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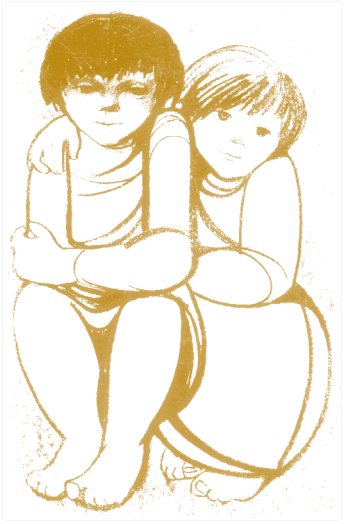

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NASCER E CRESCER - BIRTH AND GROWTH MEDICAL JOURNAL PRIZE BEST ORIGINAL PAPER

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

PROCEDURES

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

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

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

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

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

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

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

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

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

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EDITORIAL

IS CHILDREN-CARE IN THE HOSPITAL SETTING SAFE?

OS CUIDADOS ÀS CRIANÇAS EM AMBIENTE HOSPITALAR SÃO SEGUROS?

Bilhota Xavier[1]

Portugal was one of the countries in the world with the highest infant and neonatal mortality. In the early 1990s, more than one hundred health units and services without the minimum conditions were closed. The others were equipped with pediatricians and nurses trained in the provision of hospital care to newborns and with minimal equipment required for the resuscitation and stabilization of newborns who needed special care. Also, at the beginning of this decade, neonatal transport of intensive care was implemented through the National Institute of Medical Emergency (INEM), fostering complementary articulation between Perinatal Support Hospitals (PAH) and Perinatal Differentiated Support Hospitals (PAHD), which are equipped with neonatal intensive care units. These and other measures allowed Portugal to become one of the countries in the world with the lowest infant mortality, including neonatal mortality, greatly increasing the survival rate of large preterm infants and the reduction of cerebral palsy.

However, the sustainable development of these significant changes cannot be achieved without ensuring that health services are safe, those that are provided at hospital level to children, including newborns.

Only at the beginning of this century, did the concept of safety in areas such as fire, equipment failure, patient falls and the risks of infection began to emerge.

There was also the belief that health professionals, physicians, and nurses with high quality training, always behaved with care and awareness and sought to avoid or minimize errors, considered as inevitable "complications" of care.

In 1999 the U.S. Institute of Medicine published the well-known *"To Err is Human: Building a Safer Health System"* raising the awareness of the mortality secondary to "medical errors" in U.S. hospitals. Based on the results obtained in Colorado, Utah and New York studies, it was extrapolated that at least 44,000 and perhaps even 98,000 people died per year in hospitals due to "medical errors, and of those, 7,000 deaths were drug-related and would be preventable.

These data were a wake-up call to the whole world and led to a reflection on the need to urgently implement measures that would increase health care safety.

The concept of health error, adverse event or sentinel event began to be introduced and a paradigm shift from penalizing to seeking to identify the causes for these errors and implementing mechanisms to mitigate the possibility of their repetition developed. Also it became clear that these errors were rarely due to a single professional. On the contrary, in the majority of the cases, the real cause of an adverse incident or event in health care was not due to human error, but to a set of actions and interactions, processes, team relations, communications, human behavior, technology, organizational culture, institutions' care policies, and the nature of the hospital environment itself.

The harm done to patients can never be corrected, just by urging healthcare professionals to be more careful.

It is necessary that institutions promote the development of policies, procedures and norms and their practical application to reduce the errors of identification of the patient, the infections associated with health care, errors of prescription, preparation, and administration of medicines, to ameliorate the communication between professionals and with parents and adolescents, among others, implementing a culture of quality and safety in each institution.

Audits of all these processes are crucial to measure the evolution of this culture and identify the less correct practices and implementing corrective measures.

Medical errors in pediatric and neonatal hospitalization are not well known. What is known is that at these ages the probability of error is far superior, due to patient's fragility, heterogeneity of different age groups and the particularities that represent small infants

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and premature infants. In all areas the safety processes should be redoubled, but the preparation and administration of drugs is particularly important. Most medicines are formulated for adults, and neonatal and pediatric dosing requires specific calculations and tasks, each of which significantly increases the possibility of error. Children are less able to physiologically tolerate a medication error and fail to communicate effectively about any possible adverse effects, which the drugs may be causing.

Not by chance in the beginning of the second decade of the 21st century (2010), the Ministry of Health Portuguese acquired from the Agency of Calidad Sanitaria de Andalucía (ACSA), the manual of standards that began to serve in Portugal as a National Model of Health Accreditation. This initiated the certification processes in hospital services that provided health care to children and women, and also the beginning of the accreditation processes of a hospital institution as a whole, according to Caspe Healthcare Knowledge Systems (CHKS) and Joint Commission International (JCI).

Also, in the view of the need to improve the quality and safety of childcare the Pediatric Society for Quality and Patient Safety (SPEQS) was established within the Portuguese Society of Pediatrics (SPP) in 2017. If at first the membership of this initiative was reduced, perhaps because it addressed a science that was foreign to the majority, it has been growing in recent years, as evidenced by the participation in the ongoing online course promoted by SPEQS, and by the questions posed to board members afterwards.

Also, the invitation to write this editorial, reflects the growing interest that these themes have been assuming.

In addition to those mentioned above, other challenges arise for health professionals working with children:

Involve children, adolescents, and families as partners in the development of increasingly safe health care, promoting health literacy, care, which should be seen as a basic right.

Promote an emerging, alternative approach to patient safety, called "Safety II" that focuses on making health care proactively safer, by emphasizing the conditions in which healthcare professionals are most successful and which implies motivation and awareness in the interest of sharing these best practices with professionals of other institutions.

Last, but not the least, the consolidation of the Pediatric Quality Network is the greatest challenge.

Mission to assure that no single child is harmed in the care we provide.

To contribute to

HIGHER QUALITY AND CHILD-AND FAMILY-FRIENDLY HEALTH SERVICES

Portugal era dos países do mundo com maior mortalidade infantil e neonatal. No início da década de 90 foram encerrados mais de uma centena de unidades e serviços de saúde em que se nascia sem as mínimas condições. Os outros foram dotados de pediatras e enfermeiros com formação na prestação de cuidados hospitalares, em particular a recém-nascidos e dotados de equipamentos mínimos, que permitissem a reanimação e estabilização dos recém-nascidos que precisavam de cuidados especiais. Também no início dessa década foi implementado o transporte neonatal de cuidados intensivos através do Instituto Nacional de Emergência Medica (INEM), fomentando a articulação complementar entre Hospitais de Apoio Perinatal (HAP) e Hospitais de Apoio Perinatal Diferenciados (HAPD), estes apetrechados com unidades de cuidados intensivos neonatais. Estas e outras medidas permitiram que Portugal passasse a ser um dos países do mundo com menor mortalidade Infantil, incluindo a neonatal, aumentando em muito a taxa de sobrevivência dos grandes prematuros e a redução da paralisia cerebral.

No entanto o desenvolvimento sustentável destas significativas mudanças, não poderá ser conseguido, sem garantir que os serviços de saúde são seguros, em particular aqueles que são prestados a nível hospitalar a crianças, incluindo recém-nascidos.

Só no início do presente século, começou a surgir a ideia de segurança em áreas, como o incêndio, a falha do equipamento, as quedas de pacientes e os riscos de infeção.

Havia também a crença de que os profissionais de saúde, médicos e enfermeiros com formação de grande qualidade, se comportavam sempre com cuidado e consciência e procuravam evitar ou minimizar erros, considerados como inevitáveis "complicações" dos cuidados.

Em 1999 o Instituto de Medicina dos Estados Unidos (EUA) publicou o conhecido "*To Err is Human: Building a Safer Health System*" chamando a atenção para a elevada mortalidade secundária a "erros médicos", nos hospitais dos EUA. Baseado nos resultados dos estudos do Colorado e Utah e Nova Iorque foi estimado que 44 000 pessoas e talvez 98000 morriam em hospitais todos os anos, e dessas7.000 mortes estavam relacionadas com o medicamento e seriam evitáveis.

Estes dados foram um alerta para todo o mundo e levaram à reflexão sobre a necessidade de implementar urgentemente medidas que aumentassem a segurança dos cuidados de saúde.

Começou a ser introduzido o conceito de erro em saúde, evento adverso ou evento sentinela e a mudança de paradigma de em vez penalizar, procurar identificar as causas para esses erros e implementar mecanismos para minorara a possibilidade da sua repetição, e a constatação de que esses erros raramente se deviam só a um único profissional.

Pelo contrário, a verdadeira causa de um incidente ou acontecimento adverso nos cuidados de saúde não se deveu na larga maioria das situações a um erro humano, mas sim a um conjunto de ações e interações, processos, relações de equipa, comunicações, comportamento humano, tecnologia, cultura organizacional, políticas de cuidados das instituições, bem como à natureza do ambiente hospitalar.

Os danos causados aos doentes não poderão nunca ser corrigidos, apenas exortando os profissionais de saúde a terem mais cuidado.

É preciso que as instituições promovam a elaboração de políticas, procedimentos e nomas e a sua aplicação prática, que possam minorar os erros de identificação do doente, reduzir as infeções associadas aos cuidados de saúde, os erros de prescrição, preparação e administração de medicamentos, aumentar a comunicação entres profissionais e com os pais e adolescentes, entre outras, implementando em cada instituição uma cultura de qualidade e segurança.

As auditorias a todos estes processos são cruciais para medir a evolução dessa cultura e identificar quais as práticas menos corretas, no sentido de implementar medidas corretivas.

Não são conhecidos os erros cometidos nos cuidados prestados a crianças e recém-nascidos. O que sabe é que nestas idades a probabilidade de erro é largamente superior, pela sua fragilidade, heterogeneidade dos diferentes grupos etários e pelas particularidades que representam os pequenos lactentes e prematuros.

Em todas áreas os processos de segurança devem ser redobrados, mas a do medicamento é particularmente importante. A maioria dos medicamentos é formulada para adultos, necessitam de alterar a dosagem original do medicamento, que requer cálculos e tarefas específicas, cada uma aumentando significativamente a possibilidade de erro, as crianças são menos capazes de tolerar fisiologicamente um erro de medicação e não conseguem comunicar de forma eficaz sobre quaisquer efeitos adversos que os medicamentos possam estar a provocar

Não por acaso no início da segunda década do sé XXI, em 2010, o Ministério da Saúde Português adquiriu à Agencia de Calidad Sanitaria de Andalucía (ACSA) o manual de padrões que passou a servir em Portugal de Modelo Nacional de Acreditação em Saúde, que iniciou os processos de certificação, como se impunha, nos serviços hospitalares que prestavam cuidados de saúde às crianças e mulheres, e também o início dos processos de acreditação de uma instituição hospitalar no seu todo, pelos modelos Caspe Healthcare Knowledge Systems (CHKS) e Joint Commission International (JCI).

Também por ser reconhecida a necessidade da melhoria da qualidade e segurança dos cuidados às crianças, em 2017 foi constituída a Sociedade Pediátrica da Qualidade e Segurança do Doente (SPEQS), no âmbito da Sociedade Portuguesa de Pediatria (SPP). Se ao princípio a adesão a esta iniciativa foi reduzida, até talvez por abordar uma ciência que era estranha à maioria, nos últimos anos ela tem sido em crescendo, como é evidenciada pela participação no curso online promovido pela SPEQS, que está a decorrer e pelas questões que à *posteriori* têm vindo a ser colocadas aos elementos da direção.

Também o convite para a redação deste editorial, se pode enquadrar no interesse crescendo que estes temas têm vindo a ter.

Para além dos já referidos, outros desafios se colocam aos profissionais de saúde que trabalham com crianças:

Envolver as crianças, adolescentes e famílias, como parceiros no desenvolvimento de cuidados saúde cada vez mais seguros, promovendo a literacia em saúde, cuidados estes, que devem ser tidos como um direito básico.

Promover uma abordagem emergente, alternativa na segurança do paciente, designada como “Safety II” que se centra em tornar os cuidados de saúde proactivamente mais seguros, através da ênfase nas condições em que os profissionais de saúde têm mais sucesso e que implica a motivação e conscienlização no interesse em partilhar essas boas práticas, com os profissionais de outras instituições.

Já a consolidação da Rede Pediátrica da Qualidade é o maior desafio.

Missão, garantir que uma única criança não seja prejudicada nos cuidados que lhe prestamos.

Contribuirmos cada vez mais, para termos

SERVIÇOS DE SAÚDE, COM MAIS QUALIDADE e AMIGOS DAS CRIANÇAS E DAS FAMÍLIAS

Nascer e Crescer - Birth and Growth Medical Journal
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ORIGINAL ARTICLES

FOLIC ACID, VITAMIN B12, AND PSYCHOTIC SYMPTOMS AMONG YOUNG PSYCHIATRIC INPATIENTS

ÁCIDO FÓLICO, VITAMINA B12 E SINTOMAS PSICÓTICOS NO INTERNAMENTO PSIQUIÁTRICO DE CRIANÇAS E JOVENS

Filipa Pedro dos Reis[1], Luísa Duarte[1], Teresa Cartaxo[1], Vítor Santos[2]

ABSTRACT

Introduction: Folic acid and/or vitamin B12 deficiency are known to be associated with neuropsychiatric disorders. However, the association between serum levels of these molecules and psychotic symptoms is not established. The aim of this study was to investigate the association between folic acid and vitamin B12 serum levels and the presence of psychotic symptoms among child and young adult psychiatric inpatients.

Material and Methods: This was a retrospective cohort study of 165 patients under 25 years of age admitted due to psychiatric disorders between 2005 and 2018 and with folic acid and vitamin B12 serum levels assessed during hospitalization. Two groups of patients were defined according to presence or absence of psychotic symptoms. Rehospitalization was also assessed.

Results: Folic acid serum levels were significantly lower (p=0.01) in children and young adults hospitalized for psychiatric disorders with psychotic symptoms compared to patients of the same age with acute psychiatric illness without psychotic symptoms. A similar non-significant trend was found for vitamin B12. Rehospitalization rates were also higher in the first group.

Conclusion: Results from this study suggest that low folic acid serum levels are associated with psychotic symptoms regardless of the baseline diagnosis.

Keywords: folic acid; psychiatric hospitalization; psychopathology; psychosis; vitamin B12

RESUMO

Introdução: Sabe-se que a deficiência em ácido fólico e/ou em vitamina B12 está associada a perturbações neuropsiquiátricas. Porém, a relação entre os níveis séricos destas moléculas e sintomas psicóticos não está estabelecida. O objetivo deste estudo foi investigar a relação entre os valores séricos de ácido fólico e vitamina B12 e a presença de sintomas psicóticos em crianças e jovens internados por patologia psiquiátrica.

Material e Métodos: Foi conduzido um estudo de coorte retrospetivo incluindo 165 doentes com idade até aos 25 anos internados por patologia psiquiátrica entre 2005 e 2018 e com valores séricos de ácido fólico e vitamina B12 determinados durante o internamento. Os doentes foram divididos em dois grupos consoante presença ou ausência de sintomatologia psicótica. Foi ainda determinada a ocorrência de reinternamento.

Resultados: Foram observados níveis séricos de ácido fólico significativamente mais baixos (p=0.01) em crianças e jovens adultos internados com patologia psiquiátrica associada a sintomatologia psicótica quando comparados com doentes da mesma faixa etária com patologia psiquiátrica aguda sem sintomas psicóticos. Uma tendência semelhante, mas não significativa, foi encontrada para a vitamina B12. Observou-se ainda uma prevalência significativamente maior de reinternamentos no primeiro grupo.

Conclusão: Os resultados deste estudo sugerem que a diminuição do nível sérico de ácido fólico está associada a sintomatologia psicótica, independentemente da situação diagnóstica de base.

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Palavras-chave: ácido fólico; hospitalização psiquiátrica; psicopatologia; psicose; vitamina B12

INTRODUCTION

Folic acid is a substrate in the intracellular methylation reactions essential to normal brain development and function. Methylation is important in deoxyribonucleic acid (DNA) synthesis, stability, and repair, gene expression, neurotransmitter synthesis and destruction, and in homocysteine metabolism.[1,2]

Folic acid deficiency is one of the most widespread nutritional deficiencies worldwide, with acknowledged adverse health consequences.[1] Folic acid deficiency may contribute to the pathogenesis of neuropsychiatric disorders, including memory loss, cognitive development delay, mood disorders, *delirium*, and psychotic disorders.[3]

Vitamin B12, also called cobalamin, is the only vitamin of the human body containing cobalt and functions as a cofactor for methionine synthetase.[4] Vitamin B12 deficiency is associated with neurologic, psychiatric, and neuropsychiatric disorders, including neuropathy, myelopathy, myeloneuropathy, cerebellar ataxia, optic atrophy, and cognitive disorders, as dementia, psychosis, and mood disorders.[5-7]

There are multiple reasons for the simultaneous study of folic acid and vitamin B12 deficit, including the close relationship between the metabolic pathways of the two vitamins and the comorbidities associated with the neuropsychiatric syndromes that both can elicit.[6]

Both vitamins have an essential role in the central nervous system functioning at any age, particularly in the homocysteine to methionine conversion, which is mediated by methionine synthetase and a crucial step for nucleotide synthesis and for gene and non-gene methylation.[6]

One-carbon metabolism (OCM) is essential for nucleotide synthesis of DNA and other molecules. This cycle is an intricate system involving transfer of a methyl group amongst multiple conformations.[2]

The primary cause of OCM alterations is impaired folic acid and vitamin B12 levels. One of the best understood consequences of this is an increased level of homocysteine, a highly toxic metabolite for neural and vascular development.[8]

The 2009 study by Kale *et al* had already sustained OCM changes in early psychosis, stating that it might have implications on psychosis neurodevelopmental pathophysiology, progression, and treatment.[9] These changes, which include increased homocysteine and decreased folic acid and vitamin B12 serum levels, are hence frequently reported in patients with first-episode psychosis (FEP).[9-11]

Multiple studies throughout the years have associated folic acid and vitamin B12 deficiency with psychiatric disease, particularly schizophrenia, although not consensually.[5,8-25] However, as far as we are aware, no study to date has related such vitamin deficiencies with isolated psychotic disease and independently of the individual's psychiatric diagnosis, specifically in children and young adults, during the acute phase. Therefore, the aim of this study was to retrospectively analyse the association between folic acid and vitamin B12 serum levels and psychotic symptoms in children and young adults hospitalized due to psychiatric disease.

