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ADULTOS e IDOSOS

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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO. DENOMINAÇÃO DO MEDICAMENTO: Dioralyte, pó para solução oral. **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA: Substâncias activas** g/saqueta: Glicose 3,56; Cloreto de sódio 0,47; Cloreto de potássio 0,30; Citrato dissódico 0,53. **INDICAÇÕES TERAPÊUTICAS:** Correcção da perda de líquidos e electrólitos nos lactentes, crianças e adultos. Tratamento da diarreia aquosa de várias etiologias, incluindo as gastrenterites, em todos os grupos etários. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Cada saqueta deve ser sempre dissolvida em 200 ml de água. O volume de Dioralyte reconstituído a tomar deve ser decidido pelo médico assistente, tendo em consideração o peso do doente e o estado e gravidade da situação. Um princípio básico no tratamento da diarreia é a substituição da perda de líquidos e a manutenção de uma ingestão de líquidos suficiente para repor a sua perda nas fezes. A ingestão diária deve ser baseada num volume de 150 ml/Kg de peso nos lactentes e 20–40 ml/Kg de peso nos adultos e crianças. Uma aproximação razoável é a seguinte: -lactentes – 1 a 1,5 vezes o volume alimentar habitual; - crianças – 1 saqueta após cada dejecção diarreica; - adultos – 1 ou 2 saquetas após cada dejecção diarreica. Inicialmente, podem ser necessárias maiores quantidades de Dioralyte para assegurar uma reposição precoce do equilíbrio hidro-electrolítico. Nos estadios iniciais do tratamento da diarreia, todos os alimentos, incluindo o leite de vaca e o leite artificial, devem ser interrompidos. Não se deve no entanto interromper o aleitamento materno. Nas crianças amamentadas sugere-se que se dê à criança o mesmo volume de Dioralyte do que o da alimentação normal, seguindo-se o aleitamento. Pode ser necessário, durante este período, a expressão do leite residual da mama. Após 24-48 horas, quando os sintomas desaparecerem, a dieta normal deve ser retomada gradualmente para evitar o agravamento da situação. O regime sugerido para o tratamento da diarreia infantil grave baseado no peso corporal em Kg é apresentado no quadro anterior. Quando a diarreia é acompanhada de vómitos, sugere-se ingestão frequente de pequenas quantidades de Dioralyte. No entanto, é importante que seja tomado o volume total necessário de Dioralyte. Quando o funcionamento dos rins é normal torna-se difícil superhidratar por via oral e quando existem dúvidas acerca da dosagem correcta, mais vale tomar a mais do que a menos. **CONTRA-INDICAÇÕES:** Não se conhecem contra-indicações ao Dioralyte. No entanto, existem algumas situações em que o tratamento com Dioralyte é inapropriado, tais como por exemplo, situações de oclusão intestinal requerendo intervenção cirúrgica, ou em caso de vómitos persistentes e desidratação grave ou diarreia infantil grave em que será necessária uma terapêutica por via intravenosa. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** O Dioralyte só deve ser reconstituído com água. Cada saqueta deve ser sempre reconstituída em 200 ml de água. Uma solução mais fraca do que a recomendada não contém a concentração óptima de glicose e electrólitos e uma solução mais forte do que a recomendada pode provocar desequilíbrio electrolítico. Se a diarreia não melhorar rapidamente, os doentes deverão ser reavaliados. Nos idosos, a administração de soluções contendo glucose e electrólitos deve ser cuidadosa em caso de alterações renais ou hepáticas graves ou em outras situações em que o balanço electrolítico normal se encontre alterado. Nos lactentes, deve interromper-se durante 24 horas a alimentação com leite de vaca ou leite artificial, que deverão ser reintroduzidos gradualmente quando a diarreia tiver diminuído. Não se deve interromper o aleitamento materno. **EFEITOS INDESEJÁVEIS:** Podem ocorrer náuseas ou vómitos após a administração da solução, em particular quando esta é ingerida com demasiada rapidez. Estão também descritos casos isolados de desconforto abdominal e de obstipação.Data da revisão do texto: Janeiro de 2004.**TITULAR DA AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO: KORANGI - Produtos Farmacêuticos, Lda. Medicamento não sujeito a receita médica. Para mais informações contactar o Titular da Autorização de Introdução no Mercado**

