm). Urine CMV PCR testing was positive, confirming cCMV infection, with a peripheral blood viral load higher than 5,000 copies/mL. Maternal serology at the time of diagnosis was the same as prior to conception, with negative IgM and no elevation of IgG titers. Ophthalmological evaluation of the newborn performed on the ninth day of life was normal, but neonatal hearing screening revealed lack of bilateral response. Due to auditory and neuroimaging (cranial US) findings, the child started antiviral treatment with oral valganciclovir (16 mg/kg per dose every 12 hours), with neutropenia (absolute neutrophil count of 600/uL) as the only side effect detected on the seventh day of treatment. Evolution was marked by good clinical and biological improvement, with jaundice and petechiae regression and platelet count increase to normal levels on the 16th day of life. Brain magnetic resonance imaging (MRI) performed on the 20th day of life showed diffuse hypersignal along the cerebral hemispheres on T2-weighted images, especially in the temporo-parietal regions. Lateral ventricles were large, with no signs of intraventricular tension. No calcifications or other abnormalities were identified. Antiviral *therapy* was administered for *six months*.

Regular follow-up visits have been conducted since discharge. On the second month of life, mild bilateral sensorineural hearing loss (15%) was detected. At four months of age, the patient was fully recovered from hearing loss Brain MRI was repeated at twelve months of age, showing multiple white matter hyperintense lesions on T2-weighted sequences and FLAIR sequences on *both cerebral hemispheres*, mainly in the corona radiata and temporal regions, associated with ventriculomegaly. These findings were consistent with sequelae from cCMV infection (**Figure 1**). The boy is currently seventeen months old and presents normal hearing and ophthalmological and neurodevelopment evaluation.

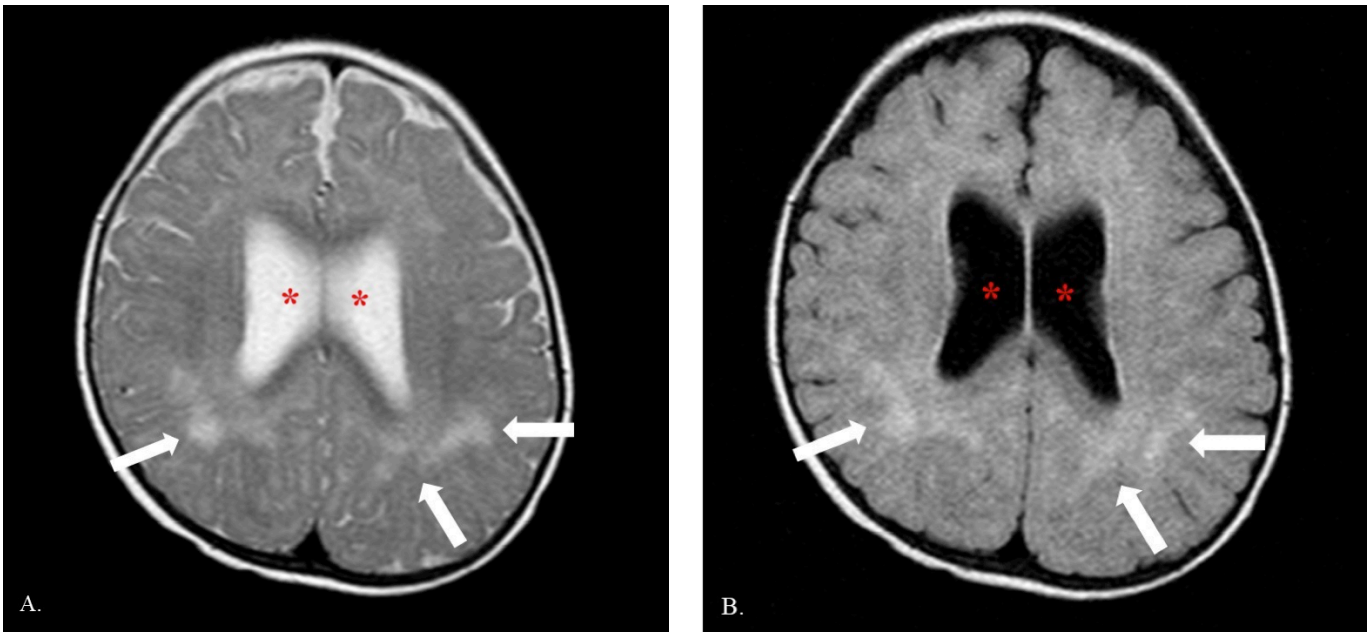

Figure 1 - Brain MRI findings. T2-weighted (A) and FLAIR (B) images showing multiple white matter hyperintense lesions (arrows) combined with ventriculomegaly (asterisks).