MATERIAL AND METHODS

This was a retrospective cohort study of inpatients from the departments of Psychiatry and Child and Adolescent Psychiatry of Centro Hospitalar e Universitário de Coimbra, in Portugal. The study included patients aged up to 25 years old, hospitalized from 2005 to 2018, with folic acid and/or vitamin B12 serum level measurements retrieved during hospitalization. Data from patients who fulfilled the above-mentioned inclusion criteria were retrieved from their medical records and included age, sex, presence or absence of psychotic symptoms during hospitalization, final diagnosis, folic acid serum levels retrieved during hospitalization, vitamin B12 serum levels retrieved during hospitalization, and occurrence of psychiatric rehospitalizations. The study had no exclusion criteria.

Patients enrolled were divided in two groups according to presence or absence of psychotic symptoms during hospitalization. To determine the presence of such symptoms, researchers looked for changes in thinking and/or sensory perception reported in the medical release note. Since this was a retrospective study, no scales or scores were systematically applied to evaluate psychotic symptoms.

Information regarding patients' final diagnosis was also retrieved from the medical discharge note and compiled according to the nosological classification of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5™) (American Psychiatric Association, 2013).[26]

Folic acid and vitamin B12 serum levels were determined from blood samples collected during hospitalization using an ADVIA Centaur immunoassay system (Siemens, Lisboa, Portugal). Direct competitive chemiluminescence immunoassay methods were performed to assess serum levels of both molecules. The expected variation of vitamin B12 serum levels in healthy subjects is between 211 and 911 pg/mL and of folic acid is > 5.38 ng/mL.

Participants' anonymity was always assured, as well as confidentiality of all data collected throughout the study.

Data was analyzed using the *Statistical Package for the Social Sciences* (SPSS) version 23.0 software.

The Kolmogorov-Smirnov normality test was used for distribution analysis of continuous quantitative variables, followed by non-parametric Mann-Whitney *U* test and Spearman's Correlation test. Qualitative variables were analyzed using the Chi-Square Independence ($\chi 2$) test.

Statistically significant differences were assumed for p values < 0.05. These were marked with * on tables.

RESULTS

A total of 165 patients were included in this study and divided in two groups: patients with psychotic symptoms during hospitalization (PS group; n=83) and patients without psychotic symptoms during hospitalization (nPS group; n=82).

PS group included 61 males (73.5%) and 22 females (26.5%), with an average age of 20.7 years (ranging from 12 to 25 years). nPS group included 33 males (40.2%) and 49 females (59.8%), with a similar average age of 20.7 years (ranging from 12 to 25 years).

Patients' final diagnosis was organized in 11 different groups, according to the DSM-5™ nosological classification (**Table 1**). In the PS group, most individuals were diagnosed with Schizophrenia Spectrum and Other Psychotic Disorders (75.91%), with 24.09% having other diagnoses (Depressive Disorders, Bipolar and Related Disorders, Personality Disorder, Neurodevelopmental Disorders and Substance-Related and Addictive Disorders). In the nPS group, the distribution of diagnosis across the nosological classification was wider, but no patients had Schizophrenia Spectrum and Other Psychotic Disorder (**Table 1**).

Table 1 - Final diagnosis of patients included in the study, according to the DSM-5™ (*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, American Psychiatric Association, 2013) nosological classification

	Total		PS group		nPS group	
Final diagnosis	***n***	**%**	***n***	**%**	***n***	**%**
Schizophrenia Spectrum and Other Psychotic Disorders	63	38.18	63	75.91	-	-
Depressive Disorders	28	16.97	5	6.03	23	28.06
Bipolar and Related Disorders	17	10.30	12	14.46	5	6.10
Feeding and Eating Disorders	14	8.49	-	-	14	17.07
Trauma- and Stressor-Related Disorders	10	6.06	-	-	10	12.20
Personality Disorder	9	5.45	1	1.20	8	9.76
Neurodevelopmental Disorders	9	5.45	1	1.20	8	9.76
Obsessive-Compulsive and Related Disorders	5	3.03	-	-	5	6.10
Disruptive, Impulse-Control, and Conduct Disorders	4	2.43	-	-	4	4.87
Substance-Related and Addictive Disorders	3	1.82	1	1.20	2	2.43
Anxiety Disorders	3	1.82	-	-	3	3.65

nPS – group without psychotic symptoms; PS – group with psychotic symptoms

The nPS group displayed significantly higher serum folic acid levels than the PS group (p=0.01) (**Table 3**). Conversely, no statistically significant difference was found between both groups regarding serum vitamin B12 levels (p=0.30) (**Table 2**). Although folic acid and vitamin B12 serum levels were higher in females than in males, this difference was not statistically significant (p=0.28 and p=0.48, respectively) (**Table 2**). Regarding psychiatric rehospitalizations, both folic acid and vitamin B12 serum levels were lower in rehospitalized patients. Nonetheless, this was also a non-statistically significant difference (p=0.33 and p=0.27, respectively) (**Table 2**).

On one hand, a weak negative correlation was found between folic acid serum levels and age (rs=-0.035) and between vitamin B12 serum levels and age (rs=-0.159), although only the latter was statistically significant (p=0.042) (**Table 3**). On the other hand, a weak positive correlation was found between folic acid and vitamin B12 serum levels (rs=-0.108), which was not statistically significant (p=0.181) (**Table 3**).

Table 2 - Association between psychotic symptoms and folic acid serum levels (µg/L), psychotic symptoms and vitamin B12 serum levels (pg/mL), sex and folic acid serum levels (µg/L), sex and vitamin B12 serum levels (pg/mL), folic acid (µg/L) serum levels and rehospitalizations (yes/no), and vitamin B12 (pg/mL) serum levels and rehospitalizations (yes/no)

Variable		Descriptors	Test	*P*	*effect size*
Folic acid	**PS**	*MR*=68.8, *IQR*=4.1	*U*=2291	0.01*	*r*=-0.20
	nPS	*MR*=87.1, *IQR*=4.1			
Vitamin B12	**PS**	*MR*=78.7, *IQR*=205	*U*=3047	0.30	*r*=-0.08
	nPS	*MR*=86.4, *IQR*=205			
Folic acid	**Sex – male**	*MR*=74.6, *IQR*=4.1	*U*=2660	0.28	*r*=-0.09
	Sex – female	*MR*=82.4, *IQR*=4.1			
Vitamin B12	**Sex – male**	*MR*=80.2, *IQR*=205	*U*=3076	0.48	*r*=-0.06
	Sex – female	*MR*=85.6, *IQR*=205			
Folic acid	**Rehospitalization – yes**	*MR*=71.7, *IQR*=4.1	*U*=1951	0.33	*r*=-0.08
	Rehospitalization – no	*MR*=80.0, *IQR*=4.1			
Vitamin B12	**Rehospitalization – yes**	*MR*=74.9, *IQR*=205	*U*=2070	0.27	*r*=-0.09
	Rehospitalization – no	*MR*=84.7, *IQR*=205			

IQR – interquartile range; MR – median of ranks; nPS – group without psychotic symptoms; PS – group with psychotic symptoms

Table 3 - Correlation between folic acid serum levels (µg/L), vitamin B12 serum levels (pg/mL), and age (years)

Variables	Age	Folic acid	Vitamin B12
Age	-	rs=-0.035 ; p=0.669	rs=-0.159 ; p=0.042*
Folic acid	rs=-0.035 ; p=0.669	-	rs=0.108 ; p=0.181
Vitamin B12	rs=-0.159 ; p=0.042*	rs=0.108 ; p=0.181	-

rs - Spearman's correlation coefficient

Lastly, a statistically significant association was found between presence of psychotic symptoms and rehospitalization (*p*=0.030), with patients with psychotic symptoms having a significantly higher probability of at least one rehospitalization (30%) than those without psychotic symptoms (16%) (**Table 4**).

Table 4 - Relationship between psychotic symptoms and rehospitalizations (yes; no)

Variables	Age	Folic acid	Vitamin B12
Age	-	rs=-0.035 ; p=0.669	rs=-0.159 ; p=0.042*
Folic acid	rs=-0.035 ; p=0.669	-	rs=0.108 ; p=0.181
Vitamin B12	rs=-0.159 ; p=0.042*	rs=0.108 ; p=0.181	-

df – degrees of freedom; nPS – group without psychotic symptoms; PS – group with psychotic symptoms

* Statistical significance (p<0.05)

DISCUSSION

This study's results show that folic acid serum levels are significantly lower in children and young adults hospitalized due to psychiatric disease associated with psychotic symptoms compared with same-aged psychiatric patients without psychotic symptoms. No statistically significant difference was found regarding vitamin B12 serum levels.

PS and nPS groups had a very similar patient number (83 and 82 patients, respectively) with the same age range (20.7 years on average for both groups). There was a male preponderance (73.5%) in the first group and a female preponderance in the second (59.8%). However, folic acid and vitamin B12 serum levels did not significantly vary with sex or age, contrarily to what happened with rehospitalizations. In this study, psychotic symptoms were found to increase the probability of at least one rehospitalization.

As far as we are aware, this is the first study directly investigating psychotic symptoms in youth independently of psychiatric diagnosis and testing their relationship with folic acid and vitamin B12 serum levels. In this sample, nPS group individuals also had an acute psychiatric disease and were hospitalized.

Patients' final diagnosis was organized into eleven nosological groups according to the DSM-5™. Although most patients in the PS group had Schizophrenia Spectrum and Other Psychotic Disorders (75.91%), 24.09% had other diagnoses (Depressive Disorders, Bipolar and Related Disorders, Personality Disorder, Neurodevelopmental Disorders and Substance-Related and Addictive Disorders). This was expected, since psychotic symptoms are frequently associated with Schizophrenia Spectrum and Other Psychotic Disorders and less common across other diseases. Still, these were included in the PS group and results were robust, suggesting that the presence of psychotic symptoms is apparently related to significantly lower folic acid serum levels in children and young adults, regardless of the diagnosis.

A study from 2006 described a high frequency of low folic acid levels in patients with a recent psychiatric hospitalization compared with healthy controls, but the presence or absence of psychotic symptoms was not assessed.[15]

A recent meta-analysis by Firth *et al* (2017) reported that, in patients with FEP, poor nutritional status, namely regarding folic acid, is independent and sometimes precedent of treatment with antipsychotics compared with healthy controls.[12] These findings were compatible with an Indian study reporting low folic acid and vitamin B12 levels in untreated FEP patients.[9] That study also showed that lower folic acid levels in those patients could not be attributed to dietary differences.[9] On the other hand, in the study by Ayesa-Arriola *et al* (2012) folic acid and vitamin B12 levels did not differ amongst non-affective FEP patients and healthy controls, what makes the relationship between FEP and folic acid levels debatable in comparison with the general population without psychiatric diseases.[11]

Another meta-analysis had already reported folic acid and vitamin B12 deficiency in patients with schizophrenia, while a Korean study stated that high folic acid levels seemed to decrease the risk of this disease and a Dutch study found an increased risk of low folic acid levels.[8,13,16,17,21] However, a clear association between folic acid levels and schizophrenia remains controversial.[4,8,10,11,13,14,16,18,24]

It should be noted that a statistically significant negative correlation was found between folic acid levels and severity of negative symptoms in a large number of non-smoking schizophrenic outpatients.[19] The study by Song *et al* (2014) also found that low folic acid serum levels and high homocysteine serum levels were associated with more severe symptoms in schizophrenia, particularly on the negative symptom domain.[14] This seems to support an association between low folic acid serum levels and severity of negative symptoms in schizophrenic patients. However, a different study did not find this association.[11] The present study focused on positive rather than negative symptoms.

Low folic acid serum levels were also found in depressed patients.[18] Conversely, Reif *et al* (2005) [25] found no statistically significant difference regarding folic acid or vitamin B12 in an ethnically homogeneous female population with different psychiatric disease, and Ipcioglu *et al* (2008)[23] found no statistically significant effect

of FEP or depression on folic acid or vitamin B12 serum levels, suggesting that patients did not differ from healthy controls.

Vitamin B12 deficiency has been reported to be frequent among hospitalized psychiatric patients, particularly with schizophrenia, with no hematological consequence for most of them.[22] In the study by Jayaram *et al* (2013), psychiatric symptoms including schizophrenia, psychotic episodes, affective bipolar disorder, and depressive disorder were reported in patients with vitamin B12 deficiency, but psychotic symptoms were not independently assessed.[20] Also in a recent study by Kapoor *et al* (2017), a higher prevalence of neuropsychiatric symptoms, including psychosis, was found in vegetarians, as well as an association with vitamin B12 but not with folic acid deficiency.[5]

In line with what was previously described regarding folic acid, also low vitamin B12 levels seem to be associated with more severe negative symptoms in schizophrenia.[10] However, other studies report otherwise, with higher (but not statistically significant) vitamin B12 serum levels in patients with chronic schizophrenia.[24]

Except for Reif *et al* (2005), all studies referred to in this discussion selected healthy individuals as control group.[25] In all of them, psychotic symptoms were not independently assessed, but rather the diagnosis of FEP, schizophrenia, depressive disorder, among others, or psychiatric disease in general, what precludes direct comparisons between those studies and the present one.

This study has several limitations that should be acknowledged. Firstly, it is a retrospective study with a relatively small sample of patients, and groups were not homogenized regarding sex. Secondly, no known exclusion criteria were applied regarding folic acid and vitamin B12, like smoking, alcohol ingestion, and exposure to certain drugs or specific genetic characteristics.[2] Additionally, no further analytical parameters were collected concerning time from the first hospitalization day and folic acid and/or vitamin B12 serum levels assessment. Another limitation is the fact that the presence or absence of psychotic symptoms was only determined based on patients' discharge note. Finally, a control group with healthy subjects was missing in this study.

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ORIGINAL ARTICLE

PARENTAL SUPPORT AND PERCEIVED SELF-EFFICACY – A STUDY OF PARENTAL PERCEPTIONS IN AN EARLY CHILDHOOD CHILD PSYCHIATRY UNIT

APOIO PARENTAL E COMPETÊNCIA PARENTAL PERCECIONADA – ESTUDO DE PERCEÇÕES PARENTAIS NUMA UNIDADE PEDOPSIQUIÁTRICA DE PRIMEIRA INFÂNCIA

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ABSTRACT

Introduction: Perceived parental self-efficacy (PSE) has shown an association with positive parental behavior, highlighting its benefit in promoting child well-being and healthy development. The identification of its potential determinants remains a focus of attention in mental health when assessing parental perceptions and cognitions or planning parental interventions.

Material/Methods: This was a cross-sectional study in an Early Childhood Child Psychiatry Unit. All parents of babies and toddlers assessed for the first time were included and completed a Parenting Sense of Competence (PSOC) scale (portuguese translation, α= 0.75-0.83) and two additional questions concerning perceptions of support from the other parent and family of origin. Average PSOC was compared between both parents and correlations with perceptions of support were tested. Statistical analysis was conducted in SPSS® version 21 through descriptive analysis and variable correlation (t-test and Pearson r).

Results: A total of thirty-four questionnaires were completed. Average PSOC was similar between father and mothers (73.44 vs 72.24, p=0.533). Fathers perceived themselves as more supported than mothers, either from the family of origin (5.09 vs 4.21, p=0.001), as from the other parent (4.91 vs 4.09, p=0.011). A positive correlation was found between father's PSOC and perception of support from the family of origin (r=0.639, p <0.01).

Conclusions: Among mothers of children followed in this Child Psychiatry Unit, support perceptions did not correlate with perceived parental self-efficacy. However, father's perceived self-efficacy could relate to perceptions of support, raising clinical attention on how fathers and their family of origin can influence the relational triad. Perceptions of parental support should be explored when considering within-family horizontal relations as a potential mechanism influencing vertical relations through its association with perceived self-efficacy.

Keywords: early childhood; parental perception; parental support; self efficacy

RESUMO

Introdução: A Competência Parental Percecionada (PSE) tem sido associada a comportamentos parentais positivos e, consequentemente, promotores do bem-estar e desenvolvimento harmonioso da criança. A identificação dos seus potenciais determinantes continua a ser um foco de atenção em saúde mental ao avaliar as perceções e cognições parentais ou ao planear intervenções com os mesmos.

Materiais/Métodos: Este foi um estudo transversal com uma amostra clínica de uma Unidade de Pedopsiquiatria da Primeira Infância. Todos os pais de crianças avaliadas pela primeira vez foram incluídos e preencheram o questionário de Sentimento de Competência Parental (Parenting Sense of Competence); tradução portuguesa, α=0.75-0.83) e duas perguntas sobre a perceção de apoio recebido pelo outro

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progenitor e pela família de origem. Foram corretamente preenchidos 34 questionários. A perceção média de competência parental foi comparada entre ambos os pais e foi testada a correlação com as perceções de apoio. A análise estatística foi efetuada no software SPSS® versão 21 através de análise descritiva e correlação de dados (t-test e Pearson r).

Resultados: Um total de 34 questionários foram preenchidos. O Sentimento de Competência Parental não diferiu significativamente entre pai e mãe (73.44 vs 72.24, p=0.533). Os pais percecionam-se como mais apoiados, quer pela família de origem (5.09 vs 4.2, p=0.001), quer pelas mães (4.9 vs 4.09, p=0.011). Foi identificada no pai uma correlação positiva entre o Sentimento de Competência Parental e o Sentimento de Apoio pela Família de Origem (Pearson r=0.639, p<0.01).

Conclusão: Entre as mães, as perceções de apoio não se correlacionaram com o sentimento de competência parental. Contudo, a correlação encontrada entre os pais enfatiza como a respetiva família de origem poderá influenciar a tríade relacional. As perceções de apoio parental deverão ser exploradas ao considerar as relações horizontais intrafamiliares como um potencial mecanismo de influência das relações verticais, pela sua associação com a competência parental percecionada.