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EDITORIAL

Child development pediatrician: from the early to the new challenges

Pediatra do desenvolvimento infantil: dos primeiros aos novos desafios

Mónica Pinto

Hospital Beatriz Ângelo, Loures, Portugal

Child development clinics have undergone a significant transformation since they were created, evolving from rudimentary diagnostic centers to comprehensive, multidisciplinary facilities designed to address a wide range of developmental issues in children. This evolution reflects broader changes in medical knowledge, societal attitudes, and health care systems. Understanding this progression offers valuable insights into how we can further improve support for children with developmental challenges.

The concept of specialized care for children with developmental disorders began to take shape in the late 19th and early 20th centuries. Early pioneers, such as Gesel, Piaget, Prechtl, Dubowitz, Brazelton, Mary Sheridan, Amiel-Tison, Kanner, to name just a few, were instrumental in this movement. These early efforts were primarily focused on the observation and documentation of child development milestones but laid the groundwork for a systematic approach to identifying and understanding developmental disorders[1]. However, at that time, child development clinics were often included in broader pediatric or psychiatric services, lacking the specialization and comprehensive approach seen today.

The mid-20th century marked a significant turning point with the establishment of specialized child development clinics. These clinics emerged in response to the growing recognition that developmental disorders required distinct approaches and expertise.

Advancements in medical knowledge led to an increased understanding of various developmental disorders, including autism, cerebral palsy, and learning disabilities, and highlighted the need for dedicated diagnostic and therapeutic services. Parents of children with developmental disorders started to form advocacy groups, demanding better services and support. It was at this point that clinics began to incorporate a multidisciplinary approach, involving pediatricians, psychologists, speech and language therapists, psychomotor therapists, and occupational therapists. This comprehensive model allowed for more accurate diagnoses and effective interventions tailored to each child's needs[1].

The latter part of the 20th century saw further integration and expansion of child development clinics with the creation of multidisciplinary teams, a concept that became standard practice. These teams work collaboratively to provide holistic care, addressing the medical, psychological, and social aspects of developmental disorders[1].

In Portugal, there was a growing awareness of the importance of addressing these issues and, as in other countries, there was a rise in similar multidisciplinary teams and child development centers in the 1970s and the 1980s. There was also a rapid growth in the development and implementation of early intervention programs aimed at identifying developmental delays as early as possible, often starting

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with screenings in infancy. Child development clinics began to forge partnerships with educational institutions. This collaboration ensured that children were accommodated in terms of their education and received support, facilitating better outcomes both academically and developmentally. Advances in medical technology, including improved imaging techniques and genetic testing, enhanced the diagnostic capabilities of clinics. These technologies allowed for more precise identification of underlying causes of developmental disorders. Increased public awareness about developmental disorders, driven by advocacy groups and media coverage, led to a greater demand for specialized services.

The evolution of child development clinics has continued into the 21st century, marked by several key trends and innovations:

- Modern child development clinics emphasize holistic and family-centered care. This approach recognizes the critical role of families in the therapeutic process and aims to empower parents with knowledge and resources to support their children effectively.
- The advent of telehealth and digital tools has revolutionized access to care. Telehealth services allow families in remote or underserved areas to receive expert consultations and therapy sessions. This was extremely significant in our country during the Covid-19 lockdown, allowing children and families to remain in touch with their team of providers. The impact of Covid-19 as reported by Dias et al.[2] was severe in these children and there are several issues that need to be further adjusted.
- There is a growing focus on inclusivity and the need to address the unique requirements of diverse populations. Clinics are increasingly aware of cultural, linguistic, and socioeconomic factors that influence access to care and the effectiveness of interventions. Efforts to provide culturally sensitive services and reduce disparities are central to modern practices.
- Child development clinics now often work with broader community services, including schools, social services, and recreational programs[3]. This integration ensures a more cohesive support network for children and their families.
- Ongoing research continues to inform best practices in diagnosing and treating developmental disorders. It is important that curiosity driven researchers, such as Sampaio e Caseiro[4] keep digging into new aspects to further increase knowledge about these disorders. Innovations in neuroscience, genetics, and behavioral science are constantly being integrated into clinical practice, enhancing the effectiveness of interventions.