DISCUSSION

Exposure to CMV can occur from almost all body fluids.[1] CMV can be maternally transmitted during pregnancy or perinatal period from exposure to genital secretions during delivery. In addition, the infection can occur postnatally after exposure to human milk, blood products, or community sources.[1] Very premature babies are at higher risk of symptomatic CMV infection acquired from human milk, due to their immature immune system and paucity of maternal antibodies.[6] Postnatal CMV infection in this population can present as sepsis-like illness, including respiratory symptoms (pneumonitis), hepatomegaly, thrombocytopenia, neutropenia, and lymphocytosis.

During pregnancy, CMV transmission can occur due to maternal primary infection in previously seronegative women. Alternatively, in women who are seropositive before pregnancy, cCMV infection may result from reactivation or acquisition of a new CMV strain.

It was previously believed that non-primary infections had a low transmission rate due to preconceptional immunity. However, it has been recently reported that cCMV infection can occur more often in infants of preconceptionally seropositive women.[3,7]

Sensorineural hearing loss, the main long-term complication of this congenital infection, occurs in 12.6% of all cases (18% of symptomatic and 9% of asymptomatic infants).[8] It is estimated that one in every five cases of pediatric sensorineural hearing loss is due to cCMV infection. Prognosis improves with earlier infection detection and intervention, thereby making it potentially preventable or treatable.[9]

Despite detailed knowledge about the epidemiology and pathogenesis of this disease, CMV screening during pregnancy remains controversial. Testing costs, the high proportion of asymptomatic infants, potentially adverse psychosocial effects, and absence of effective preventive measures against fetal transmission are acknowledged barriers to screening implementation. Because of this, asymptomatic cases not identified at birth may be diagnosed too late to initiate antiviral therapy, which is associated with beneficial effects on hearing and neurodevelopment if initiated within the first month of life.[9]

In Portugal, the Directorate-General of Health (DGS) recommends preconceptional screening of CMV-specific antibodies which, in cases of clinical or ultrasonographic primoinfection suspicion, enables comparing laboratory values and facilitates diagnostic procedures.[10]

The gold standard in the serological diagnosis of primary CMV infection is maternal seroconversion based on detection of IgG antibodies against CMV or presence of serum anti-CMV specific IgM antibodies combined with low-avidity anti-CMV IgG antibodies.

IgG antibodies show low antigen avidity during the early weeks after primary infection. They progressively mature, initially acquiring moderate and then high avidity. This process reflects immune response maturation, with high-avidity IgGs maintained for many years.[11] Therefore, low CMV IgG avidity is an accurate indicator of primary infection within the preceding three to four months, whereas high avidity can be considered a good indicator of non-primary infection or past infection.

Early cCMV diagnosis following non-primary maternal infection is difficult in both the prenatal and postnatal periods due to ambiguous interpretation of maternal serology and fetal US and to non-specific neonatal presentation.[4,12] In most series, diagnosis of recurrent

infection is based on an increase of CMV IgG titer (along with high CMV IgG avidity index) and/or positive CMV IgM. However, positive CMV IgM and significant CMV IgG raise can be observed in other, much more frequent clinical situations than CMV NPI: nonspecific immune system stimulation, maternal auto-immune disorders, and other cross-reacting herpetic infections.[13,14] Additionally, according to the literature, in proven cases of maternal CMV NPI, very different serologic and molecular patterns may occur: positive or negative CMV IgM, significant CMV IgG raise or stability, positive or negative blood viral load, or fluctuant CMV IgG avidity.[4] This explains why routine serologic testing may fail to help diagnosis, and disease identification can be challenging based on this approach. The number of seropositive women with NPI during pregnancy is in fact unknown.[15-17] Another unresolved issue is whether transplacental transmission is most often consecutive to reactivation or reinfection.

In the present case report, no CMV IgG titer increase was observed and IgM titers remained negative in the peripartum period. The authors believe that this fact was probably due to virus reactivation during pregnancy. Indeed, the immune system may have not been stimulated in this patient because the CMV strain responsible for NPI was the endogenous one.[4]

The fetal compartment can be studied through non-invasive (US) and invasive (amniocentesis) methods. The latter should be carried out more than 6 weeks after the presumed maternal infection and after 20–21 weeks of gestation.[5,18] Multiple US changes can be found in infected cases, including periventricular calcification, cerebral ventriculomegaly, echogenic bowel, or fetal growth restriction (FGR). However, US sensitivity is poor, allowing to correctly identify no more than 20% of infected infants.[19] Fetal echogenic bowel is a nonspecific marker commonly observed in normal fetuses that may confuse or mask cCMV infection diagnosis, as in this case. In contrast, amniocentesis followed by real-time PCR provides an optimal means for diagnosing fetal infection, with good specificity and sensitivity (92–98% and ≈90%, respectively).[20] However, the pros and cons of this invasive procedure should be discussed on a case by case basis.