Palavras-chave: apoio parental; competência parental percecionada; perceção parental; primeira infância

INTRODUCTION

The present study started from a reflection on the potential benefit of identifying parental perceived self-efficacy (PSE) determinants, as it has been linked to a number of relevant parental and child outcomes.[1,2] PSE can be defined as the level of confidence felt by caregivers during daily parenthood challenges. It can be usually classified in three distinct dimensions: task-especific, domain-specific, and general or broad, based on Bandura's conceptual framework.[3,4] According to previous investigations, it is an important determinant of positive parental behavior and hence of good development and child well-being.[1,2,5,6] When looking at the underlying factors regarding PSE, there is considerable evidence of parental depression and infant behavior as two important variables inversely correlated in cross-sectional studies.[7,8] Self-efficacy as initially conceptualized could be useful in parenting challenges, reciprocally interacting with performance. Although parental depression and measures of psychological well-being have been studied, there is a lack of information regarding each parent individually. Regarding fathers, much remains to be known about PSE during early childhood. Regarding mothers, an inverse relation has been shown between PSE and depressive and anxious conditions, as well as an insecure attachment pattern.[7,8] From the toddler perspective, better adjustment capacity, greater enthusiasm, and less avoiding behavior and negativism have been shown in those taken care of by parents with higher PSE.[2,7,8]

The New Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood DC:0-5 pays particular attention to relational information (which can be included in a new Axis I diagnostic category) as a movement to better classify the network of close relationships surrounding the child.[10] During clinical practice in a Child Psychiatry Unit, assessment of parental perceptions holds an important position, as it can influence not only behavior but also how relational experience is integrated. From this starting point, this study aimed to explore how parental beliefs could relate to their own psychologic well-being and explore the role of family interactions as a relevant mediator.

From the importance of a perception-mediated construct, this study sought to investigate the relevance of other perceptions potentially relevant for parents, namely parental support. Specifically, the study aimed to assess parental perceptions of mutual support and support from each parent's family of origin, thus exploring horizontal relations within the family as a potential mechanism influencing vertical (parent-child) relations through association with PSE. More than quantifying help and behavior, the study's main interest was to investigate how support is mentally integrated as a feeling or cognition, accessible through perceptions rather than through inventory and description of concrete actions. The hypothesis under investigation is the existence of a link between perception of mutual support or perception of support from the family of origin and parental PSE.

MATERIALS AND METHODS

Study design: Cross-sectional, clinical sample.

Sample: Parents of babies and toddlers assessed for the first time in an Early Childhood Child Psychiatry Unit.

Exclusion Criteria: 1) Children attending foster residential care or raised by other than biological or foster parents; 2) Death of a parent; 3) Physical abuse or any legal situation.

Data collection: Self-completed parental Parenting Sense of Competence (PSOC) scale (portuguese translation, reported internal consistency α=0.75-0.83) and two additional questions concerning perception of support from the other parent (SOP) and from the family of origin (SFO) completed at the end of the first medical appointment or at the beggining of the second one.

Presence of the other parent when completing the form was registered by the physician, in an effort to look at possible bias generated by inhibition or interference when declaring support perceptions. Two distincts situations were identified: simultaneity and non-simultaneity.

Assessment scale: Portuguese version of PSOC: Escala de Sentimento de Competência Parental – ESCP).[11] Support perceptions were addressed through two additional questions also evaluated in a Likert scale concerning support perception from the other parent and from one's own family of origin. Formulation of additional questions had a similar presentation to the original PSOC instrument: "I feel supported and understood by the father/mother of the child" and "I feel supported and understood by my family". Answers were quantitative and dichotomous – negative from 1 to 3 and positive from 4 to 6.

PSOC is a self-reported questionnaire with 17 different items which allow to evaluate perception of general sense of competence in two main dimensions: self-efficacy and parental satisfaction, with reported Cronbach alpha values of 0.75 and 0.76, respectively. The scale has been redesigned to its current formulation by Johnston and Mash and does not include a cutoff threshold. It has been tested in the portuguese population, and a factorial analysis considering satisfaction, self-efficacy, and interest confirmed its validity.[11]

Statistical analysis

Statistical analysis was performed using SPSS® version 21. Inferential analysis was performed through t-test for unpaired samples and variable correlation was performed through Pearson r. The level of significance admitted in the presente study was 0.05.

RESULTS

Descriptive analysis

A sample of 34 correctly completed questionnaires was collected, with an average maternal and paternal age of 32.8 and 37.3 years, respectively. Regarding educational level, most parents had higher education (20 mothers and 18 fathers), followed by highschool (11 mothers and 11 fathers) and basic (three mothers and five fathers) education.

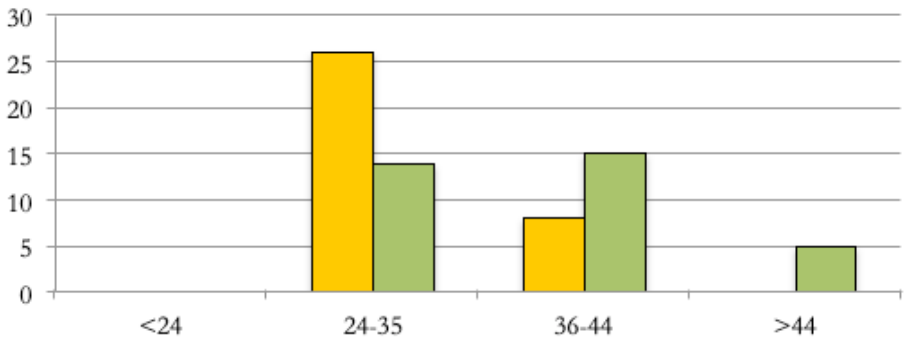

Figure 1 - Parental distribution by age

Inferential analysis

No significant differences were found between average PSOC in fathers versus mothers (73.44 vs 72.24, p=0.533). Perception of SFO in fathers achieved a superior average score than in mothers (5.09 vs 4.21, p=0.001). Perception of SOP in fathers was also higher compared to mothers (4.91 vs 4.09, p=0.011).

Table 1 - PSOC (Parenting Sense of Competence), SFO (Perceived Support from Family of Origin) and SOP (Perceived Support from the Other Parent)

Father			
	Mean	Std. Deviation	N
PSOC-Father	73.441	6.500	34
SFO-Father	5.089	0.865	34
SOP-Father	4.911	1.055	34
Mother			
PSOC-Mother	72.235	9.607	34
SFO-Mother	4.205	1.122	34
SOP-Mother	4.088	1.564	34

Table 2 - Parenting Sense of Competence (PSOC) in Mothers and Fathers – average correlation

Average correlation (PSOC) Mother vs Father								
	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
PSOC Father - PSOC Mother	1.205	11.167	1.915	-2.69	5.102	0.63	33	0.533

Table 2.1 - Perception of Support from Family of Origin (SFO) in mothers and fathers

Average correlation (SFO) Mother vs Father								
	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
SFOFather - SFOMother	0.882	1.451	0.248	0.375	1.388	3.544	33	0.001

Table 2.2 - Perception of Support from the Other Parent (SOP) in mothers and fathers

Average correlation of SOP Mother vs Father								
	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
SOP Father -SOP Mother	0.823	1.783	0.305	0.201	1.445	2.693	33	0.011

When analyzing presence of the other parent as an interference factor individually, mother's PSOC did not significantly change when answering in presence of the father (simultaneity situation; 69.76 vs 76.11, p=0.187). Father's average PSOC in presence of the mother also did not significantly change (73.16 vs 72.0, p=0.706). When analyzing simultaneity effect, neither parental PSOC reached statistical significance, despite a descending trend observed in mother's PSOC in the simultaneity situation.

Table 3 - Presence of the other parent during evaluation and PSOC correlation

Presence of other parent during questionnaire and PSOC correlation (mother vs father)							
	Paired Differences						
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
				Lower	Upper			
Simultaneity vs non-simultaneity-Mother	-7.888	16.381	5.460	-20.481	4.703	-1.445	8	0.187
Simultaneity vs non-simultaneity-Father	2.333	9.291	5.364	-20.748	25.414	0.435	2	0.706

Results: Father

A positive correlation was found between PSOC and perception of SFO in fathers (r=0.639, p<0.01).

No significant correlation was found between PSOC and perception of SOP in fathers (r=0.289; p=0.098), as well as between perception of SOP and perception of SFO.

Table 4 - Correlation analysis of Parenting Sense of Competence (PSOC) and perception of Support from Family of Origin (SFO) in fathers

SFO-Father		
PSOC-Father	Pearson Correlation	0.639**
	Sig. (2-tailed)	<0.001

**Correlation is significant at the 0.01 level (2-tailed).

Table 5 - Correlation analysis of Parenting Sense of Competence (PSOC) and perception of Support from the Other Parent (SOP) in fathers

SOP-Father		
PSOC-Father	Pearson Correlation	0.289
	Sig. (2-tailed)	0.098

Results: Mother

When analyzing maternal results, no correlation was found between PSOC and perception of SOP or SFO.

Also no association was found between perception of SOP and perception of SFO in mothers.

Table 6 - Correlation analysis of Parenting Sense of Competence (PSOC) and perception of Support from the Other Parent (SOP) in mothers

SOP-Mother		
PSOC-Mother	Pearson Correlation	0.089
	Sig. (2-tailed)	0.615

Table 7 - Correlation analysis of Parenting Sense of Competence (PSOC) and perception of Support from Family of Origin (SFO) in mothers

SFO-Mother		
PSOC-Mother	Pearson Correlation	0.192
	Sig. (2-tailed)	0.276

Table 8 - Correlation analysis of Perception of Support from the Other Parent (SOP) and perception of Support from Family of Origin (SFO) in mothers

SFO-Mother		
SOP-Mother	Pearson Correlation	0.11
	Sig. (2-tailed)	0.535

DISCUSSION

As an overview, one might discuss how parental support perceptions could be integrated in the process of developing parental sense of competence. In addition to bringing some insights on how PSE could relate to caregiver's horizontal network of significative relations, we included fathers in the study design, looking for differences in perceptions between both genders. The impact of family relationships on PSE remains understudied,[2] and results from this study may indicate that it is important to separate relationships individually within the family (i.e. marital support and support from family) for environmental assessment, reinforcing the idea of different constructs.

PSE as a measure of parental satisfaction and efficacy is known to promote healthy development of babies and toddlers in the clinical setting. More than quantifying tasks, examining parental behaviors, or assessing marital status or general agreement concerning raising and educational issues, this study looked at perceptions, which can be regarded as one of the structural components of psychic life, called to act during parenthood everyday challenges. The present study does not seem to support an association between higher levels of PSE and more positive family functioning or greater marital satisfaction in the mother, as previously demonstrated.[2]

Considering the constant emotional interplay between a child and his/her caregiver during early childhood psychic development, it is acknowledged that relational quality and reciprocity could be easily influenced by the emotional status of the caregiver, as it will influence the child's acquisition of new functional and emotional capabilities. Therefore, the required relational capabilities of the caregiver could in some way depend on the emotional availability from (or, more importantly, on the way it is perceived by) other relevant people with who he relates closer to. The relationship-based therapies delivered during some of our clinical interventions highlight the importance of emotions, not only expressed by the children, but also by caregivers, some of which are secondary to perceptions, cognitions, or beliefs regarding their own individual experience.

There is a growing body of literature focusing on coparenting and whole-family dynamics. Distinct patterns of triadic family interactions have been discerned and the coparenting construct itself can be seen as a specific form of triadic or higher-level family process early in the family life cycle.[14] The role of the father within the triadic interaction influences the child's well-being, not only through his own process of attachment, but also through cooperative and warm interactions, thus increasing coparenting quality.

According to Belsky's conceptualization of parental behavior, this is the result of the interplay between the child's temperament and gender, parental personality traits, and social contextual influences. At present, it remains unclear how PSE varies with environmental factors or gender.

When looking at the literature, personal determinants like depression and stress have been inversely correlated with maternal PSE.[1,2] PSE may be sensitive to various contextual factors, without identifying family relationships as one of them.[12] However, other authors suggest it could depend on the support and encouragement of one's partner.[3] The apparent conflicting evidence regarding mother's PSE and environmental factors could result from a mostly internalizing functioning compared to fathers, reinforcing the idea of greater independence from outer compared compared with inner variables. In this context, studying parental perceptions could help to clarify the reach of a frequently projective description (towards the family of origin or other parent) regarding the cause of the child's difficulties/symptoms/needs or alternatively their own.

The authors' expectation was to find differences according to the subpopulation of parents, since perception of support could be affected by emotional instability, conflict within the parental couple, or personality traits which could be tested in subsequent analyses. On the other hand, mothers rehearsing a symbiotic appeal or with a mainly fusional vertical relationship with their children usually perceive themselves as more competent. In situations of a burdening diagnosis on axis I, it could also contribute to a lower perception of parental self-efficacy, as previously suggested in the literature.[1-8]

Regarding gender differences, perception of SFO averaged higher in fathers than in mothers in this study. Additionally, perception of SOP was found to be higher in fathers. No differences were found considering PSE between parents, although theoretically the clinical environment and the fact that most children were boys could interfere with parental perceptions, mostly through the child's behavior, as the literature finds mothers to rate themselves with lower PSE in a temperamental child.[8] Our clinical population of parents, vulnerable by the burden of disease or infant condition, could easily face anxiety, depressive symptoms, or simply tiredness. Additionally, very heterogeneous clinical situations were behind each child psychiatry visit.

The correlation of father's PSE with their family of origin is in line with existing data, since family environment has been considered a significant factor in father behavior and father-child relationship.[13] That could add some insights on how within-family relationships influence men's self-efficacy and parenting behavior.

LIMITATIONS

This study has some limitations that should be acknowledged, as the fact that the assessment was based on self-reported measures and the selection bias of the clinical population of parents enrolled, without sorting children characteristics, behavior, or temperament. Also, the study's cross-sectional design does not allow causal interpretations. The fact that perception of support was evaluated with a quantitative and dichotomous question may have interfered with answering accuracy, since it implies judgment (although it was stratified in negative [1–3] and positive [4–6]). Although simply and directly formulated, this assessment method is not validated as a

perception evaluating instrument. Also, although assumptions for the use of parametric tests (t-test) have been verified in the present study (i.e., normal distribution for samples < 30), the small sample size may have influenced the results obtained.

CONCLUSION

The initial purpose of identifying associations between parental perceptions and PSE was partially achieved, with a positive correlation between father's PSE and perception of SFO. Regarding mothers, no significant correlation was found between PSE and perception of support, neither from the father nor from the family of origin. Mothers and fathers did not differ significantly concerning perceived self-efficacy.

Although perception of support from the other parent does not seem to correlate with PSE according to study results, considering the study's limitations and reduced sample, further insights into gender differences are recommended to individualize clinical therapies.

Further studies are necessary to understand how father's PSE could be influenced by relevant people with whom he relates closer to during the process of raising babies and toddlers in face of developmental difficulties, thereby adding valuable information when assessing relational context or wider psychosocial elements. In further studies, it could be interesting to correlate parental perceptions with child's primary diagnosis.

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CASE REPORTS

LANGUAGE REGRESSION AS A MANIFESTATION OF EPILEPSY

REGRESSÃO DA LINGUAGEM COMO MANIFESTAÇÃO DE EPILEPSIA

Joana Ferreira[1], Sofia Lopes[1], João Carmona Lopes[2], Cristina Ferreira[1], Catarina Magalhães[1]

ABSTRACT

Introduction: Childhood epileptic encephalopathies are age-dependent brain disorders in which ictal and interictal epileptogenic activity is the apparent cause of progressive cognitive and neuro-psychological impairment.

Case report: A previously healthy four-year-old boy presented to the Emergency Department with a history of receptive and expressive language regression with four days of evolution, associated with seizure onset. Clinical features and electroencephalographic findings led to diagnosis of Landau-Kleffner syndrome. The boy was treated with valproate, clobazam, and prednisolone, with language improvement.

Discussion/Conclusion: Landau-Kleffner syndrome is a rare epileptic encephalopathy with pathognomonic sudden aphasia, epilepsy, and *paroxysmal* electroencephalographic abnormalities. The condition should be suspected in children with normal development who show a deterioration of established language skills. Early diagnosis and treatment are important to improve outcome.

Keywords: cognition; epilepsy; epileptic syndromes; Landau-Kleffner syndrome

RESUMO

Introdução: As encefalopatias epiléticas são um conjunto de síndromes dependentes da idade, em que a atividade paroxística ictal e interictal é responsável por deterioração cognitiva e neuropsicológica.

Caso Clínico: Um rapaz de quatro anos de idade, previamente saudável, foi admitido no Serviço de Urgência devido a um quadro de regressão da linguagem compreensiva e expressiva com quatro dias de evolução, associado ao surgimento de crises epiléticas. As características clínicas e alterações no eletroencefalograma conduziram ao diagnóstico de síndrome de Landau-Keffner. O rapaz foi tratado com valproato, clobazam e prednisolona, com melhoria da linguagem.

Discussão/Conclusão: A síndrome de Landau-Kleffner é uma encefalopatia epilética rara, caracterizada por afasia adquirida, epilepsia e anomalias paroxísticas eletroencefalográficas. Deve haver suspeita clínica perante uma criança com desenvolvimento normal que inicia um quadro de regressão da linguagem. O diagnóstico precoce e tratamento adequado são importantes para melhorar o prognóstico.