Despite significant advancements, child development clinics face ongoing challenges:

- Many clinics operate with limited resources, affecting their ability to serve all children in need. This group of disorders, being highly prevalent in the population, results in an increased burden for primary care services, or even for general pediatrics, so it is important to create new multidisciplinary teams in child development centers integrated into both primary care settings and hospital settings. Increased funding and support is crucial to expanding services and reducing wait times.
- There is a nationwide shortage of specialists trained in pediatric developmental disorders. Addressing this shortage requires investment in training programs and incentives to attract professionals to this field. I am glad that the need for a pediatric sub-specialty in this field was finally acknowledged in our country, because it was the first step in the right direction, but there are many more to be taken.
- Ensuring equitable access to services remains a challenge, particularly for families in overcrowded city areas, rural and remote villages, or low-income areas. Expanding telehealth services and community outreach can help bridge this gap, but integrating these tools into everyday practice requires careful planning and training to ensure they are used effectively and ethically.

Looking forward, child development clinics must continue to focus on innovation, inclusivity, and accessibility. By leveraging advances in technology, fostering interdisciplinary collaboration, and advocating for policies that support comprehensive care, these clinics can better serve children and families, providing early intervention programs and ensuring that all children can reach their full potential.

In conclusion, the journey of child development clinics from their early beginnings to modern multidisciplinary centers reflects the dynamic nature of medical science and societal progress. As we move forward, continued dedication to improving these essential services will be crucial in addressing the diverse needs of children with developmental challenges, fostering their growth, and enhancing their quality of life.

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ORIGINAL ARTICLE

A systematic method to evaluate newborn weight loss and its influence on breastfeeding success

Catarina Schrempp da Silva Gaio Esteves[1], Maria C. Soares Martinez Veiga de Macedo[2], José P. Pereira[3], Ana Rodrigues[1], and Ana C. Feijó Serrano de Matos Amaro[1]*

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Abstract

Introduction and objectives: Increasing evidence shows that newborn weight loss is significantly influenced by the type of labour among other factors, implying a wider understanding of weight loss and its context to intervene accordingly. Given the importance of breastfeeding and the impact of infant formula use on its success, we aimed to understand the impact of the application of nomogram weight loss tool in initiating infant formula. **Methods:** This study included 206 newborns in a non-randomised clinical trial, who were divided into two groups. In the intervention group, weight loss was managed through the use of the "Early Weight Loss Nomogram", rather than with clinical experience associated with weight loss percentage, the standard type of care. We analysed the characteristics of mothers, newborns, and labours and their influence on each group. **Results:** We found that the introduction of formula milk due to weight loss tended to diminish (61.3% vs. 38.7%, p = 0.082) and nurses' suggestions dropped to zero in the intervention group. The intervention group reported a longer period of exclusive breastfeeding, up to nearly six months of age. The babies who were not breastfed during the first hour of life were more often supplemented (78.6% vs. 21.4%, p < 0.001) and those with skin-on-skin contact were given a lower proportion of formula milk (69.8% vs. 30.2%, p < 0.001). **Discussion:** Application of the nomogram allowed the introduction of formula milk in more selected cases. This tool should be applied in healthcare units because it increases health professionals' awareness of the criteria for formula supplementation.

Keywords: Newborn weight loss. Breastfeeding. Supplementation. Infant formula. Nomograms.

Avaliação da perda ponderal do recém-nascido através de um método sistemático e a sua influência no sucesso do aleitamento materno

Resumo

Introdução e objetivos: Há evidência que demonstra como a perda ponderal do recém-nascido é influenciada por vários fatores, sendo importante uma compreensão contextualizada da mesma e intervir criteriosamente. Dado o impacto que a utilização de leite artificial tem no sucesso do aleitamento materno, estudámos a influência da aplicação de um nomograma de perda ponderal na introdução de leite artificial. **Métodos:** O estudo clínico não randomizado incluiu 206 recém-nascidos. No grupo de intervenção, a perda ponderal foi avaliada com o uso do "Nomograma de Perda Ponderal", em contraste com o grupo de controlo que foi avaliado pela perda ponderal percentual, o método de avaliação mais amplamente utilizado. Analisamos as características da mãe, do recém-nascido e do tipo de parto, e a sua influência em cada grupo. **Resultados:** No