After birth, cCMV is diagnosed through identification of the viral genome in urine, blood, saliva, or cerebrospinal fluid in the first three weeks of life.[9]

In the present case, the combination of prenatal (echogenic bowel and FGR), clinical (petechiae, jaundice, and hepatosplenomegaly) and laboratory (t*hrombocytopenia* and hyperbilirubinemia) findings raised suspicion of cCMV diagnosis. The decision to initiate antiviral treatment was based on neuroimaging findings (even though they were not pathognomonic) together with auditory findings.

No antiviral drugs are currently licensed for cCMV treatment.[21] Expert recommendations are based on two randomized controlled trials (RCTs) of six weeks of ganciclovir and in one RCT of six months of valganciclovir.[22,23] Due to lack of evidence from a significant number of RCTs, the literature is unclear on whether mild and asymptomatic cases and those with isolated hearing loss should receive antiviral therapy.[9]

Much of the debate around treating less severely affected babies relates to the potential side effects of current antiviral drugs. Significant neutropenia is frequently observed in infants undergoing antiviral treatment. This is less commonly reported with valganciclovir than with ganciclovir (21% vs 65%) and generally occurs during the first month of treatment, as in the present case.[21]

The pathological neuroimaging findings in this patient at 12 months of age raised the possibility of worse prognosis in absence of treatment. Despite these changes, the child displayed normal neurodevelopment. Additionally, this case also highlights the unpredictability and great individual variability of CMV infection.

It should be reinforced that all women who are or intend to become pregnant, especially those who contact with young children, are at increased risk of CMV exposure and should be educated that the risk of infection can be significantly reduced by safe-handling techniques, such as use of latex gloves and rigorous hand washing after handling diapers or following exposure to respiratory secretions.[24]

CONCLUSION

In conclusion, this case highlights the pitfalls of CMV serology interpretation in non-primary infection during pregnancy. Since preexisting maternal CMV immunity provides incomplete protection, cCMV should be considered in fetuses or newborns with suggestive signs of infection, even in preconceptionally seropositive mothers, as early diagnosis has the potential to reduce the risk of negative outcomes.

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IMAGING CASES

DERMATOLOGY CLINICAL CASE

CASO CLÍNICO DERMATOLÓGICO

Cátia Vilas Boas Leitão[1], Isabel Ayres Pereira[1], Joana Tenente[1], Marta Vila Real[2], Ana Oliveira[3], Ana Luísa Leite[4]

A four-month-old girl was observed at the Emergency Department due to an acute bacterial conjunctivitis. The patient had no other complaints and no relevant prior medical history. Physical exam revealed hyperpigmented macular lesions in the lower limbs (**Figure 1**) and hyperpigmented and papular lesions in the abdominal region, disposed according to Blaschko's lines (**Figure 2**). The mother mentioned presence of cutaneous lesions in the same locations since birth, which progressively changed appearance and became hyperpigmented.

The child had normal growth, psychomotor development, and neurological examination. Family history was also unremarkable, with no parent displaying similar lesions.

The patient was referred to Pediatric and Dermatology consultations, with no skin lesion alterations after three months. At the age of 18 months, she attended a Neuropediatric consultation that showed normal growth and psychomotor development and no alterations on physical and neurological examination. Skin lesions were less pigmented and no new lesions were identified.

What is your diagnosis?

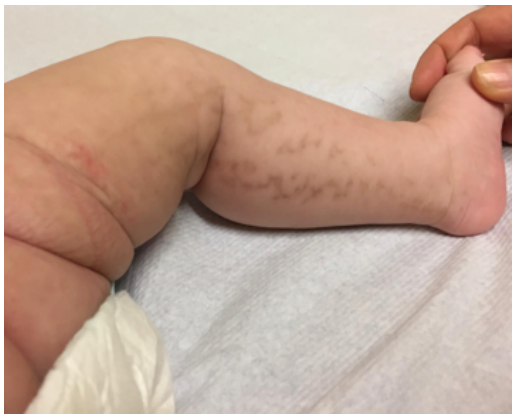

Figure 1 - Skin lesions in the left limb

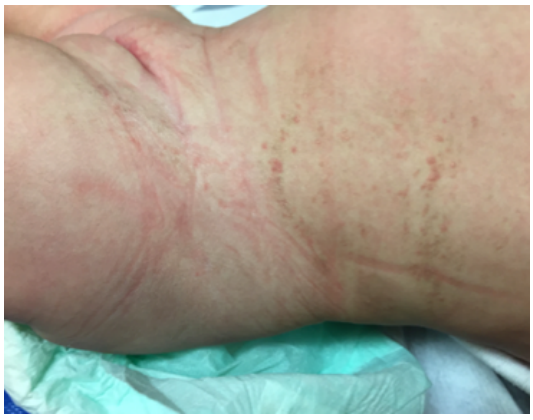

Figure 2 - Abdominal skin lesions

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DIAGNOSIS

Incontinentia pigmenti (IP, MIM#308300).