Palavras-chave: cognição; epilepsia; síndromes epiléticas; síndrome de Landau-Kleffner

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INTRODUCTION

Landau-Kleffner syndrome (LKS), also known as acquired epileptic aphasia, was first described by Landau and Kleffner in 1957.[1]

LKS is defined as an epileptic encephalopathy, in which epileptic activity results in a deterioration of cognitive, sensory, and/or motor functions. According to several authors, LKS is currently considered a clinical variant or subtype of encephalopathy related to electrical status epilepticus during slow sleep (ESES). However, the International League Against Epilepsy (ILAE) considers the two conditions as separate entities.[2]

The most prominent LKS defining feature is acquired aphasia, whereas epileptic seizures are infrequent and not a prerequisite for diagnosis.[3]

The typical type of aphasia is verbal auditory agnosia consisting of failure to provide semantic significance to different sounds. Loss of receptive language is followed by or concurrent with expressive aphasia, a marked reduction in spontaneous speech. Other clinical manifestations include cognitive impairment and behavioral problems. Such impairment may be global or focal, based on location of epileptic discharges, and progressive, presumably related to increasing epileptiform activity.[4]

Herein the authors report the case of a previously healthy four-year-old boy with LKS and discuss the electroclinical features, treatment, and prognosis of this clinical entity based on a literature review.

CASE REPORT

A four-year-old boy was admitted to the Emergency Department with regression in language abilities with four days of evolution. His parents reported that he produced only a few words with no sentences and speech seemed more hesitant. Verbal auditory agnosia was also present, with the boy having difficulty in understanding what parents told him and answering common questions. Additionally, he forgot previously known words and relied on gestures to aid in communication with parents. Simultaneously, the family reported that the boy had episodes of consciousness suspension and eyelid myoclonia several times a day characterized by suddenly stopping activity, tilting the head backwards, and fluttering the eyelids. These episodes had a sudden onset and offset and usually lasted only a few seconds.

No family history of epileptic seizures was reported. Birth history was unremarkable and developmental milestones were normal until this event.

On admission, the patient's vital data and anthropometry were normal. No facial dysmorphism was present. Neurological examination was unremarkable, except for language, as the boy was unable to understand verbal instructions and displayed occasional episodes of mostly imperceptible verbal language, even to his caregivers.

Faced with this clinical presentation, neurological and systemic causes were considered, including structural brain injuries, epileptic encephalopathies, infectious or autoimmune encephalitis, and metabolic or toxic diseases.

Analytical study (complete blood count, serum electrolytes, calcium, and blood glucose) was normal. Urine drug screen was negative. Brain computed tomography (CT) scan revealed no abnormality. Electroencephalogram (EEG) revealed spike-and-wave epileptiform activity prominent in the left centrotemporal region, which became virtually continuous when the child fell asleep (**Figure 1 and 2**), and generalized 2- to 3-Hertz spike-and-wave discharges, accompanied by eyelid myoclonia, occurring in wakefulness (**Figure 3A and 3B**). Brain magnetic resonance imaging (MRI), audiogram, and tympanogram were normal.

Once LKS diagnosis was established, treatment was started with valproate 20 mg/kg/day and clobazam 0.25 mg/kg/day for three days, followed by 0.5mg/kg/day. On the third day of treatment, seizure frequency improvement and slight verbal language recovery were observed: word output increased, although speech remained mostly imperceptible. The remaining neurological examination was normal.

Fifteen days after starting treatment, the child retrieved perception ability. He was able to understand more complex requests and answer questions easily. Marked improvement in expressive language and vocabulary was also observed, accompanied by an intelligible speech and ability to form complete sentences.

After almost three months of follow-up, ESES pattern persisted in EEG, prompting initiation of prednisolone at a dose of 4 mg/kg/day. At the end of the first month of triple therapy, EEG result returned to normal.

Clobazam was maintained for five months. High-dose corticosteroids were used for one month and tapered down over seven months. After that, the child remained on monotherapy with valproate.

When the boy completed two years of follow-up, and despite normal language function and absence of seizures, ESES pattern reappeared on EEG, prompting the addition of clobazam treatment and up-titration of valproate dosage to 28.5 mg/kg/day. Control EEG was performed two months later, showing EEG activity resolution. GRIN2A mutation screening by multiplex PCR sequencing was negative.

Currently, at the age of seven years, the boy attends the second grade of primary school with good academic performance, takes hip-hop dance classes, and shows normal neurodevelopment.

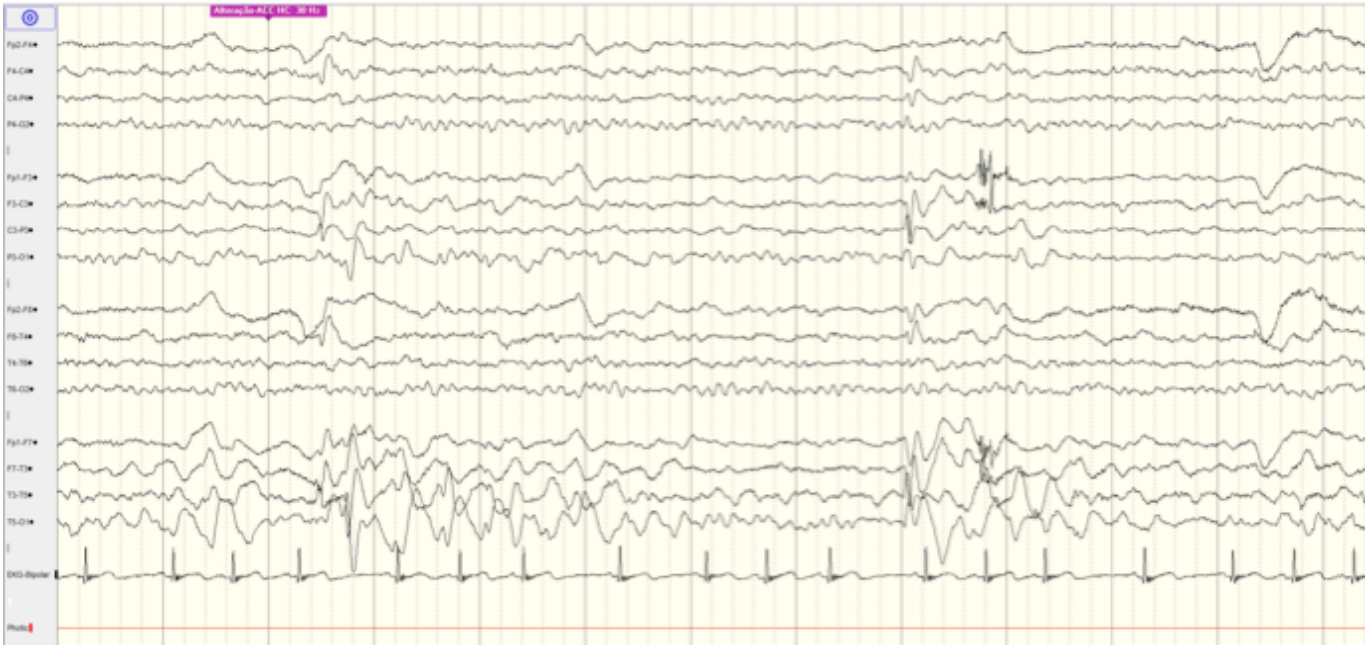


Figure 1 - EEG during wakefulness showing epileptiform activity, prominent in left centrotemporal region

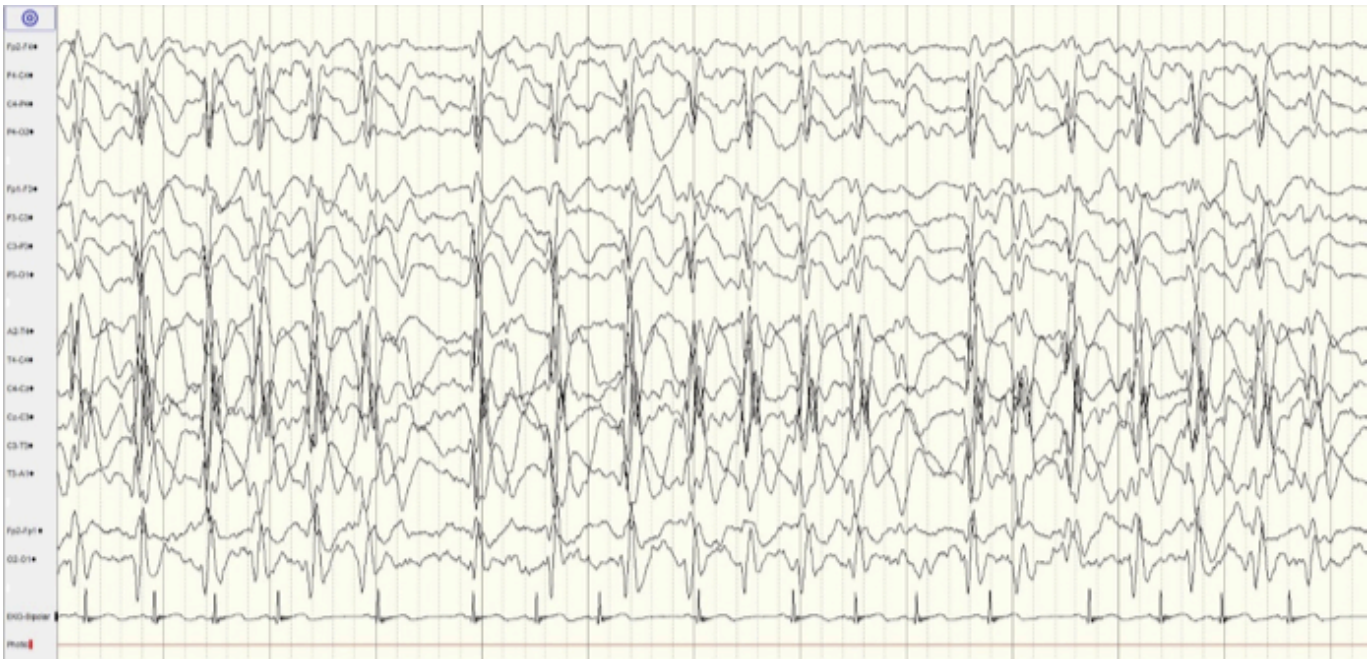
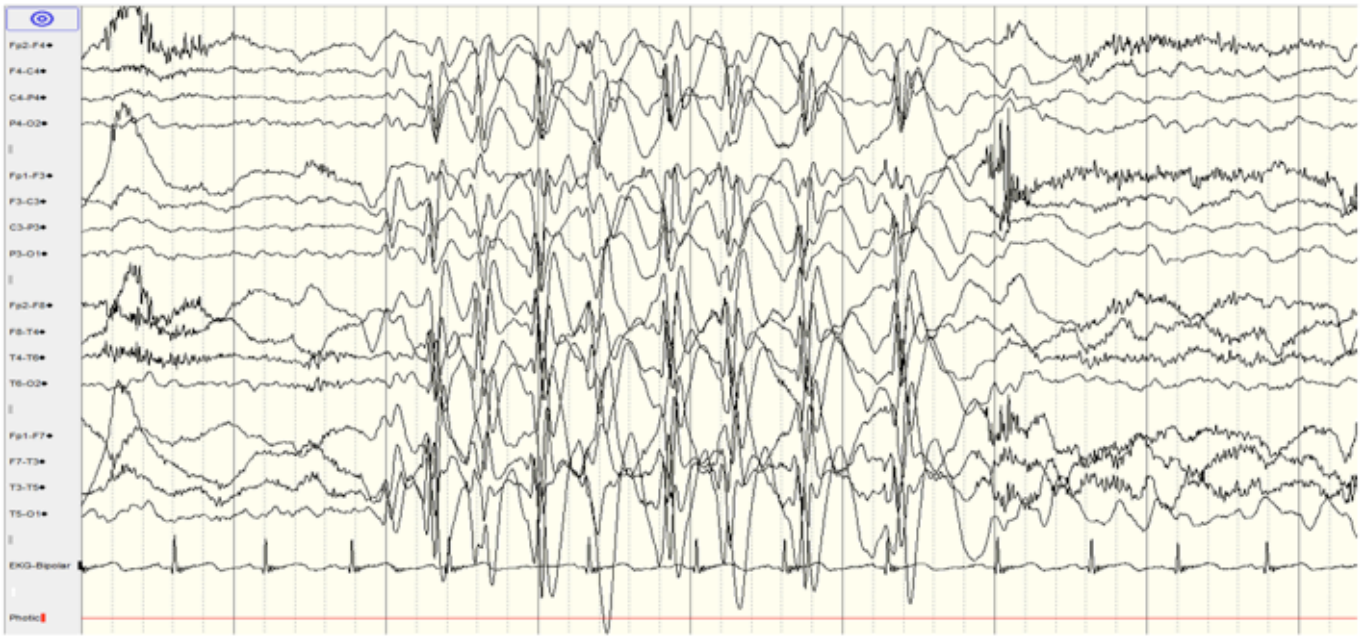


Figure 2 - EEG showing spike-and-wave epileptiform activity, virtually continuous when the child fell asleep



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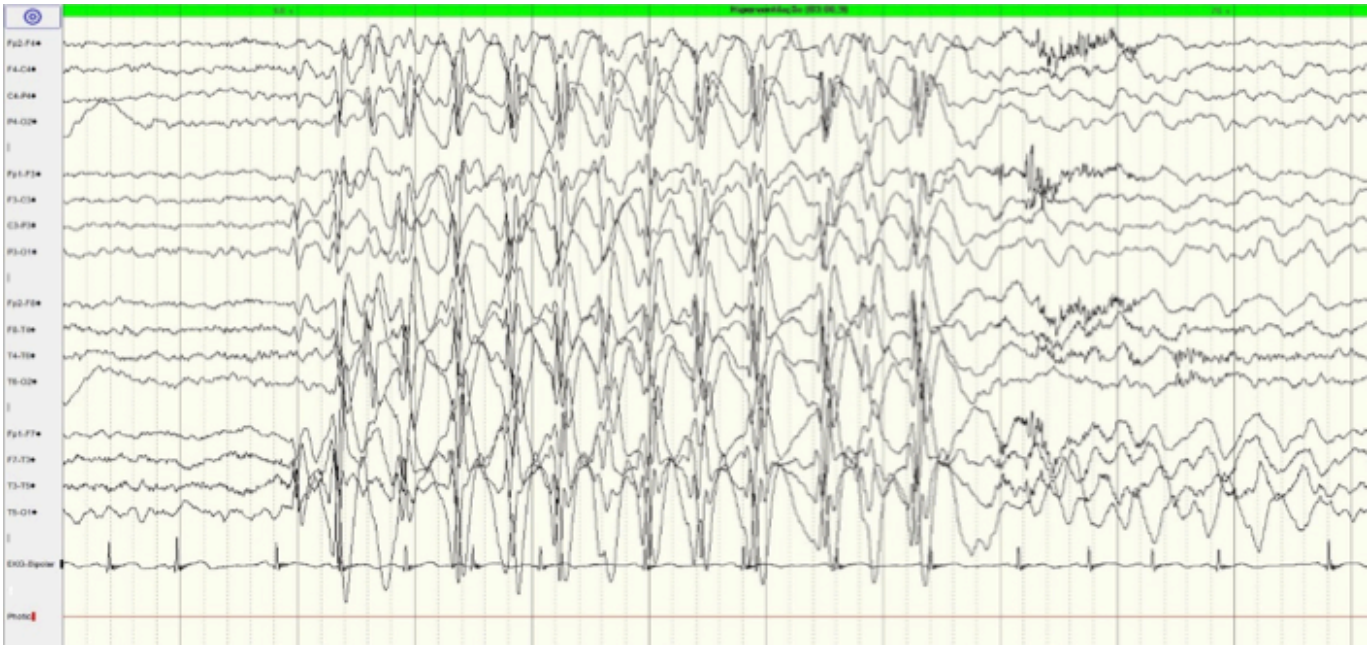

B

Figure 3 - EEG during wakeful rest (A) and hyperventilation (B) showing generalized spike-and-wave discharges (accompanied by eyelid myoclonia).

DISCUSSION

LKS is a rare childhood disorder with associated acquired aphasia and epileptiform EEG abnormalities.[2] Although its true incidence and prevalence are unknown, boys are affected twice as frequently as girls.[5] Similarly to most cases reported, in the present case the age of onset was four years.[6] LKS commonly occurs between the ages of three and seven years, although onset as early as 18-22 months and as late as 13-14 years has been described.[6]

The disorder begins with severe disturbance of auditory language comprehension, combined with substantial expressive language disruption.[6] Concordantly, the present case showed both expressive and receptive language difficulties, despite normal hearing tests.

About two thirds of children with LKS have personality disorders and behavioral disturbances. The most frequently observed behavioral problems are attentional deficits, impulsivity, distractibility, and hyperactivity.

Seizures are present in approximately 75% of cases but are usually infrequent.[4] EEG abnormalities are required to establish the diagnosis.[4,7-9] Generalized, bilateral, focal, or multifocal spike and wave discharges may be present, usually with central or temporal lobe predominance. When the child falls asleep, epileptiform activity becomes virtually continuous and is classified as status epilepticus during sleep (SES).[4]

With sophisticated imaging and nuclear medicine techniques, the epileptiform process can be shown to originate in the language cortex of the dominant temporal lobe and secondarily to spread to the homologous cortex in the other hemisphere and beyond.[10] No structural abnormalities are typically seen on routine neuroimaging with CT scan or MRI. However, volumetric analysis of MRI in four children with typical LKS has shown volume reductions of 26 to 51 percent in the bilateral superior temporal areas, regions that correspond to the auditory association cortex.[11,12] It is unclear whether this focal cortical atrophy is the cause of LKS or the result of intractable epileptiform activity.[11,12]

Language deterioration in these children may be caused by interruption of normal cortex maturation in the temporal lobes during a critical development period when the brain is making new synapses and removing others. Pervasive epileptiform activity is thought to activate and perpetuate synaptic connections that would, in the course of normal development, be removed.

The involvement of both temporal lobes eliminates the possibility that an uninvolved temporal lobe can subsume the function of the other, as often occurs in children with lesions that disrupt the dominant speech cortex early in development.[4]

The exact etiology of this disorder is unknown, but a genetic predisposition has been postulated.[4,7] Mutations in *GRIN2A* gene have been described in up to 20% of individuals with LKS.[4] A number of additional genes, including *SRPX2,*[13] *RELN*, *BSN*, *EPHB2*, and *NID2*,[14] have also been implicated. Mutations in *RBFOX1*, *RBFOX3*, and *CNKSR2* [15] genes have been reported in patients with disorders along the epilepsy-aphasia spectrum.