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grupo de intervenção, a introdução do leite artificial devido a perda ponderal do recém-nascido diminuiu (61.3% vs. 38.7%, p = 0.082) e não ocorreu em nenhum caso por sugestão da equipa de enfermagem. No grupo de intervenção, verificou-se um maior período de aleitamento materno exclusivo, até aos 6 meses de idade. Os recém-nascidos que não foram amamentados durante a primeira hora de vida foram mais frequentemente suplementados (78.6% vs. 21.4%, p < 0.001) e aqueles que tiveram oportunidade de contacto pele-pele verificaram uma menor probabilidade de introdução de leite artificial (69.8% vs. 30.2%, p < 0.001). **Discussão:** A aplicação do nomograma permitiu a introdução do leite artificial em casos mais selecionados. Esta ferramenta deverá ser usada de modo a ser mais criteriosa a introdução de leite artificial, promovendo o sucesso do aleitamento materno com impacto na saúde pública.

Palavras-chave: Perda ponderal do recém-nascido. Aleitamento materno. Suplementação. Fórmula. Nomograma.

Keypoints

What is known

- Globally, clinical experience and absolute weight loss percentage determine the initiation of supplementation with formula milk.
- It is common to have a higher than expected weight loss percentage; it occurs earlier than expected, and significantly differs according to the type of labour.
- Infant formula given during the first days of life is related to a higher risk of early cessation of breastfeeding.

What is added

- Newborn weight loss should be contextualised because several factors contribute to weight loss. Application of the nomogram allows health professionals to contextualise the newborn's weight loss, introducing formula milk in more selective cases.
- Its application in populations with high caesarean section rates can be especially useful.
- After applying the nomogram, we found higher rates of exclusive breastfeeding at 6 months of age.

Introduction

Breastfeeding is the ideal way to nourish healthy newborns as well as newborns with any medical condition, such as pre-term babies. Human milk is recognised as the natural way of feeding newborns and is known for its enormous advantages for the health of babies and mothers' health[1]. Given these facts, UNICEF and WHO recommend exclusive breastfeeding for the first six months of life, supplemented with other foods until two years of age or more[2].

It is extremely important to address low breastfeeding rates in developed countries in order to improve health and reduce costs. This means understanding that breastfeeding is more than just food and that all healthcare professionals should take responsibility for this public health issue[3].

On a national level, a study showed that initiation of breastfeeding was 87.1%, but only 21% exclusively breastfed until six months of life, below the reported worldwide level of 38%[4]. One of the WHO's aims for 2025 is to reach 50% of exclusive breastfeeding until six months of age, reaffirming the importance of initiatives that promote the continuation of breastfeeding[5]. According to MB McCoy et al., infant formula given during the first days of hospital stay is associated with a two to six times higher risk of early weaning[6]. Frequently, the decision to give infant formula is associated with the perception of excessive weight loss.

Overall, it is known that a full-term newborn can lose up to 10% of their weight during the first days of life and recover their birth weight between the 10th and 14th day of life. However, Ian M Paul et al. have shown that a higher weight loss is common, occurs earlier than expected, and significantly differs according to the type of labour, and this difference persists throughout the weight recovery period, which can be longer than expected. A study performed by Kaiser Permanente hospitals in Northern California between 2009 and 2013 created a weight nomogram analysing the data of 161,471 newborns, which shows hour-by-hour weight loss trajectories during birth hospitalisation for generally healthy-term newborns and their recovery during the first 30 days of life[7]. Increasing evidence has demonstrated that using this nomogram allows a significant reduction in the introduction of infant formula[8]. We aimed to understand the impact of its usage in our population on exclusive breastfeeding and breastfeeding duration, compared to managing accordingly with clinical experience regarding weight loss percentage.

Methods

Our study was a nonrandomised clinical trial that included 206 newborns born between July and August 2020 at Hospital CUF Descobertas, a private hospital located in Lisbon, Portugal. The characteristics of mother and baby demographics, type of labour and feeding

method, and hospital stay were analysed. Pre-term newborns (classified as those born before 37 weeks of pregnancy) and newborns who needed admission to special care units were excluded, except if phototherapy was the only reason for admission to special care.