Clinical diagnosis of incontinentia pigmenti (IP) was established and later confirmed by genetic testing, which identified a heterozygous *IKBKG* pathogenic variant with deletion of exons 4 to 10.

Brain magnetic resonance image (MRI) was requested, and the patient was referred to Ophthalmology, Stomatology, and Genetic Counseling consultations.

DISCUSSION

Incontinentia pigmenti, or Bloch-Sulzberger syndrome, was first described in 1906. It is a rare X-linked genodermatosis, with an estimated incidence of one case per 40,000-50,000 newborns.[1-4]

IP is a neuroectodermal dysplasia affecting tissues embryologically derived from the ectoderm.[2] It is a genetic disease inherited as an X-linked dominant trait, caused by a defect in the *IKBKG/NEMO* gene. The most common pathogenic variant is a recurrent exon 4 to 10 deletion, as in this case report. It is usually lethal in males (with the exception of cases of mosaicism, *Kleinefelter* syndrome (47,XXY), or hypomorphic mutations in *IKBKG* gene), while heterozygous females survive (due to functional mosaicism), accounting for 95% of living affected individuals.[2,4,5] The disorder's phenotypic expression is variable, ranging from very mild to severe cases.[5]

Clinical manifestations usually start at birth or early childhood.[2] Regarding clinical findings, skin lesions are the sole major IP criteria and are present in all patients, displaying a specific pattern (along Blaschko lines), stage progression, and timeline. These lesions typically evolve through four stages, although lesions in different stages can simultaneously occur: (i) stage one (or vesicular stage) is identified in 90% of patients and characterized by linear papules and vesicles present at birth or within the first weeks of life; (ii) stage two (or verrucous stage) is identified by wart-like verrucous papules and keratotic patches and occurs within the first few weeks or months of life in 70% of patients; (iii) stage three (or hyperpigmented stage) consists in the development of linear or whorled hyperpigmentation lesions appearing in early infancy and slowly disappearing during adolescence and is observed in up to 98% of patients; and (iv) stage four (or hypopigmented stage) is characterized by patchy areas of hypopigmentation and cutaneous atrophy and is present in 75% of cases during adolescence, persisting into adulthood.[2,3,6]

IP differential diagnosis, based on dermatological findings, is extensive and depends on the stage of lesions.

Other organs may be affected in 70–80% of patients.[6] Hair anomalies (alopecia, sparse hair, hypoplasia, or absence of eyebrows), nail alterations (yellowish pigmentation, dystrophy, or transverse or longitudinal slits), periungual and subungual keratotic tumors, and dental abnormalities (partial anodontia, hypodontia, delayed dentition, cone/peg-shaped teeth, impactions) are present in approximately 30% of IP cases. Breast and musculoskeletal abnormalities can also be present.[2-6]

IP females have heterogeneous and often severe clinical signs. Neurological defects (seizures, motor and mental retardation, microcephaly, brain ischemia) are present in 30% of patients, and ophthalmological anomalies (strabismus, cataracts, optic atrophy, retinal vascular pigmentary abnormalities, microphthalmia) in up to 70%. Eye and brain impairment are associated with significant morbidity and disability.[2-6]

IP clinical diagnostic criteria were proposed in 1993 and revised in 2014.[7] If genetic testing is unavailable, presence of one major criterion or two or more minor criteria is necessary for diagnosis.[7] Major criteria include presence of typical skin lesions in any of the four stages. Minor criteria include anomalies of the hair, nails, and teeth, retinal and extra-retinal abnormalities, alterations of the central nervous system, palate, and breast, and typical skin histologic findings.[7]

Clinical diagnosis can be confirmed by genetic testing, which also establishes the inheritance mode and allows for genetic counseling, when needed. Genetic testing and counseling enable prognostic evaluation, prenatal testing, and risk assessment for relatives[4]. Although expensive, it is readily available, has high sensitivity, and obviates the need for other invasive diagnostic tests, as skin biopsy.[4]

There is no cure for IP and treatment is limited to symptom management.[2] As the condition can have multiorgan involvement, all cases should have a multidisciplinary approach involving Dermatology, Neuropediatrics, Ophthalmology, Stomatology, and Genetics.[1-5] Brain MRI should be performed in all patients at baseline and repeated in cases of seizures, neurological abnormalities, or retinal neovascularization, since not all findings are present at birth. A thorough ophthalmologic examination must be performed early.[2,3,5]

With this case, the authors aim to emphasize the importance of a complete physical examination, as it has the potential to identify rare genetic conditions as IP. In the present case, a careful examination enabled lesion detection and clinical suspicion led to timely IP diagnosis in the child, prompting appropriate multidisciplinary follow-up.