Other reported etiologies include neurocysticercosis, progressive encephalitis, acute disseminated encephalomyelitis, toxoplasmosis, temporal lobe tumors, cortical malformations (eg, polymicrogyria), and vascular insults.[4,7]

LKS is defined as an epileptic encephalopathy. This means that the epileptic activity per se may contribute to language decline and behavioral impairment, either partially or completely.[2]

Therefore, this is one of the few settings in which treating EEG abnormalities, even when seizures are fully controlled or absent, may be important, as electrical epileptic activity itself is assumed to contribute to progressive cerebral function disturbance. Thus, treatment goal is not simply to control seizures, but also to eliminate the underlying EEG abnormality, in order to prevent/reverse the loss of neurologic function. Given these treatment goals, it should come as no surprise that conventional antiepileptic drugs (AEDs) are of limited benefit when used as sole therapy. If epileptic activity and language impairment persist with AEDs in the course of a few weeks, steroid therapy should be started.[16] This has been done in the present case, aggressively treating the patient after diagnosis with a combination of valproate, benzodiazepines, and oral steroids, enabling, not only to suppress clinical seizures, but also to eliminate the underlying EEG abnormality to modify the course of the disease.

There is no international consensus regarding treatment of this condition. Rapid initiation of drug therapy has proven to be important for prognosis. Valproate, levetiracetam, and clobazam (or other benzodiazepines) are the most frequently used antiepileptic drugs, but can sometimes have partial or transient effects on the clinical and electrographic picture. Steroids have shown efficacy in improving both EEG activity and language.[17]

Intravenous immunoglobulin therapy has yielded varying results. It may nevertheless be considered in patients who are refractory to antiepileptic drugs or steroids, or in those with language impairment recurrence upon steroid withdrawal.[18]

Some patients may benefit from surgical treatment, but the approach must be individualized.[4,19]

LKS long-term outcome is not completely clear. The disease outcome is variable, and serious language disturbances occasionally remain until adulthood.[20]

Some studies suggest that aphasia onset before or after the age of five years has an important impact on long-term outcomes.[8]In the present case, it is possible that onset at the age of four years may be related to worse outcome and explain the relapse of EEG abnormalities two years after diagnosis, despite language and seizure improvement. As a result, we believe that long-term follow-up is necessary.

With this case, the authors intend to increase awareness of this rare condition, emphasizing that in one-quarter of cases clinical seizures are not present and language regression is the main characteristic feature. Early diagnosis, before global deterioration develops, appears to be crucial for effective treatment with minimal neuropsychological

sequelae.

CONCLUSION

Landau-Kleffner syndrome is a rare, age-related encephalopathy. It occurs in previously healthy children with normal language skills and development. The exact etiology is unknown. EEG abnormalities are required for diagnosis. Early treatment is associated with improved seizure control and cognitive outcomes.

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CASE REPORTS

MOEBIUS SYNDROME - IMPROVING OUTCOME WITH COMBINED STATE-OF-THE-ART SURGICAL AND REHABILITATION TREATMENTS

SÍNDROME DE MOEBIUS – MELHORAR O PROGNÓSTICO COM TRATAMENTOS CIRÚRGICOS E DE REABILITAÇÃO DE PONTA

João Paulo Castro[1,3], Luís Afonso Vouga[2,4], Inês Santos Jorge[2], Maria Paz Cunha[2], Rosa Amorim[2], Lurdes Palhau[2]

ABSTRACT

Moebius Syndrome (MBS) is a rare disorder, characterized by congenital, non-progressive facial palsy and other cranial and limb defects. A typical "mask-like" appearance, drooling, and indistinct speech comprise the dominant features.

Treatment focuses on correcting deformities and enhancing functionality. Surgical free functional muscle transfer (FFMT) is the gold standard for facial reanimation. A comprehensive rehabilitation program addressing motor, cognitive, and social impairment is paramount, despite the scarcity of knowledge regarding MBS rehabilitation, especially concerning central nervous system reorganization.

A six-year-old boy with MBS received treatment in our Department since the age of four months, including speech, physical, and occupational therapy. Recently, he underwent facial reanimation surgery.

The authors believe that rehabilitation improved the patient's outcome by enhancing cortical representation before and neuroplasticity after surgery. Coordination of both interventions seems pivotal to fully address MBS.

Keywords: facial paralysis; Moebius syndrome, occupational therapy, physiatry, physical therapy, rehabilitation, speech therapy

RESUMO

A síndrome de Moebius (MBS) é rara e caracteriza-se por paralisia facial e outros defeitos congénitos não-progressivos do crânio e membros. O fácies inexpressivo, a sialorreia abundante e o discurso ininteligível constituem as características dominantes.

O tratamento visa corrigir deformidades e otimizar a função. A transferência de enxerto muscular funcional (FFMT) é o *gold standard* na cirurgia de reanimação facial. Um programa de reabilitação abrangente dirigido às limitações motoras, cognitivas e funcionais também é fundamental, apesar da escassez de conhecimento acerca da reabilitação na MBS, sobretudo no que diz respeito à reorganização do sistema nervoso central.

Um rapaz de seis anos com MBS recebeu tratamento no nosso Departamento desde os quatro meses, incluindo terapia da fala, fisioterapia e terapia ocupacional. Recentemente, foi submetido a cirurgia de reanimação facial noutra instituição.

Os autores acreditam que a reabilitação melhorou o resultado final, ao potenciar a representação cortical antes e a neuroplasticidade após a cirurgia. A coordenação entre ambas as intervenções parece essencial para o tratamento holístico do MBS.

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Palavras-chave: fisiatria, fisioterapia, paralisia facial, reabilitação, síndrome de Moebius, terapia da fala, terapia ocupacional

INTRODUCTION

Moebius syndrome (MBS) was first described by Paul Moebius in 1892 and is characterized by the association between facial palsy and other cranial and limb deformities.[1,2] Prevalence is estimated to be 1/50.000 to 1/500.000 live births, with equal incidence in both sexes.[3]

Initially thought to be a sporadic disorder associated with *in utero* events, recent gene (PLXND1 and REV3L) discoveries highlighted a cause for familial cases and reports demonstrated an autosomal and X-linked inheritance.[4-6]

Minimum diagnostic criteria are "*congenital, non-progressive, bilateral or unilateral, symmetrical or asymmetrical facial and abducens nerve palsies, in the presence of full vertical gaze*".[5] The typical "mask-like" face of MBS patients leads to impaired non-verbal communication that, together with drooling and indistinct speech, are the dominant features of this heterogeneous syndrome.[4] Evaluation by a geneticist is important whenever a different diagnosis is suspected and to predict risk for future offspring.[5]

Treatment focuses on correcting deformities and enhancing functionality. Advances in microsurgical techniques have made surgical free functional muscle transfer (FFMT) the gold standard for treating long-standing facial paralysis.[7] A rehabilitation program addressing motor, cognitive, and social impairment is paramount. Interventions can aim to improve feeding, swallowing, saliva management, facial movement, speech intelligibility, social skills, and communication quality. The combination of surgery and rehabilitation is likely to improve clinical and functional outcomes. New surgical techniques, such as nerve-graft muscle anastomoses, have introduced new neural pathways contributing to the expansion of neuro-rehabilitative approaches by means of exploiting brain plasticity. Findings that motor cortex participates in sensory information processing challenged the classic view of movement circuitry and gave support to the use of sensory stimulation techniques in therapy.[8] The same occurred with mirror neuron system (MNS) findings, which have contributed to explain learning of motor patterns through observation and imitation, also empirically included in many rehabilitation techniques.[3] There is however a paucity of knowledge regarding the role of rehabilitation specifically in MBS patients and particularly regarding central nervous system (CNS) reorganization. The present case report aims to draw attention to the pivotal role of an integrated and comprehensive rehabilitation program for MBS patients.

CASE REPORT

A three-month-old male infant was referred to our consultation presenting asymmetrical facial paralysis, convergent strabismus with vertical gaze sparing, axial hypotony, *pes adductus*, and difficulties in food ingestion, noted soon after birth. Cerebral magnetic resonance imaging (MRI) revealed agenesis of bilateral facial and left abducens nuclei (CN IX, X, and XI were visible in their route towards the jugular foramen), confirming MB diagnosis. The patient started a rehabilitation program with physical, speech, and occupational therapy one month later. Initial observations revealed low yield suction due to incomplete mouth closure, asymmetrical tongue elevation, and left cheek hypotony. Speech therapy (ST) was initially planned to treat dysphagia (soup and minced fruit were introduced at the age of five months), with improvement in suction and swallowing coordination, food acceptance and retainment, and saliva/water swallowing as initial goals. Simultaneously, social interaction, turn-taking, initiative, and communicative intention were also worked upon. Later, vocalization and communicative action/context pairing were improved. Growing up, the boy revealed slight developmental delay – head control at six months, fine manipulation at nine months, supported sitting at 12 months, and walking at 20 months. Around the age of 20 months, he produced his first rudimental words, steering rehabilitation towards language and speech training, while promoting compensatory strategies for dysphagia (volume and consistency management). Taping and proprioceptive neuromuscular facilitation (PNF) were added to increase afferent stimuli and enhance cortical representation. Rehabilitation continued on a weekly, one-hour intervention basis. During this time, the patient underwent several surgeries: correction of pyloric stenosis (4 months); eye occlusion inability (18 months); tonsillectomy, adenoidectomy, and tympanic ventilation tube insertion (22 months). At four years old, he was proposed for reanimation surgery at a foreign institution. By that time, he no longer presented any significant appendicular or axial motor deficit, language delay, or dysphagia, but kept a significant articulation disorder. On verbal articulation test (VAT)[9], he was unable to produce bilabial consonants and depended on cueing to perform sibilant phonemes, except for fricatives, which were also unattainable. Speech intelligibility, assessed during a three-minute interview, was below 30% (speech rate near normal for age). Saliva pooling and dripping were significant. He scored 17 [15-32-0] on the *Sunnybrook Facial Grading System* (FGS).

The patient underwent a two-stage surgical intervention: cross-facial nerve grafting from the right facial nerve (using right sural nerve) at 4.5 years; and gracilis FFMT, with double innervation (from cross-facial nerve graft and from the masseteric branch of the left trigeminal nerve) nine months later. On the third week post-surgery, an intensive, supervised, inpatient rehabilitation protocol for facial activation was started, which according to the patient's mother consisted of *smiling* paired with masseteric muscle activation (bite) and electrical neuromuscular stimulation of the left side. Despite

absence of guidelines regarding electrical stimulation therapy parameters in children, the literature has shown safety and efficacy of this intervention in muscle mass improvement and strength.[10] On the 42nd day, first active movements were noted. Maximal range of motion (ROM) was achieved on the 75th day, after which the boy was discharged and resumed treatment at our hospital. He presented with full-amplitude labial movement, significant saliva control improvement, and smile symmetry. Three months later, he was able to smile independently of biting.

Presently, after 36 sessions, speech intelligibility is above 50%. The patient displays good saliva control with little need of reminder and is able to correctly perform both sibilant and bilabial phonemes, the latter (as with fricatives) needing only occasional cueing. He scores 33 [15-48-0] on FGS, with notable improvement in *symmetry of voluntary movement*. No pain or mastication difficulties were noted during rehabilitation. He was enrolled in school and seems perfectly integrated.

DISCUSSION

MBS is a rare cause of facial palsy. Patients typically have a "mask-like" appearance that may impact social interaction and personality development. Despite usually normal intelligence, motor, emotional, and language development delay is frequent.[6-11] This means that, even when achieving normal development (as 90% seem to do at the age of five), the complexity of care and lack of emotion recognition may affect the child's relationships. Although this may support the need for early surgical intervention, it also highlights the importance of prompt rehabilitation, aiming to enhance family awareness, functional status and child participation, and post-surgical acquisitions. The present patient started ST early in life to ameliorate feeding and communication impairment. Strengthening and fine motor control of cheeks, lips, and velopharyngeal valve benefited feeding and communication. Compensatory mechanisms, such as labio-dental approximation and jaw protrusion, have improved bilabial tasks, like lip closure, saliva control, and intelligibility.

Surgical treatment aims to restore volitional facial movement and correct associated malformations.[4] Gracilis FFMT has become widely accepted as the best option, due to ease of access, size, single neuron innervations, and low morbidity to donor site.[2,7] Due to MBS heterogeneity, choice of donor nerve is not consensual and should be preceded by thorough neurological, neurophysiologic, and imaging assessment. In the present case, the surgeons opted to use both contralateral facial (for more synchronous and spontaneous smile) and ipsilateral masseteric nerve (for optimal and rapid reinnervation). Follow-up of patients treated using this approach has shown adequate commissure excursion, oral competence, and improved speech, but reports of fat infiltration and atrophy and fibrosis of the muscle transplant have been described and associated with long-term functional decline.[12]

Patients must start rehabilitation soon after surgery. Fairgray and Miles reported the case of a patient that presented the first signs of improvement only after beginning ST, 11 months later.[13] Great functional improvements with rehabilitation may be related both to stimulation of available functional structures and post-surgical neuroplasticity phenomena. This process has been defined as the "ability of the human brain to reorganize its functional organization in response to environmental stimuli".[6] Several studies have demonstrated cortical reorganization after injury and repair of different body segments.[14] This reorganization is achieved through repetitive, intense, and goal-oriented movement – cortical activation is higher with purposeful movements.[15] Two other features of brain function and organization may also play a very important role in MBS rehabilitation. First, the fact that cortical representation of the mouth and hand overlap each other; second, the existence of MNS that facilitates cortical and muscle activation, whether one is doing or just observing a purposeful movement.[15,16] Based on these concepts, Ferrari *et al* designed a protocol proposing *Synergistic Activity Therapy* (SAT) and *Facial Imitation Therapy* (FIT).[3] SAT works through simultaneous smiling and clenching of the hand. For the authors, clenching the hand should facilitate recruitment of mouth motor programs for smiling, due to cortical overlap areas. Synergistic hand-mouth movements in human activity are well described across the literature, making sense that these might be closely represented at a cortical level. On the other hand, FIT uses visual information to activate MNS and facilitate the same programs. When a video of a person smiling for three seconds is shown to healthy subjects, facial expression visualization activates a mirror circuitry and action-related areas involving the inferior frontal gyrus, premotor cortex, and parietal lobe leading to smile imitation. This drove the hypothesis that smile observation could improve smile recovery in MBS patients.[3] Indeed, this patient's attempt to move the lips was facilitated by the synchronous observation of a smile performed by another individual. Preliminary results for this protocol are encouraging and reports that some patients submitted to FFMT could independently and voluntarily activate the muscle graft have highlighted the role of neuronal plasticity in MBS neurorehabilitation.[6] In the present case, dysphagia, saliva control, and speech articulation therapy was proposed when surgery had not yet been considered. We strongly believe that presurgical rehabilitation program later contributed to better surgical outcomes, by enhancing cortical representation of the structures worked upon through stimulation of sensory pathways and, probably, MNS activation. Furthermore, incomplete palsy of the right side may have enabled construction of neural circuitry and motor programming of different movements that would subsequently more easily "transfer" to the contra-lateral hemisphere, possibly aided by MNS as well. On this matter, Marre and Hontanilla reported the case of a child with bilateral facial palsy who developed spontaneous movement of the commissural musculature on one side after gracilis FFMT to the contra-lateral side and intensive therapy.[6]

Whatever the method, intensive training of a behaviorally relevant

task and a "plastic" younger brain appear to be determinant to succeed. It is believed that patients should maintain rehabilitation treatment for a minimum period of 30 months to enhance cortical adaptation of smile, after which may proceed to home-based rehabilitation, with periodic consultation.[2] Although we are not against this recommendation, we feel it falls short of what should be a more ambitious, comprehensive, and continuous intervention within a rehabilitation program including speech, physical, and occupational therapy.

CONCLUSION

Promising advances in surgical and rehabilitation field have enabled great improvements in MBS patients' quality of life. The combination of specialized surgical and rehabilitation care together with good family support are crucial to improve patients' prognosis. This study presented the case of a child who benefited from both surgical and medical interventions, despite absence of a formal coordination between both. Although such coordination is desirable to further enhance results, the authors highlight the importance of multi-professional and integrated therapeutic programs to better suit patients' functional and holistic outcomes.

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CASE REPORTS

KAWASAKI DISEASE IN A FIVE-MONTH-OLD INFANT

DOENÇA DE KAWASAKI NUM RECÉM-NASCIDO DE CINCO MESES

Juliana Maciel[1], Daniel Meireles[2], Mariana Magalhães[3], Sara Gonçalves[4], Sofia Ribeiro Fernandes[4], Paula Cristina Fernandes[4]

ABSTRACT

Introduction: Kawasaki disease, an acute self-limited vasculitis of small and medium arteries of unknown etiology, is the leading cause of heart disease in children in most developed countries. If untreated, it can lead to coronary artery dilatation and aneurysm, placing patients at risk for coronary thrombosis, myocardial infarction, or sudden death.

Case Report: A previously healthy five-month-old boy presented with a history of respiratory symptoms and fever, being admitted for respiratory syncytial virus bronchiolitis. He maintained fever for five days associated with progressive clinical worsening and sequential development of conjunctival injection, cracked lips, swelling of hands and feet, and polymorphous rash of the limbs. Diagnostic procedures showed increased levels of inflammatory markers, hyponatremia, hypoalbuminemia, sterile pyuria, and aseptic meningitis. Despite an initial normal echocardiogram, Kawasaki disease was suspected and the boy started intravenous immunoglobulin on the fifth day. On the seventh day, echocardiogram showed signs of pancarditis and mild coronary artery ectasia and acetylsalicylic acid was started. The boy was discharged, but eight days later echocardiogram revealed major and diffuse coronary artery ectasia in a follow-up consultation and he was readmitted to start corticosteroid therapy. After five months, the boy displayed normalization of cardiac changes, without further complications.

Comments: Kawasaki disease below six months of age is rare and associated with a high risk of coronary artery aneurysm. It is important to recognize the clinical and laboratory criteria associated with this entity and start early treatment, avoiding cardiac complications.