They were divided into two groups: a control group that included those born in July 2020 and an intervention group that included those born in August 2020. In the control group, newborns' weight loss was managed according to clinical experience regarding the weight loss percentage, which is considered as the standard type of care; and in the intervention group, weight loss was interpreted and managed through the use of the "Early Weight Loss Nomogram". The nomogram is available at *https://newbornweight.org*, a tool that considers several data such as birth weight, time and date of birth, type of labour, and feeding method. Specifically, in our study, given its objectives, the feeding method experienced was exclusive breastfeeding. Birth weight loss is shown through a percentile graph. When birth weight loss was above the 75th percentile according to the nomogram, supplementation with expressed breast milk was administered. After six hours, if there was no improvement in newborn weight and we found difficulties expressing breast milk, we gave formula milk. Breastfeeding support was optimised, aiming to return to exclusive breastfeeding. Data were collected among birth registrations, nurse teams, and with the mother. The collected data were saved in Microsoft Excel®.

Written informed consent was obtained from all participant mothers. The study protocol was approved by the ethics committee of Hospital CUF Descobertas and complied with the principles of the Declaration of Helsinki.

Statistical analysis

SPSS 23 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, EUA) software was used for statistical analyses. Normal data distribution was verified using the Kolmogorov-Smirnov test. Significant differences between the groups were analysed using the t-test and Mann-Whitney U test, as appropriate. Pearson's chi-square test and Fisher's exact test were used to compare qualitative data. Differences were considered statistically significant when $p < 0.05$.

Results

The demographic and clinical characteristics of the mothers and newborns are presented in table 1 and 2, respectively. Of total 204 mothers, the protocol was not applied to 98, and the protocol was applied to the remaining 106 mothers.

For the total sample, the mother's mean age was 34.7 years and 74.5% (n = 152) had attended or finished college. 47.6% (n = 97) had had a previous delivery, and 28.9% (n = 59) reported having difficulties breastfeeding with their previous children. As a median, mothers were breastfed for up to three months as children themselves. The father was present in 88.2% (n = 180) of deliveries.

For mother's parameters, age, education, parity, breastfeeding difficulties in prior pregnancy, mother's duration of breastfeeding, mother's comorbidities, and father presence during labour, the participants did not present any differences at the beginning of the study, proving the homogeneity of the recruited sample.

The percentage of health problems among mothers was similar. There were 21 (10.2%) mothers with gestational diabetes, 11 (5.3%) with hypothyroidism, 9 (4.4%) with arterial hypertension, 1 (0.5%) with anxiety disorder, 1 (0.5%) with depressive syndrome and 1 (0.5%) with polycystic ovary syndrome. The other nine mothers had other health issues not detailed in the clinical process.

A total of 206 newborns were characterised (there were 2 twin pregnancies). There were 51.9% (n = 107) males. The mean gestational age was 38 weeks and 6 days, the mean birth weight was 3,159 grammes, and the mean discharge weight was 2,952 grammes. The median weight loss percentage was 6.70%, and no differences were found before and after application of our protocol, 7.22% and 6.24%, respectively ($p = 0.072$).

The median Apgar score in the first, fifth, and tenth minutes was 9, 10, and 10, respectively. The median length of hospital stay was 62 hours. There were no statistically significant differences between the groups for these parameters. Globally, there was a similar distribution between genders, but a statistically significant difference occurred in gender ($p < 0.05$) between before and with protocol application, with a higher percentage of female newborns in the group in which the protocol was applied.

Regarding the type of labour, 59.7% (n = 123) were caesarean sections and 59.3% were performed electively. Vaginal delivery corresponded to 15.1% (n = 31), 21.8% (n = 45) used suction cups, and 3.4% (n = 7) used forceps. Skin-on-skin contact was guaranteed in 25.9% (n = 53) and breastfeeding during the first hour of life occurred in 86.4% (n = 178). No statistically significant differences were found between the previous variables.

Formula milk was given to 49.5% (n = 102) of the newborns. The same relative frequency was found before and after our protocol application (49.5%), for n = 49 and n = 53, respectively. There was no statistically significant difference regarding the introduction of formula milk ($p = 0.996$).