ABSTRACT

Incontinentia pigmenti is an X-linked neuroectodermal dysplasia. It is a rare genetic disease with multiorgan involvement, and hence a multidisciplinary approach is of paramount importance. Although diagnosis is based on clinical findings, genetic molecular testing can be performed to confirm diagnosis and allow future genetic counselling.

The authors describe the case of a 4-month-old girl accidentally diagnosed with incontinentia pigmenti following routine physical examination in the Emergency Department. Timely diagnosis enabled appropriate multidisciplinary approach and follow-up.

Keywords: Blaschko lines; genodermatoses; incontinentia pigmenti; rare disease

RESUMO

A incontinência pigmentar é uma displasia neuroectodérmica ligada ao cromossoma X. É uma doença rara com atingimento multiorgânico, pelo que o seguimento multidisciplinar destes casos é fundamental. Apesar de ser uma patologia com diagnóstico clínico, pode ser efetuado teste molecular genético para confirmação do mesmo e aconselhamento genético futuro.

Os autores relatam o caso de uma lactente de quatro meses com diagnóstico ocasional de incontinência pigmentar durante a observação médica numa ida ao Serviço de Urgência. O diagnóstico atempado permitiu uma abordagem e seguimento multidisciplinares apropriados.

Palavras-chave: doença rara; genodermatoses; incontinência pigmentar; linhas de Blaschko

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IMAGING CASES

IMAGING CLINICAL CASE

CASO CLÍNICO IMAGIOLÓGICO

Catarina Cristina[1], Inês Serras[1], Ema Santos[2], Rui Alves[2], Dulce Serrano[1]

A two-month-old, previously healthy male infant was admitted to the pediatric Emergency Department with nausea, vomiting, constipation, and refusal to feed for two days. In the neonatal period, meconium passage with stimulation occurred at 18 hours of life. On admission, the infant had an important abdominal distension, bowel sounds, and painless abdominal palpation, with no palpable masses. Abdominal radiograph revealed exuberant bowel distension (**Figure 1**), with slight improvement after rectal decompression and exit of thick stools without blood or mucus. Contrast enema showed a recto-sigmoid transition zone with caliber inversion between the rectum and sigmoid (**Figure 2**).

What is your diagnosis?

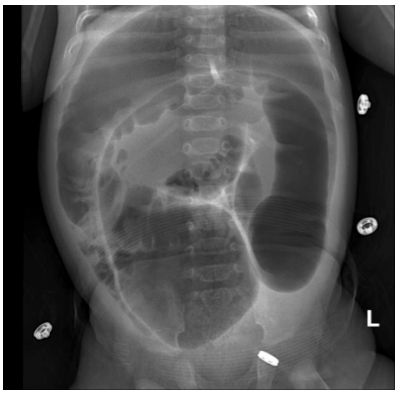

Figure 1 - Abdominal radiograph showing severe bowel dilatation

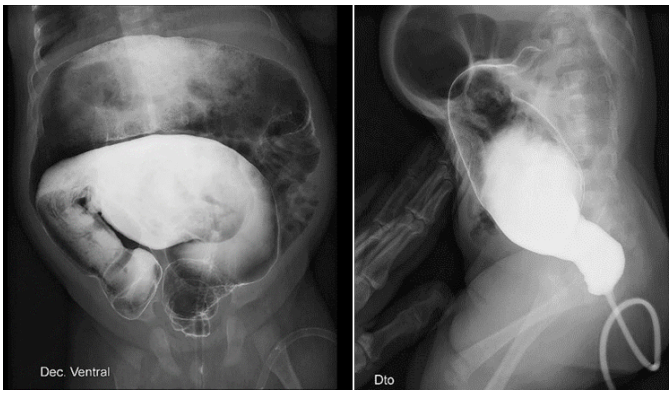

Figure 2 - Contrast enema showing a transition zone in the rectosigmoid junction

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DIAGNOSIS

Hirschsprung disease

Patient orientation

Contrast enema showed a recto-sigmoid transition zone (anatomical transition between the narrow distal aganglionic segment and the dilated proximal ganglionic segment), a pathognomonic finding of Hirschsprung disease (**Figure 2**). At seven months of age, extemporaneous histochemical analysis of sequential colonic biopsies revealed absence of ganglion cells in the sigmoid, compatible with Hirschsprung disease, and Swenson's pull-through was performed (**Figure 3**).