Keywords: coronary artery ectasia; infant; Kawasaki disease

RESUMO

Introdução: A doença de Kawasaki, uma vasculite aguda e autolimitada das artérias de pequeno e médio calibre de etiologia desconhecida, é a principal causa de doença cardíaca em idade pediátrica nos países desenvolvidos. Em ausência de tratamento, pode levar a ectasia e aneurisma das artérias coronárias, colocando os doentes em risco de trombose coronária, enfarte agudo do miocárdio e morte súbita.

Caso Clínico: Um lactente de cinco meses do sexo masculino, previamente saudável, foi internado com diagnóstico de bronquiolite aguda a vírus sincicial respiratório. Manteve febre e agravamento do estado geral durante cinco dias, associado ao aparecimento sequencial de hiperemia conjuntival, queilite, edema das mãos e dos pés e exantema polimorfo das extremidades. Os exames complementares de diagnóstico demonstraram elevação da proteína C reativa, hiponatremia, hipoalbuminemia, piúria estéril e meningite assética. Perante

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suspeita de doença de Kawasaki, e apesar de um ecocardiograma inicial normal, foi iniciada imunoglobulina endovenosa ao quinto dia. O ecocardiograma foi repetido ao sétimo dia, revelando sinais de pancardite e ectasia das artérias coronárias, tendo sido iniciado ácido acetilsalicílico. O rapaz teve alta, mas foi reinternado oito dias depois por agravamento da ectasia das coronárias para tratamento com corticoide, que manteve durante quatro semanas. Apresentou normalização das alterações cardíacas aos cinco meses de seguimento, sem novas intercorrências.

Comentários: A doença de Kawasaki em idade inferior a seis meses é rara e caracteriza-se por evolução mais grave e maior risco de desenvolvimento de aneurisma das artérias coronárias. É importante reconhecer os critérios clínicos e laboratoriais associados a esta entidade, de forma a implementar um tratamento precoce e evitar complicações cardíacas.

Palavras-chave: doença de Kawasaki, ectasia das artérias coronárias, lactente

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited vasculitis of small and medium arteries, with a predilection for the coronary arteries, predominantly occurring in young children.[1-12] Untreated, it can lead to coronary artery (CA) ectasia, being the leading cause of acquired heart disease in developed countries.[1-8]

The condition's etiology remains unknown and diagnosis relies on characteristic clinical features.[5,6,8]

It is important to recognize the early signs and symptoms of the disease in order to initiate intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA) before the tenth day of illness and reduce the development of coronary abnormalities.[3,4,8,10]

CASE REPORT

A previously healthy five-month-old boy was admitted to the Pediatric Critical Care Unit (PCCU) due to suspicion of sepsis/meningitis. He was transferred from another hospital where had been admitted for the last five days with a history of fever and cough, being diagnosed with respiratory syncytial virus bronchiolitis. The boy was previously healthy and had no recent travel abroad, animal exposure, or recent immunizations. His father had had acute tonsillitis and the five-year-old brother had a herpetic gingivostomatitis a few days earlier. Sequential onset of signs was reported before he was admitted to PCCU, including conjunctival injection, cracked lips, swelling of hands and feet, and polymorphous rash of the limbs. On the third day of hospitalization, clinical worsening was noted, with periods of decreased consciousness and signs of respiratory distress and need for oxygen. Electroencephalogram, brain computed tomography, and chest x-ray were performed, which revealed no abnormalities. Blood, urine, and liquor analyses showed leukocytosis with neutrophilia, elevated C-reactive protein, hyponatremia, hypoalbuminemia, elevated clotting time, sterile pyuria, and aseptic meningitis (negative cerebrospinal fluid culture, polymerase chain reaction for enterovirus, herpes 1 and 2, and streptococcus pneumoniae). Before the boy was transferred, broad-spectrum antibiotics, albumin infusion, and vitamin K were started and an echocardiogram was performed, revealing mild tricuspid insufficiency. On PCCU admission, the patient completed five days of fever and physical examination revealed an irritable infant with a temperature of 37.5ºC, elevated capillary refill time, poor general condition, dry, cracked and erythematous lips (**Figure 1**), swelling of extremities (**Figure 2**), and polymorphous rash of the limbs (**Figure 3**). Since he met KD criteria, IVIG 2 g/kg over 12 hours was started. After 48 hours, echocardiogram revealed ectasia of the left main coronary artery (LCA) (2.5 mm, Z-Score +2.6) and left anterior descending artery (LADA) (2 mm, Z-Score +2.4), CA perivascular brightness, mild pericardial effusion, mild mitral and aortic regurgitation, and normal left ventricular function and ASA 4 mg/kg/day was started. During hospitalization, albumin levels and clotting times normalized, and thrombocytosis developed (686.000/uL). Parvovirus, human immunodeficiency virus, hepatitis C virus, and Epstein-Barr virus serologies were negative. Immunoglobulin levels were within normal range. The ophthalmologic evaluation was normal. On the 9th day of hospitalization, fingertip and toe tip peeling were observed. The boy had good clinical evolution, with apyrexia after IVIG, and was discharge 11 days later with ASA. In a follow-up consultation eight days after discharge, he was readmitted due to worsening echocardiographic changes. Echocardiogram revealed major and diffuse ectasia of the right coronary artery (3 mm, Z-Score +4.8), LCA (3.5 mm, Z-Score + 5.7), and LADA (3 mm, Z-Score +5.7) (**Figure 4**). Electrocardiogram showed pathological 7-mm Q-wave in the inferior leads, but negative myocardial ischemia markers in blood tests. Double antiplatelet therapy with clopidogrel and ASA was started, together with a 3-day regimen of intravenous methylprednisolone followed by oral prednisolone for four weeks.

During follow-up, the patient displayed normalization of cardiac changes after five months and clopidogrel therapy was discontinued, maintaining treatment with ASA by the 9th month of follow-up. No further complications or readmissions were reported.

Figure 1 – Kawasaki disease: erythematous, cracked lips

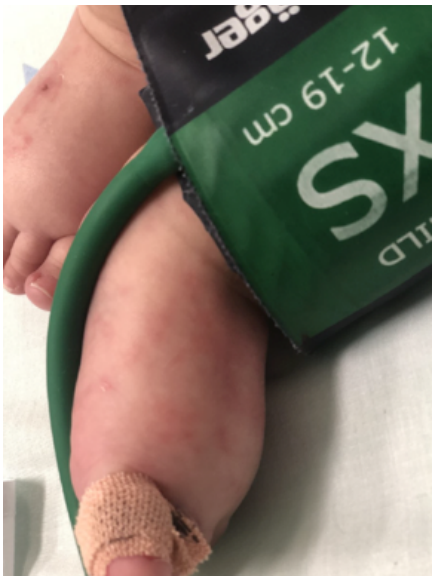

Figure 2 – Kawasaki disease: swollen and erythematous feet

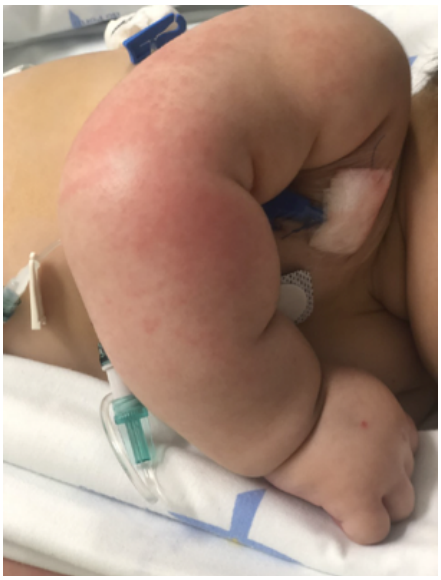

Figure 3 – Kawasaki disease: polymorphous rash with maculopapular lesions on extremities

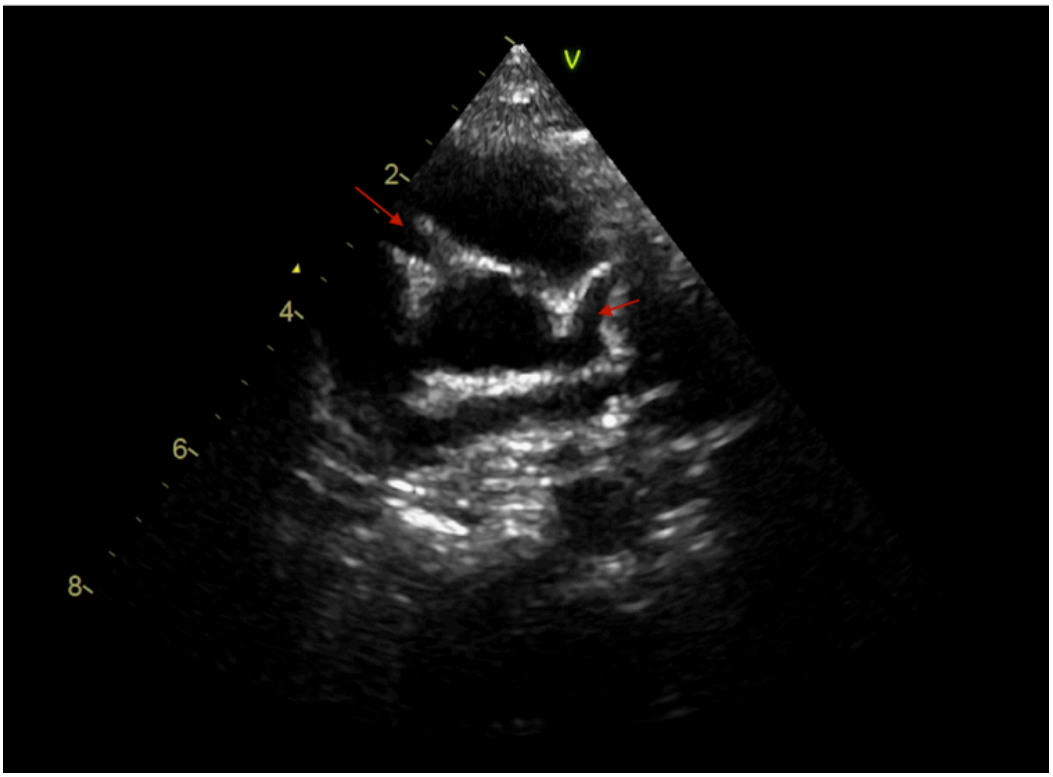

Figure 4 – Ectasia of the right coronary artery (Z-Score +4.8) and left common and descending coronary artery (Z-Score + 5.7).

DISCUSSION

KD was first recognized as a clinical entity in 1961 by Dr. Tomisaku Kawasaki.[6,8] Incidence is higher in boys and is most common in winter and spring, as seen in the present case.[8,12]

The condition's etiology remains unknown, but clinical and epidemiologic features suggest an infectious origin.[7,8,13] One study showed that 8.8% of KD patients have documented respiratory viral infection.[13] The study authors concluded that those patients had a higher frequency of CA ectasia and that the presence of concomitant viral infection should not exclude KD diagnosis.[13,14] It should be noted that the present patient had a positive test for syncytial respiratory virus, being initially admitted for acute bronchiolitis, which delayed KD suspicion.

The classic KD diagnosis is based on a history of fever with five or more days of evolution associated with at least four of five clinical features: polymorphous rash, oropharyngeal mucous membrane changes, conjunctival injection, extremity changes, and lymphadenopathy.[2,5-8,12,14] This patient met criteria for classic KD, except regarding lymphadenopathy, which is usually present in 50% of cases.[12] A specific diagnostic test for KD is not available, but some characteristic laboratory features of the disease are identified, as leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate and C-reactive protein, normocytic, normochromic anemia, thrombocytosis, sterile pyuria, hypoalbuminemia, hyponatremia, serum alanine aminotransferase level >50 U/L, plasma lipid abnormalities, and cerebrospinal and synovial fluid pleocytosis, most of which observed in the present patient.[6,8,11,12] Echocardiographic abnormalities supporting KD include CA aneurysm, Z-score of LADA or RCA of 2.5 or higher, pericardial effusion, mitral regurgitation, and decreased left ventricular function.[6,8,11,12] Initial echocardiogram in the first week of illness is typically normal and does not rule out the diagnosis.[12]

According to North American recommendations, the primary treatment for KD is IV immunoglobulin and high-dose ASA (80-100 mg/kg/day).[1,2,4,8,12] Japanese guidelines suggest lower ASA doses (30-50 mg/kg/day) and a recent study showed that there was no difference in the risk of CA abnormalities in the low-dose compared with the high-dose ASA group, concluding that a dose between 3 to 5 mg/kg/day may be indicated in acute KD.[4] In the present case, low-dose ASA (4 mg/kg/day) was used, with good results. Corticosteroids may be added to the primary treatment in high-risk patients (IVIG resistance and/or evolving CA aneurysm), in order to prevent CA aneurysm progression.[1,8,12] In this case, given CA ectasia worsening, the option was for three days of intravenous methylprednisolone followed by a long oral prednisolone taper, with good clinical outcome.

Management beyond the acute stage consists in regular echocardiography, given the risk of aneurysm development, especially in the subacute stage.[8,12] CA aneurysms or ectasia occur in 15% to 25% of untreated children and in less than 5% if treatment is started within the first ten days of fever. [5,12,14] Myocardial infarction is the most common cause of death, and usually occurs in the first year after diagnosis.[8,12] After stabilization of cardiac changes, a six-to-twelve-month echocardiographic follow-up is performed in several centers.[8,12]

KD is an acute and self-limited disease, but cardiac abnormalities that develop may be progressive and children's prognosis is determined by the degree of cardiac involvement and sequelae.[8,12] Most children present resolution of aneurysm or CA ectasia in the first two years of disease, with worst prognosis occurring in children with giant aneurysms. [12]

Recurrence may occur in 2% to 4% of cases and is more common in children younger than three years.[12] In the present patient, normalization of cardiac abnormalities after five months suggested a likely favorable prognosis.

In conclusion, this case report suggests that KD should be considered in infants with concomitant viral infection and initial normal echocardiogram. Recognition of KD clinical criteria associated with laboratory findings are of paramount importance in these patients' prognosis, as early treatment is associated with fewer cardiac complications.

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CASE REPORTS

IMMUNOTHERAPY WITH *HYMENOPTERA* VENOM IN A CHILD WITH ANAPHYLAXIS

IMUNOTERAPIA COM VENENO DE HIMENÓPTEROS NUMA CRIANÇA COM ANAFILAXIA

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ABSTRACT

Systemic reactions to *hymenoptera* venom in childhood are uncommon, comprising less than 1% of cases. The prevalence proves higher in adults, encompassing 0.3–8.9%. Anaphylaxis forms the most severe of all allergic reactions and can be fatal. Specific immunotherapy based on *hymenoptera* venom is the only treatment that prevents moderate-to-severe systemic reactions. Due to immunotherapy safety and effectiveness, this treatment is indicated during childhood in cases of grade II and III systemic reactions.

The authors describe the clinical case of a fourteen-year-old male patient, son of a beekeeper, who was followed in the Allergy and Clinical Immunology Department due to anaphylaxis to *hymenoptera* venom and was under immunotherapy to *Apis mellifera* venom since the age of nine, besides complying with measures to evade *hymenoptera*.

Keywords: anaphylaxis; child; *hymenoptera*; immunotherapy

RESUMO

As reações sistémicas a veneno de *himenópteros* na infância são incomuns, atingindo menos de 1% dos casos. Em adultos, essa prevalência é mais elevada, podendo ser de 0,3 a 8,9%. A anafilaxia é a reação alérgica mais grave, podendo ser fatal. A imunoterapia específica com veneno de *himenópteros* é o único tratamento que previne reações sistémicas moderadas a graves. A segurança e eficácia da imunoterapia fazem com que este tratamento esteja indicado em casos de reação sistémica de grau II e III em idade pediátrica.

Os autores descrevem o caso clínico de um doente de 14 anos, do sexo masculino, filho de um apicultor, seguido na consulta de Imunoalergologia por anafilaxia a veneno de *himenóptero* e sob imunoterapia a veneno de *Apis mellifera* desde os nove anos de idade, para além de cumprir medidas de evicção a himenópteros.

Palavras-chave: anafilaxia; criança; *himenópteros*; imunoterapia

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INTRODUCTION

Hymenoptera is an insect order very common throughout Europe including, among others, wasps (family: *Vespidae*; genus: *Dolichovespula, Polistes, Vespula*) and bees (family: *Apidae*; genus: *Apis, Bombus*).[1] The prevalence of *hymenoptera* venom allergy (HVA) in this continent is estimated to be around 20%.[2]

These insects produce venom with potentially allergenic elements. Bee venom includes phospholipase A2 (Api m1), hyaluronidase (Api m2), melittin (Api m3), acid phosphatase (Api m4), apamin, and peptide 401, while wasp venom's composition includes phospholipase A1 (Ves v1), hyaluronidase (Ves v2), acid phosphatase, antigen 5, a neurotoxin (Ves v5), and quinine.[3] Both can trigger grade I hypersensitivity reactions mediated by immunoglobulin E (IgE), which may manifest as grade II and III local or systemic reactions, either moderate or severe (**Table 1**).[2]

Table 1 - Classification of Immediate Allergic Reactions (Ring and Messmer Scale)

Grade	Symptoms
I	Generalised cutaneous and/or mucocutaneous symptoms (urticaria, angioedema, pruritus).
II	Mild systemic symptoms (rhinorrhea, dysphonia, dyspnea, dizziness, nauseas, abdominal pain, tachycardia, hypotension, arrhythmia). Might experience symptoms of the preceding grade.
III	Severe systemic reactions (dyspnea, wheezing, stridor, laryngeal oedema, dysphagia, dysarthria, vomiting, diarrhoea, confusion, eminent death sensation). Might experience symptoms of the preceding grade.
IV	Cardiorespiratory arrest (shock, altered state of consciousness, sphincter incontinence, cyanosis, cardiorespiratory arrest). Might experience symptoms of the preceding grade.