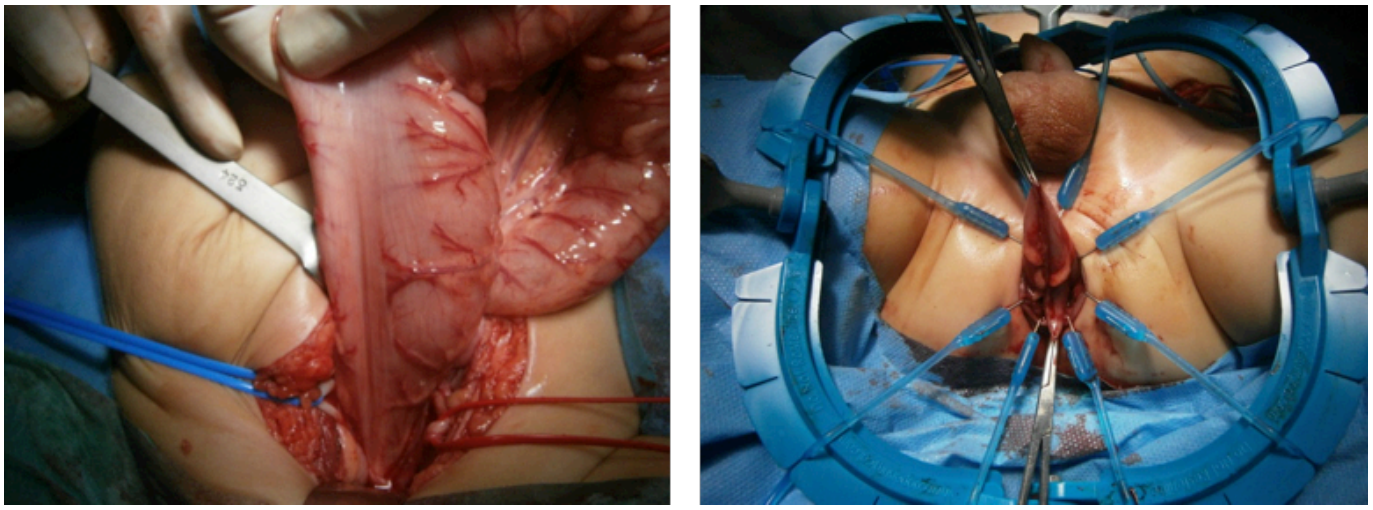

Figure 3 - Surgical images: a) Transition zone (arrow); b) Swenson procedure

DISCUSSION

Hirschsprung disease is the most common congenital gut motility disorder, with a reported incidence of approximately one in every 5,000 live births and male preponderance (4:1).[1-3] It is caused by failure of neural crest cell migration during intestinal development in fetal life or failure of neural crest cells to differentiate into mature ganglion cells, resulting in an aganglionic bowel segment that leads to absent intestinal peristalsis and functional obstruction upstream of the aganglionic zone.[1-5] Rectum and sigmoid colon are the most affected segments.[1-5] Diagnosis is suggested by meconium passage delay or history of constipation that does not respond to conventional treatment.[1-5] Imaging exams, namely radiography and contrast enema, are important tools for early diagnosis.[1-4] The definitive diagnosis is established through histochemical analysis of aganglionic segment biopsy showing absence of ganglion cells in the submucosal and myenteric plexus and, in most patients, hypertrophied nerve trunks.[1]

Hirschsprung disease treatment is surgical and involves resection of the aganglionic segment of the colon and reconstruction of the intestinal tract by bringing down the normal ganglionic bowel to the anus.[2-5]

Early recognition of this entity is important to avoid complications, such as Hirschsprung-associated enterocolitis, a potentially fatal pathology.[1-5]

Lessons from this clinical case

- Hirchsprung disease is a congenital disorder that most commonly presents in the neonatal period as intestinal obstruction.
- Diagnosis should be considered in all neonates or children with constipation that does not respond to conventional treatment.
- Imaging exams are important tools for early diagnosis.
- Early diagnosis decreases complications, improves prognosis, and positively impacts patients' quality of life.

ABSTRACT

Hirschsprung disease is the most common congenital gut motility disorder and usually diagnosed in the neonatal period. It is caused by an aganglionic bowel segment resulting in absence of intestinal peristalsis and functional obstruction. Diagnosis should be considered in all patients with constipation that does not respond to conventional

treatment. Radiography and contrast enema are important diagnostic exams, but the definitive diagnosis is established through histochemical analysis of aganglionic segment biopsy. Treatment is surgical and early recognition is important to avoid complications and improve prognosis.

Herein is reported the clinical case of a young infant presenting to the Pediatric Emergency Department with nausea, vomiting, constipation, refusal to feed, and important abdominal distension. Abdominal radiograph and contrast enema were compatible with Hirschsprung disease. Biopsy histochemical analysis confirmed the diagnosis and surgical treatment was performed.

Keywords: contrast enema; Hirschsprung disease; intestinal obstruction; meconium

RESUMO

A doença de Hirschsprung é o distúrbio congénito de motilidade intestinal mais comum e habitualmente diagnosticado no período neonatal. É causado por um segmento intestinal aganglionar, que leva a ausência de peristaltismo intestinal e obstrução funcional. O diagnóstico deve ser considerado em todos os doentes com obstipação sem resposta ao tratamento convencional. A radiografia e o enema com contraste são exames importantes para o diagnóstico, mas este só é definitivamente estabelecido por análise histoquímica da biópsia do segmento aganglionar. O tratamento é cirúrgico e o reconhecimento precoce da doença é importante para evitar complicações e melhorar o prognóstico.

É reportado o caso clínico de um lactente que se apresentou no Serviço de Urgência Pediátrica com náuseas, vómitos, obstipação, recusa alimentar e uma importante distensão abdominal. A radiografia abdominal e o enema com contraste foram compatíveis com doença de Hirschsprung. A análise histoquímica da biópsia confirmou o diagnóstico e foi efetuado tratamento cirúrgico.

Palavras-chave: clister opaco; doença de Hirschsprung; mecónio; obstrução intestinal

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IMAGING CASES

GASTROENTEROLOGICAL CLINICAL CASE

CASO CLÍNICO DE GASTRENTEROLOGIA

Mariana Portela[1], Catarina Barroso[2], José Luís Carvalho[2], Maria Miguel Gomes[1,3]

A two-year-old boy presented with a six-month history of painless hematochezia, described as a small amount of bright red blood dripping and sometimes bright red blood mixed with normal stool. He was previously healthy and with no family history of gastrointestinal diseases. The boy presented to the Emergency Department due to exteriorization of a mass after defecation (**Figure 1**). No history of fever, abdominal pain, vomiting, diarrhea, additional blood losses, or other symptoms was identified and he was hemodynamically stable. On examination, the patient had a rounded and mobile mass with nearly 3cm of diameter protruding in the anus. The remaining examination was unremarkable.

What is your diagnosis?

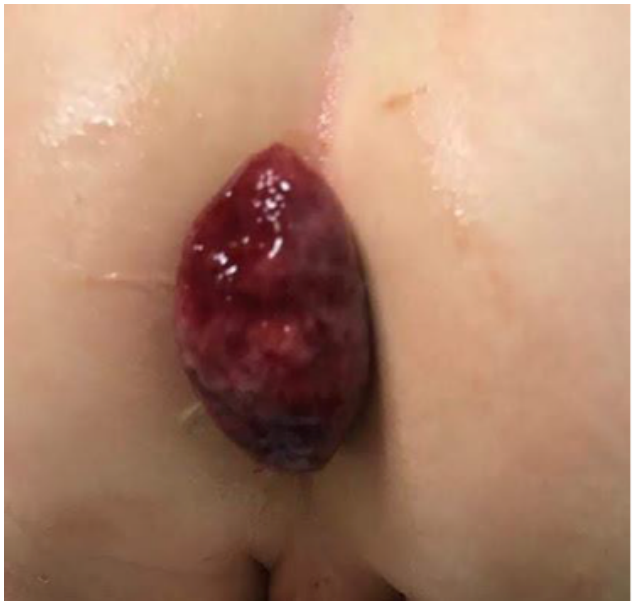

Figure 1 - Prolapsed colorectal polyp

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DIAGNOSIS

Gastrointestinal Polyp – Juvenile Polyp

DISCUSSION

Juvenile polyps resulting in lower gastrointestinal bleeding or prolapse require polypectomy. In this case, surgery consisted in pedicle cerclage and mass excision. The procedure was uneventful and the child was successfully discharged after eight hours of surveillance. Histologic examination confirmed the diagnosis of a 2.9-cm juvenile polyp (hamartoma). Total colonoscopy was planned to exclude multiple or proximal polyps, documented to occur in 24% and 15% of cases, respectively.[1]

Gastrointestinal polyps are common in children and usually benign.[1-4] The diagnosis is most often established during the first decade of life, with a peak incidence between the ages of two and six years.[2-3] The condition is predominant in the male gender.[1] Gastrointestinal polyps may occur anywhere in the alimentary tract.[1-4] In preschool children and adolescents, 85% of polyps are juvenile, 10% are adenomas, and 3% are hyperplasic.[2] Most juvenile polyps are unique and located in the rectum and sigmoid and sometimes can be accessible by rectal touch.[1-3] The most common symptom of juvenile polyps is intermittent mild hematochezia.[1,2] Rarely, they may be accompanied by hemodynamic or hematologic alterations, as stool passing through the polyp may cause bleeding.[2,3] Most polyps are pedunculated and can prolapse when located in rectum, as in the present case.[2] Usually no pain is described, but polyp traction can cause discomfort. Although the risk of malignancy associated with a solitary juvenile polyp is very small, excision is recommended to confirm benignity. The recurrence rate was considered rare in older series, but more recent studies report recurrence in 17% of patients with single juvenile polyps.[1,2] Patient surveillance depends of the number of identified polyps and family history.[2]