There is significant cross-reactivity between *Apidae* and *Vespidae* family venom. Between bees and wasps, it happens due to hyaluronidase homology and, although to a lesser extent, to cross-reactive carbohydrate determinants (CCDs). Around 30% of people who are allergic to venoms are positive for bee and wasp *in vitro*, but this rarely happens in intradermal skin test diagnosis.[4,5]

Measuring the species-specific major molecular allergens enables to diagnose the true cases of double sensitisation in such cross-reactivity instances, by detecting the simultaneous presence of IgE to both Api m1 and Ves v5.[4,5]

Molecular allergens are also useful in distinguishing between *Vespula* and *Polistes.*

Unfortunately, most patients have difficulty in identifying which insect stung them and caused the allergic reaction.[1]

Bees inject between 50 and 100 µg of venom per sting, but the value can amount to about 300 µg when the venom sac is emptied. The bee dies after the sting. The wasp, on the other hand, injects around 1.7 to 3 µg of venom, being able to inflict several stings without dying.[6]

Systemic reactions in childhood are uncommon, with an estimated prevalence between 0.15-0.8%. The prevalence is higher in adults (0.3 to 8.9%).[7] The annual mortality associated with this allergy is 0.03-0.48 deaths/1.000,000 population[1]. About 30% of anaphylaxis cases seen in Emergency Departments are associated with *hymenoptera* stings.[8]

The diagnosis is mostly based on medical history, with identification of the culprit insect assuming a crucial importance.

Even though currently available molecular allergens improve the diagnostic acuity, skin tests remain the gold standard in HVA diagnosis, with intradermal test offering the most sensitive procedure. These skin tests must be performed at least two to six weeks after the sting to avoid possible false negatives, due to the refractory period - anergy[1]. In the first few days after a sting, the injected venom-specific IgE may be low or even undetectable. If negative and in presence of a definitive history of systemic sting reaction, skin test should be repeated after one to two months, considering that refractoriness duration may be longer.[1]

HVA treatment implies the adoption of eviction measures and administration of adrenaline, antihistamine, and oral corticosteroid according to need. The only curative treatment described is the *Hymenoptera* venom-specific immunotherapy (VIT).[1] It is indicated in children with mild-to-severe systemic allergic reactions with affection of more than one organ. Children with extensive local reaction who live in *hymenoptera* endemic areas – therefore incurring in increased exposition probability – and who experience problems due to repeated reactions should be individually assessed. VIT has a 91–96% efficiency rate in cases of wasp venom allergy and 77–84% in cases of bee venom allergy. The duration of VIT treatment remains controversial.[9]

CASE REPORT

An eight -year-old male patient was referred to the Allergy and Clinical Immunology (ACI) Department due to suspicion of allergy to *hymenoptera* venom. He denied usual medications, known medications, and/or food allergies. His father was a beekeeper.-

The first sting occurred at the age of two years, in the scalp, with no local or systemic reaction. After five years, another sting in the right hand induced facial and right hemibody angioedema, dyspnea, chest discomfort with a feeling of breathness, and glottic edema – grade III systemic reaction. The boy was treated in the Emergency Department, receiving subcutaneous adrenaline injection 0.01 mg/Kg and intravenous clemastine 0.025 mg/Kg. He was discharged 12 hours later, hemodynamically stable and without symptomatology.

Skin prick tests for bee, *Vespula*, and *Polistes* venom were performed using Leti® commercial allergen extract, with results proving positive for bee venom extract (concentration of 0.01 µg/ml) and negative for *Vespula* and *Polistes* venom (tested up to the 100 µg/ml dose): negative control – saline solution 0 mm, histamine 6 mm, bee (0.01 µg/ml) 8 mm, *Vespula* 0 mm, *Polistes* spp. 0 mm. Quantification of specific IgE (kUA/L) was 41.90 for bee, 0.34 for *Vespula* spp., and 0.32 for *Polistes* spp. venoms. Intradermal tests were not performed.

In the clinical follow-up consultation, the boy exhibited no relevant physical changes. He was medicated with auto-injectable adrenaline 0.3 mg, prednisolone 40 mg *per os*, and levocetirizine 5 mg for systemic reactions, and advised about eviction measures against *hymenoptera*. Subcutaneous VIT for *Apis mellifera* by Leti® laboratories was prescribed. He started treatment at the Day Hospital according to the ultra-rush scheme (**Table 2**).

In the first and second vaccine administrations, the patient experienced severe grade III systemic reactions (diffuse pruritic exanthema, angioedema, dry cough, dyspnea, and bronchospasm), requiring intramuscular adrenaline 0.3 mg, nebulization with salbutamol 5 mg/2.5ml, and intravenous clemastine 0.025 mg/kg/dose. Such measures resulted in resolution of clinical features and enabled to continue VIT.

Subsequent administrations were performed under pre-medication, namely prednisolone 40 mg and desloratadine 5 mg *per os*. However, in the seventh and twelfth administrations, recurrence of systemic reactions during VIT administration similar to those previously described prompted the implementation of crisis treatment.

After six months of treatment, the patient stopped requiring pre-medication and experienced no further (cutaneous or systemic) reactions with VIT.

In the twelfth and again in the twenty-seventh month of treatment, the patient was accidentally stung by a bee on the left arm, experiencing only a local reaction through development of a 4-mm papule, with no other related symptomatology and spontaneous resolution. At thirty-eight months of treatment, he was again stung by a bee on the right arm, without local or systemic reactions.

Throughout treatment, bee, *Vespula*, and *Polistes* venom-specific IgE measurements were taken. Bee venom-specific IgE showed a significant decrease over time (**Figure 1**).

The patient completed five years of treatment in the end of 2019. Currently, he presents no local or systemic reactions with VIT and remains clinically stable.

Table 2 - Ultra-Rush immunotherapy to *Hymenoptera* venom. Leti ®

Initiation scheme	
Time (minutes)	Dose to be administered (µg)
0	0.1
30	1.0
60	10.0
90	20.0
150	30.0
210	40.0
100 µg dose 15 days later, 50 µg in each arm, without interval.	
Maintenance dose of 100 µg monthly – 50 µg distributed in each arm	

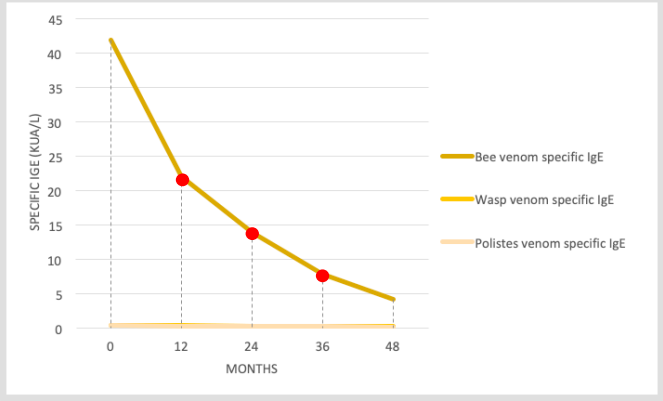

Figure 1 - Measurement of bee, wasp, and *Polistes* venom-specific IgE during the treatment period with VIT.

● Bee sting at 12, 27, and 38 months.

DISCUSSION/CONCLUSION

Several risk factors for severe systemic reactions have been described, including age (more relevant in the elderly); occurrence of a previous reaction and its severity; time elapsed between the two stings (the smaller it is, the higher the risk of a future severe systemic reaction); type of *hymenoptera* (higher risk for bee stings); elevated baseline serum tryptase; cardiovascular diseases, systemic mastocytosis, and autoimmune diseases; and use of beta-blocker drugs (reduce adrenaline efficacy during anaphylactic treatment) and angiotensin-converting-enzyme inhibitors (ACE inhibitors).[1,6]

VIT safety and efficacy make it adequate for pediatric ages. It can nonetheless be linked to both local (50%) and systemic (2–20%) reactions, possibly manageable with medication, as in the present case.[9]

The ultra-rush scheme, one of the most frequently used along with the rush scheme, was used in the present patient as a way to ensure compliance and achieve a maintenance dose as early as possible, considering that the patient lived far from the hospital. Dose-associated errors are also reduced in accelerated schemes, due to the lower number of administrations and shorter period of time.[10, 11] Additionally, ultra-/rush schemes are at least as safe as traditional ones.[12]

In this case, due to adverse reactions in the first administrations, prophylaxis was needed. Prednisolone was used – medium action glucocorticoid (12 to 36h) with anti-inflammatory activity in doses between 1 to 2 mg/Kg/day –, as well as anti-histaminic H1 – desloratadine, to prevent histamine induced effects.[13] If reactions persist, administration of anti-IgE omalizumab before VIT should be considered. This treatment is safe from the age of six years. As an alternative, maintenance dose could be reduced in 50%. One study showed that using the 50 µg instead of the 100 µg dose in children was safe but had lower efficacy, not enough to be recommended.[4] Having attained VIT maintenance dose, there is a 75–95% prevention rate of new systemic reactions after a sting, as opposed to 40–60% in non-treated patients.[2]

VIT mechanisms of action are not entirely clear. It is however acknowledged that the insect's venom-specific IgE tends to increase in treated patients in the first months and decrease afterwards, with IgG4 rapidly rising in the beginning of treatment and retaining high values throughout.[3] Changes in T cell cytokine profile also occur, with redirection of T helper cells type 2 (IL-4,5) to T helper type 1 (interferon-γ) and regulatory T cells (IL-10 and IgG4) response increase. There is also a decline in CD63 expression in mast cells' membrane.[14]

Despite representing favorable factors, specific IgEs and cutaneous reactivity may not offer an absolute correlation with therapeutic success, reason why monitoring their levels is not mandatory. Only a new sting by the culprit *hymenoptera* can confirm therapy effectiveness, but such a test poses several ethical issues.[9] In the reported case, a significant decrease of specific IgEs was observed since the beginning of treatment, contrarily to what is described in the literature. As previously mentioned, a new bee sting caused only a local reaction and a second bee sting caused no reaction at all.

Treatment duration remains controversial. Several studies indicate that clinical protection is achieved as soon as the maintenance dose is reached, with reports describing relapse rates between 22 and 27% two years after discontinuing VIT.[9] The same studies concluded that three-year-long VIT can be effective, especially in patients with only slight-to-moderate reactions.[9] It has been demonstrated that 80–90% of patients become protected after five years of treatment.[1] However, in increased risk cases, namely in patients with initial severe systemic reactions or adverse reactions during VIT or in patients allergic to bee venom with a higher risk of being stung again, a longer treatment period may be necessary, as in the present case.[1,9]

HVA, apart from interfering with patients' quality of life, can trigger potentially fatal severe systemic reactions, as anaphylaxis. It represents a medical emergency that should be directed to an ACI Department, as VIT represents the only effective treatment. Still, a wide lack of information persists regarding this allergy, with patients belatedly pointed to the ACI Department.

Molecular allergens may have a rather important role in guiding and choosing VIT for these patients' treatment. However, there is a clear need for more information and greater availability of these allergens.[1]

In this case, the use of complementary diagnostic exams, like skin prick tests, could be excluded, as the *hymenoptera* responsible for the reaction was previously acknowledged and the identified IgE confirmed the diagnosis. Iatrogenesis associated with these exams (pain, fear, allergic reaction) should be considered.

There is no consensus about maintaining auto-injectable adrenaline after finishing treatment. This option was discussed with the patient, who decided to keep the pen after the five-year treatment, as it reduced anxiety from a possible new anaphylactic reaction. Nevertheless, the patient has been field stung after treatment without systemic reactions.

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IMAGING CASES

DERMATOLOGY CLINICAL CASE

CASO CLÍNICO DERMATOLÓGICO

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A seven-year-old boy, living in Switzerland, was brought to an Emergency Department in Portugal on July due to appearance of slightly pruritic and erythematous skin lesions on the back, thighs, and buttocks. Lesions had been expanding gradually over the previous week. Fever and other systemic symptoms were denied and parents did not recall a history of insect bite. On physical examination, the boy presented four erythematous annular lesions: the first to appear was on the back, with 20 cm in diameter and a central macula (**Figure 1**); the remaining were also annular, with around 10 cm in diameter (**Figure 2**). All lesions were flat and without scale.

What is your diagnosis?

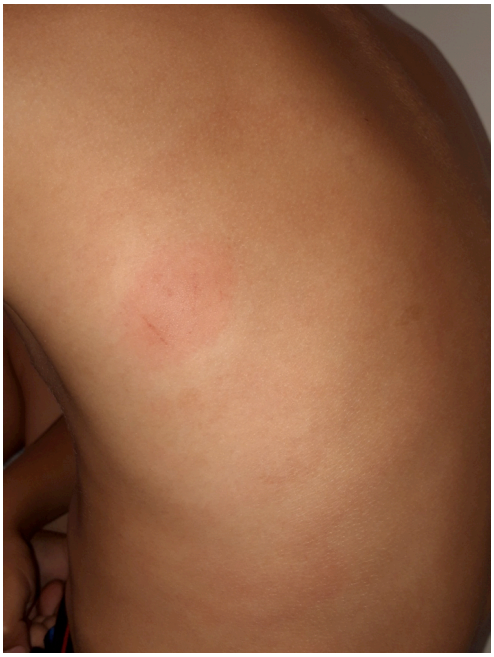

Figure 1 - Large annular rash on the back with a central macula and "bull's eye" appearance

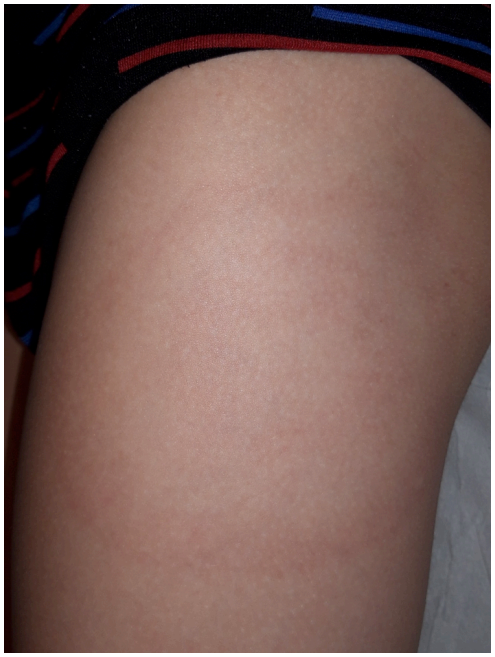

Figure 2 - Multiple erythema migrans lesion, an annular rash on the left thigh with central clearing

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DIAGNOSIS

Lyme disease

DISCUSSION

Lyme disease is a spirochaetal infection caused by *Borrelia Burgdorferi sensu lato*, which is transmitted by infected ticks of the genus *Ixodes*. Lyme disease is endemic in areas with certain ecologic conditions, like woodlands with sufficient humidity that enable the development and survival of ticks.[1] It is therefore more prevalent in regions with moderate climates, like Scandinavian and Central countries in Europe and some areas in the United States and Asia. However, its geographic distribution is expanding, and cases have been reported throughout Europe.[1,2] In Portugal, Lyme disease incidence seems to be rising, particularly in northern and central regions, with a total of 20 cases reported in 2017.[3,4]

Lyme disease has a broad spectrum of clinical manifestations divided in three stages: early localized disease, early disseminated disease, and late disease. Single erythema migrans lesion is the manifestation of early localized disease and characterized by a rash developing at the site of the tick bite between three to 30 days – typically seven to 14 – after the bite. The lesion gradually expands, reaching between 5 to up to 70 cm. It is most commonly uniformly erythematous but can also have enhanced central erythema or a "bull's eye" appearance (**Figure 1**). Erythema migrans is usually asymptomatic but can be pruritic or painful. Systemic symptoms, such as fever, fatigue, headache, neck pain, arthralgia, or myalgia may be reported at this stage. Multiple erythema migrans is the most common manifestation of early disseminated disease and thought to be due to hematogenous dissemination. It consists of multiple annular erythematous lesions similar to the primary lesion but usually smaller (**Figure 2**), and generally appears three to five weeks after the bite. Together, single and multiple erythema migrans represent about 90% of Lyme disease presentations. Other clinical manifestations of early disseminated Lyme disease include cranial nerve palsy, meningitis, and carditis, which typically presents with prolonged PR interval or rarely with complete heart block. Like in early localized stage, systemic symptoms are also common at this stage. Late Lyme disease generally presents with arthritis and occurs weeks to months after the initial infection.[2,5] Another cutaneous manifestation of Lyme disease is Borrelial lymphocytoma which, although rare, is more prevalent in children. Borrelial lymphocytoma is characterized by a nontender bluish-red nodule with one to five centimetres of diameter, which can appear simultaneously or after erythema migrans. The most frequent location in children is the ear lobe and helix.[1,4]

Lyme disease diagnosis can be established on clinical grounds if the patient presents the typical single or multiple erythema migrans lesions and lives or has recently travelled to an endemic area. In this case, laboratory and serologic testing are not necessary.[1,4,6] A history of tick bite is a strong epidemiological link, but is reported in only 30 to 40% of patients with erythema migrans.[4] In patients with non-erythema migrans presentations, laboratory confirmation with a two-tier serologic testing is required, in which a sensitive enzyme-linked immunosorbent assay (ELISA) is the first step. If first-tier ELISA test is positive or equivocal, an immunoblot test should be performed. A positive IgG immunoblot test is considered diagnostic of *B burgdorferi* infection.[1,6]

In single or multiple erythema migrans, oral antibiotic treatment with doxycycline (for patients ≥ 8 years), amoxicillin, or cefuroxime axetil for 14 to 21 days is recommended to prevent dissemination and development of late Lyme disease. When treated properly, the prognosis is excellent.[2,7]

As there is no available vaccine, the best way to prevent the disease is to reduce the risk of a tick bite. Some preventive measures are recommended, as avoiding environments potentially infested by ticks, covering bare skin, and using tick repellents. Skin surface, including scalp, should be daily inspected after a possible tick exposure and attached ticks identified should be removed. In Portugal, as in the rest of Europe, prophylaxis after a tick bite is not recommended, as tick infection rates are less than 20%. Clinical observation for the following 30 days is the only recommended measure in case of tick bite.[1,4]

In this case report, and based on clinical and epidemiologic findings, Lyme disease multiple erythema migrans diagnosis was considered. Basic laboratory testing and electrocardiogram were normal, and the patient was treated with a two-week course of oral amoxicillin, with complete erythema migrans clearance within three days. Diagnosis was later supported by ELISA serology testing positivity and immunoblot testing.