ABSTRACT

Gastrointestinal polyps are frequent in children and represent the most common cause of colorectal bleeding in this age group. Among those, juvenile polyps are the most frequently found. Intermittent mild hematochezia is the main symptom of colon polyps. Most polyps are pedunculated and, when located in the rectum, may prolapse. In most cases, juvenile polyps are solitary and located in rectosigmoid. Although malignancy risk of a solitary juvenile polyp is very small, excision is recommended to confirm benign nature. Total colonoscopy should be considered to exclude multiple or proximal polyps.

Keywords: children, hematochezia, juvenile polyp

RESUMO

Os pólipos gastrointestinais são frequentes em idade pediátrica e são a causa mais comum de hemorragia colorretal nesta faixa etária. Destes, os pólipos juvenis são os mais comuns. A hematoquézia intermitente é o principal sintoma de pólipos localizados no cólon. A maioria dos pólipos é pedunculada e, quando localizados no reto, podem prolapsar. Na maior parte dos casos, os pólipos juvenis são solitários e localizam-se no retossigmóide. Embora o risco de malignidade de um pólipo juvenil solitário seja muito baixo, é recomendada excisão para confirmar a sua benignidade. A colonoscopia total deve ser considerada para excluir pólipos múltiplos ou proximais.

Palavras-chave: crianças, hematoquézia, pólipo juvenil

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AIMS AND SCOPE

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

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

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

Ethics

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

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

A conflict of interest or funding statement is required.

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

Manuscripts undergo a double-blind peer-review process, after which the Editor may:

a) Accept it without modifications;
b) Accept it after modifications suggested by reviewers;
c) Reject it.

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

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

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

Second page

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

TEXT

Editorials

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

Original Articles

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

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Review articles should be structured in Introduction, Objectives,

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

Clinical Cases

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

Imaging Cases

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

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

Current Perspectives

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

General Rules

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

REFERENCES

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

Examples:

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

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

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

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

FIGURES AND TABLES

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

ACKNOWLEDGMENTS AND CLARIFICATIONS

Acknowledgements, declaration of interest statement, and funding

source should be mentioned in the last page of the article.

MODIFICATIONS AND REVISIONS

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

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

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

ARTICLE STRUCTURE - AUTHOR GUIDELINES

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

INSTRUÇÕES AOS AUTORES

OBJETIVOS E ÂMBITO

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

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

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

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

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

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

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

CRITÉRIOS DE AUTORIA E RESPONSABILIDADE

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

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

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

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

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

Questões éticas

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

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

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

NORMAS DE PUBLICAÇÃO

SUBMISSÃO

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

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

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

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

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

As páginas devem ser numeradas segundo a sequência referida anteriormente.

Na primeira página

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

Na segunda página

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

TEXTO

Editoriais

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

Artigos Originais

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

Artigos de Revisão

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

Casos clínicos

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

Casos de imagem

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

Cartas ao Editor

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

Perspetivas Atuais

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

Normas gerais

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

REFERÊNCIAS BIBLIOGRÁFICAS

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

Seguem-se alguns exemplos:

a. Revista médica: listar os primeiros seis autores, seguidos de *et al* (em itálico) se ultrapassar seis, título do artigo, nome da revista, ano, volume, número e páginas. Ex.: Haque KN, Zaidi MH, Haque SK, Bahakim H, el-Hazmi M, el-Swailam M, *et al*. Intravenous Immunoglobulin for prevention of sepsis in preterm and low birth weight infants. Pediatr Infect Dis 1986; 5(6): 622-65.

b. Capítulo em livro: autor(es), título do capítulo, nome(s) do(s) Editor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação, primeira e última páginas do capítulo. Ex.: Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

c. Livro: autor(es), título do livro, número da edição, cidade e nome da casa editora, ano de publicação e número de páginas. Ex.: Jenkins PF. Making sense of the chest x-ray: a hands-on guide. 2nd. London: Taylor & Francis; 2013. p. 120.

d. Referência electrónica: artigo de revista em formato electrónico. Ex.: Jeha G, Kirkland J. Etiology of hypocalcemia in infants and children. Janeiro, 2010. (Acedido em 8 de maio de 2013). Disponível em: http://www.uptodate.com.

FIGURAS E QUADROS

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

responsável legal.
- O total de figuras e quadros não deve ultrapassar os valores indicados para cada tipologia de artigo.

AGRADECIMENTOS E ESCLARECIMENTOS

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

MODIFICAÇÕES E REVISÕES

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

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

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

ESTRUTURA DOS ARTIGOS - NORMAS DE PUBLICAÇÃO

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