In conclusion, with rising prevalence of Lyme disease in some areas, it is increasingly important to recognize the different stages of the disease, to provide early treatment and prevent hematogenous dissemination and sequels. Lyme disease still has a low prevalence in Portugal, but is endemic in Central Europe, with an estimated incidence of 156 cases per 100.000 people in Switzerland.[3,8] Although evidence of typical erythema migrans is sufficient to establish the diagnosis, other manifestations are broad and unspecific, highlighting the importance of the epidemiologic history as a clue to diagnosis.

ABSTRACT

Lyme disease is a spirochaetal infection caused by *Borrelia Burgdorferi sensu lato*, which is transmitted by infected ticks of the genus *Ixodes*. It has a broad spectrum of clinical manifestations which, associated with its low incidence in Portugal, requires a high level of clinical suspicion for diagnosis. However, it is considered endemic in certain geographic areas, like Central Europe. The authors report the case of a child, living in Switzerland, who developed

multiple erythema migrans lesions. Although parents did not recall a history of tick bite, Lyme disease diagnosis was established on clinical grounds, based on erythema and epidemiologic findings. When properly treated with oral antibiotic therapy, Lyme disease has an excellent prognosis. This case highlights the importance of epidemiologic history as a diagnostic clue.

Keywords: epidemiology; erythema migrans; Lyme disease

RESUMO

A doença de Lyme é uma infeção causada pela espiroqueta *Borrelia Burgdorferi sensu lato*, transmitida através de carraças infetadas do género *Ixodes*. Apresenta uma grande variedade de manifestações clínicas que, associada à sua baixa incidência em Portugal, exige um elevado índice de suspeição clínica para o diagnóstico. No entanto, é considerada endémica em certas regiões, como na Europa Central. Os autores reportam o caso de uma criança, residente na Suíça, que desenvolveu múltiplas lesões de eritema *migrans*. Apesar de os pais terem negado picada de carraça, foi considerado o diagnóstico clínico de doença de Lyme, com base nas características do eritema e contexto epidemiológico. Quando tratada adequadamente com antibioterapia oral, a doença de Lyme tem um excelente prognóstico. Este caso sublinha a importância do contexto epidemiológico como pista para o diagnóstico.

Palavras-chave: doença de Lyme; epidemiologia; eritema *migrans*

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IMAGING CASES

GYNECOLOGICAL CLINICAL CASE

CASO CLÍNICO GINECOLÓGICO

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A previously healthy 12-year-old girl presented to the Pediatric Emergency Department complaining of urinary retention, suprapubic pain, and dysuria for two days. She denied fever or gastrointestinal symptoms. Physical examination showed a suprapubic mass compatible with a painful vesical globe and the remaining physical examination was normal. Urine culture was performed to assess a potential cystitis diagnosis, which was positive for multisensitive *Escherichia Coli*. The girl was discharged medicated with amoxicillin and clavulanic acid. She returned three days later (day 2 of antibiotics) complaining of persistent urinary retention, fever, and vaginal bleeding. She had had her menarche three months before and her last menses occurred during the last fortnight. Upon gynecological examination, diagnosis of microperforated hymen was established. Pelvic ultrasound revealed a hypoechogenic nodular formation with approximately 20 cm in diameter (**Figure 1**), well defined and homogeneous; uterus and ovaries were not visible, probably pushed by the massive formation. This formation was confirmed by magnetic resonance imaging, which showed a massive lesion occupying space, with well-defined contours and pre-thickened, reaching 16.2 x 9.7 x 8. 9 cm in longitudinal, anteroposterior, and transverse axes, respectively. The lesion had a heterogeneous fluidic content without hypervascularized components in the lesion lumen (**Figures 2 and 3**). No changes were detected in the urinary system.

What is your diagnosis?

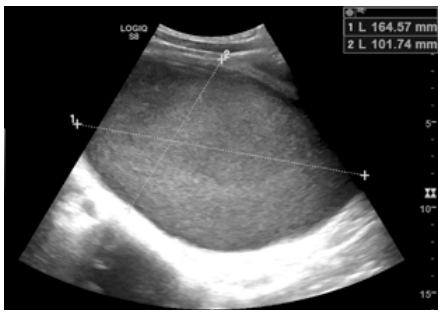

Figure 1 - Pelvic ultrasound

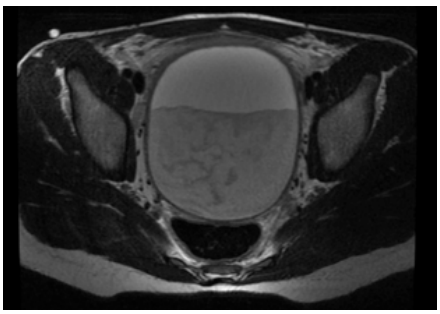

Figure 2 - Pelvic magnetic resonance imaging (transversal view)

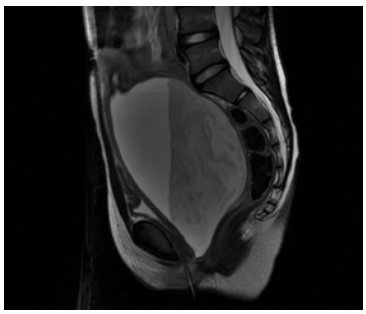

Figure 3 - Pelvic magnetic resonance imaging (lateral view)

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DIAGNOSIS

Hematocolpos

DISCUSSION

The girl underwent vaginoscopy and hymenectomy, showing a piohematocolpos which was completely drained. She was revaluated two weeks later, with complete condition resolution.

Hematocolpos is an accumulation of menstrual blood in the vagina, resulting from genital tract obstruction. It is a rare condition that occurs in adolescence, usually secondary to an imperforate or microperforate hymen. This is one of the most common congenital anomalies of the genital tract, and consists of a connective tissue membrane covered by epithelium obstructing the vaginal opening at the introitus level. Hymen is a membrane that usually develops embryologically through fusion of the caudal end of the paramesonephric ducts and the urogenital sinus. The central portion of this membrane perforates through degeneration of epithelial cells. Failure of epithelial cell degeneration and subsequent perforation leads to a hymen that is termed imperforate.[2] The differential diagnosis includes transverse vaginal septum, longitudinal vaginal septum, vaginal agenesis, and cervix atresia.[2] Symptoms as abdominal pain, dysuria, urinary retention, or amenorrhea can be present, and diagnosis implies a high degree of suspicion.[3] Menstrual history and inspection of the external genitalia showing a bluish-colored hymen should be part of the evaluation and aid in diagnosis.[4] Surgery is the recommended treatment, consisting of an incision in the vaginal hymen, and should be performed as early as possible to relieve symptoms and prevent complications.[5]

ABSTRACT

Herein is reported the case of a child observed in the Emergency Department due to urinary retention, suprapubic pain, and dysuria. Urine culture was performed upon cystitis suspicion, which was positive for *Escherichia Coli*, and the patient was treated with amoxicillin and clavulanic acid. Three days later, the child was reevaluated for persistent urinary retention, fever, and vaginal bleeding. At gynecological examination, she had an imperforate hymen. Imaging evaluation was performed, revealing an abdominal mass, suggestive of piohematocolpos. The patient was submitted to surgical drainage, with complete condition resolution.

Keywords: diagnosis; hematocolpos; menstrual blood; vesical globe

RESUMO

É descrito o caso de uma adolescente observada no Serviço de Urgência por retenção urinária, dor suprapúbica e disúria. Foi realizada urocultura devido a suspeita de cistite, que foi positiva para *Escherichia Coli*, e a rapariga foi medicada com amoxicilina e ácido clavulânico. Três dias depois, foi reavaliada por persistência da retenção urinária, febre e hemorragia vaginal. Ao exame ginecológico, apresentava um hímen imperforado. Foi realizada avaliação imagiológica, que detetou uma massa abdominal sugestiva de piohematocolpos, tendo sido realizada drenagem cirúrgica com resolução completa do quadro.

Palavras-chave: diagnóstico; globo vesical; hematocolpos; hemorragia vaginal

LESSONS FROM THIS CLINICAL CASE

All healthcare professionals attending adolescents should be alert for possible gynecological pathology.

Although hematocolpos is a rare condition, it should be considered in presence of an abdominal mass, for proper guidance.

Rapid recognition allows for timely surgical intervention, preventing complications.

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IMAGING CASES

MISALIGNED SHOULDERS

OMBROS DESALINHADOS

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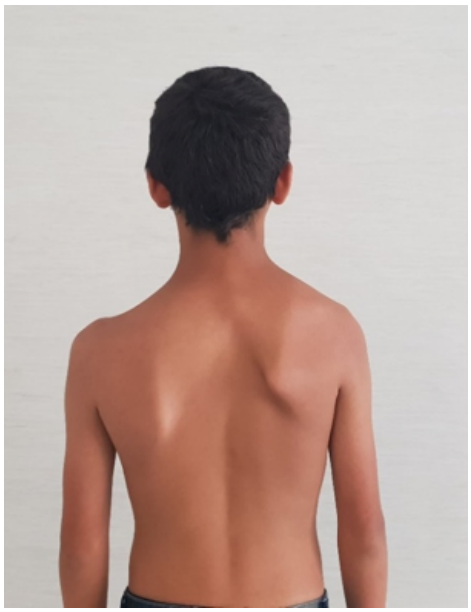
A nine-year-old boy without relevant past medical history was referred to the Orthopedic Department due to shoulder asymmetry. He denied pain, other symptoms, or functional limitation in daily activities. On physical examination, the right scapula was at a higher level compared with the left and slightly limited abduction was noted on the right shoulder. Spine x-ray was performed, revealing mild scoliosis, and computed tomography (CT) scan revealed the upper location of the right scapula with ipsilateral clavicle verticalization.

What is your diagnosis?



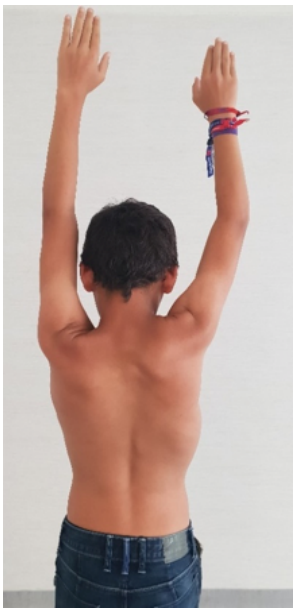


Figure 1 and Figure 2 - Asymmetry in the position of scapular poles, with slightly limited abduction on the right shoulder.

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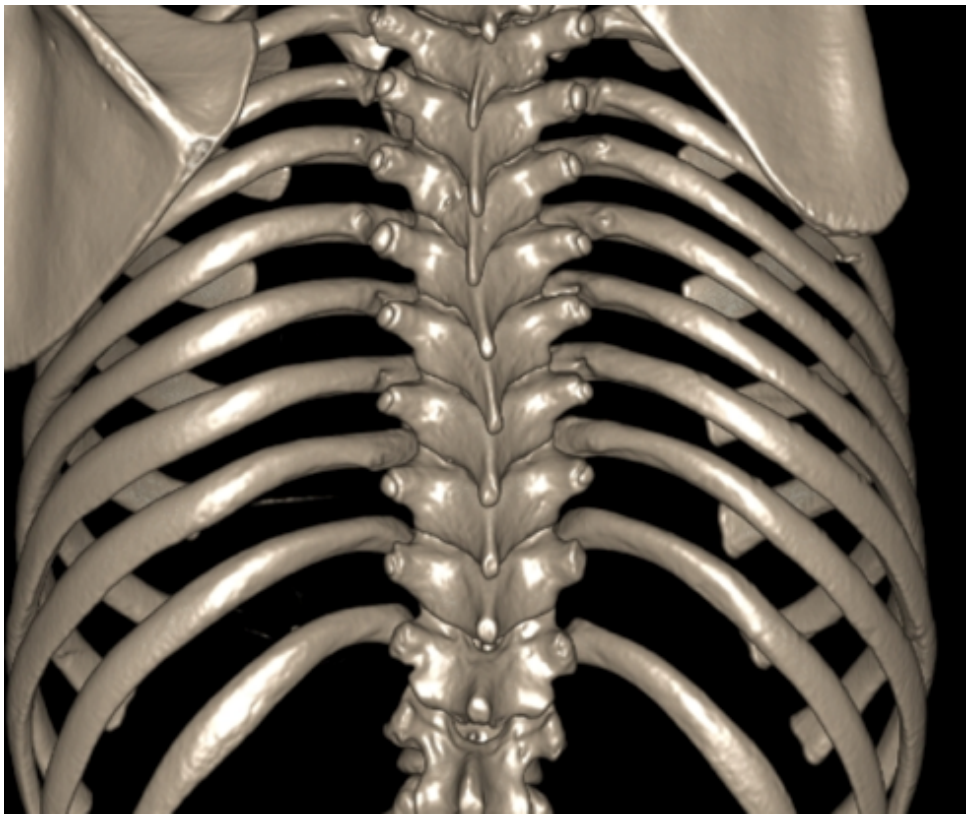

Figure 3 - 3D CT Scan

DIAGNOSIS

Sprengel Deformity

ORIENTATION

Surgical correction was not performed, since the boy had no functional limitation. Two annual follow-ups were conducted, with no changes in signs or symptoms.

DISCUSSION

Sprengel deformity is a congenital elevation of the scapula. Although rare, it is described as the most common congenital abnormality of the scapula.[1-3] It has a male predominance (3:1) and may be associated with congenital anomalies in the family.[3] The condition can occur on both sides concurrently, but is most often unilateral, with a predilection for the left side.[4]

The scapula develops embryologically during the fifth week in the upper dorsal/lower cervical region and descends up to the final anatomical position by 8-12 weeks of gestation. The pathology in Sprengel's deformity, which sits the bone 2-10 cm higher, probably represents a continuation of the scapula fetal form joined by failure in descending. Maintenance of a high scapula position can lead to other musculoskeletal defects, such as hypoplasia, medialization, adduction and prominence of the upper angle of the scapula; distal rotation and lateral angulation of glenoid cavity; changes in the position of the clavicle, cervicothoracic vertebrae and ribs; and atrophy of the shoulder musculature.[5,6] Moreover, other pathoanatomical anomalies can be found, such as omovertebral bone or costovertebral defects (spina bifida and kyphoscoliosis).[5,7]

Some syndromes are associated with Sprengel's deformity, the most common being Klippel-Feil Syndrome, present in about 19–27% of patients with Sprengel's deformity. Other linked syndromes include teratological conditions, such as anencephaly (a triad of occipital defect, spina bifida of cervical vertebrae, and fixed retroflexion of the head), X-linked dominant hydrocephalus, mental disturbance syndrome, and diastematomyelia. [4,8] In this case report, no evidence of any syndrome was found.

Among differential diagnoses, scapular winging should be considered, in which scapula alignment compared side to side for asymmetry reveals a declination of the affected shoulder, being a painful and debilitating condition. The most common reported causes are dysfunction of the serratus anterior or dysfunction of the

trapezius.[9]

Treatment can be conservative or surgical. Surgery is considered in patients with severe limitation of scapular function, neck pain, or to improve cosmesis.[5,8] Surgery should be performed between the ages of three and eight years, due to risk of nerve impairment below the age of eight. Surgical procedures involve a combination of scapular lowering with displacement of the origin or insertion of the scapular muscles on the spine/scapula and resection of the superomedial border. Associated congenital anomalies may be a contraindication to surgery.[5] Since the present child had no symptoms, surgical correction was not performed. The patients had two annual follow-ups, during which no changes in signs or symptoms were noted.

ABSTRACT

Sprengel deformity is a congenital elevation of the scapula. Herein is reported the case of a child with the right scapula at a higher level compared to the left and limited abduction of the right shoulder. Other pathoanatomical anomalies can be associated. Treatment is usually conservative, since surgery is only considered in patients with severe scapular function limitation, neck pain, or to improve cosmesis.

Keywords: conservative treatment; elevation of the scapula; Sprengel deformity

RESUMO

A deformidade de Sprengel é uma elevação congénita da omoplata. É descrito o caso de uma criança com a omoplata direita num nível mais elevado do que a esquerda e com abdução limitada do ombro direito. Outras anomalias ou síndromes podem ser associadas a esta deformidade. O tratamento é geralmente conservador, uma vez que a cirurgia é reservada a doentes com severa limitação funcional, dor no pescoço ou para melhoria estética.

Palavras-Chave: deformidade de Sprengel; elevação da omoplata; tratamento conservador

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AIMS AND SCOPE

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

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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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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".

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

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

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

NORMAS DE PUBLICAÇÃO

SUBMISSÃO

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

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

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

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

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

As páginas devem ser numeradas segundo a sequência referida anteriormente.

Na primeira página

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

Na segunda página

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

TEXTO

Editoriais

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

Artigos Originais

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

Artigos de Revisão

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

Casos clínicos

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

Casos de imagem

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

Cartas ao Editor

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

Perspetivas Atuais

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

Normas gerais

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

REFERÊNCIAS BIBLIOGRÁFICAS

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

Seguem-se alguns exemplos:

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

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

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

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

FIGURAS E QUADROS

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

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

AGRADECIMENTOS E ESCLARECIMENTOS

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

MODIFICAÇÕES E REVISÕES

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

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

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

ESTRUTURA DOS ARTIGOS - NORMAS DE PUBLICAÇÃO

Tipo de Artigo	Resumo		Palavras-chave (Português e Inglês)	Texto		Figuras e Quadros	Bibliografia
	Número máximo de palavras	Estrutura		Número máximo de palavras (excluindo Referências e Ilustrações)	Estrutura	Número total máximo	Número máximo de referências
Editorial	-	-	-	1200	-	1/2	15
Artigos Originais	250	Introdução/Objetivo 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