Table 1. Characteristics of the mothers

	Total (n = 204)	Before applying our protocol (n = 98)	During application of our protocol (n = 106)	p
Age (years)*	34.70 (± 4.33)	34.94 (± 4.09)	34.48 (± 4.54)	0.442§
Education†				
Secondary education	52 (25.5)	22 (22.5)	30 (28.3)	0.361¶
Tertiary education	152 (74.5)	76 (77.6)	76 (71.7)	
Parity†				
Multiparity	97 (47.6)	48 (49.0)	49 (46.2)	0.852¶
Breastfeeding difficulties in prior pregnancy†	59 (28.9)	35 (35.7)	24 (22.6)	0.063¶
Mother's age when she stopped being breastfeeding during her childhood (months)‡	3.0 (0.5-7.0)	3.0 (1.0-9.0)	3.0 (0.0-6.0)	0.286**
Mother's comorbidities†	53 (26.0)	25 (25.5)	28 (26.4)	0.915¶
Father present during labour†	180 (88.2)	85 (86.7)	95 (89.6)	0.528¶

*Mean (± standard deviation).
†n (percentage).
‡Median (lower quartile-upper quartile).
§t-test.
¶Pearson's Chi-square test.
**Mann-Whitney U test.

Differences in formula intake are presented in figure 1.

The reasons for the introduction of infant feed formula are described in table 3. In only 49.0% (n = 50) of newborns who received formula milk, the reason was registered in the newborn's clinical file.

Regarding the reasons for formula milk intake, 51% (n = 52) were at the mother's request and 30.4% (n = 31) were due to the newborn's weight loss. There was a reduction in infant formula introduction due to newborn weight loss before and during the protocol application, since of these 31 cases, 61.3% (n = 19) were before the protocol and 38.7% (n = 12) during protocol application; however, no statistical significance was found. The formula milk intake by nurse's suggestion was verified in 5.9% (n = 6) of cases, and all of them were before the application of the protocol; thus, significant differences were found (p = 0.014). Doctors' prescriptions represented 2.0% (n = 2) of the cases of formula introduction, with no differences between groups.

Other reasons registered for infant formula introduction were: mother's exhaustion (n = 1), long gap between newborn breastfeeding opportunities (n = 1), difficulty in breastfeeding adaptation (n = 3), hypoglycaemia (n = 1), emergency surgery needed (n = 1), short stay in neonatology nursery (n = 1) and twin pregnancy (n = 2).

After one month, all mothers were contacted regarding the type of feeding their infants were receiving, and 200 answers were collected. Exclusive breastfeeding was maintained in 62% (n = 124). Formula milk was introduced in 27.5 % (n = 55) of infants and breastfeeding was stopped in 10.5% (n = 21). A higher proportion of infants fed with formula milk was found (p < 0.05) within the protocol application group.

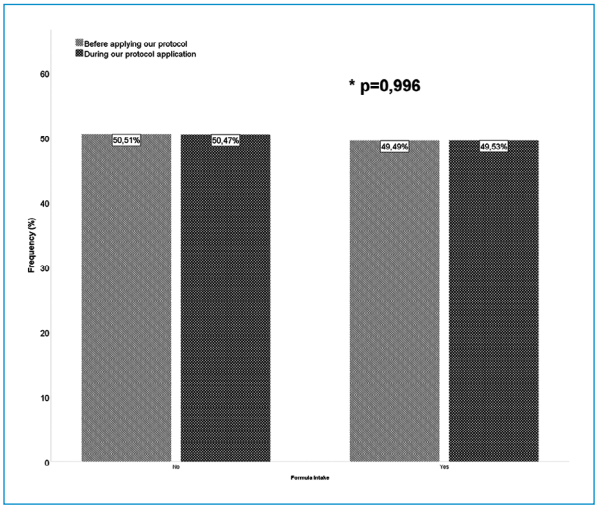

Figure 1. Differences in formula intake before and during application of our protocol.
*Pearson's chi-square test.

The type of infant feeding after the first month of life and duration of breastfeeding after two years of life are presented in table 4.

Table 2. Characteristics of the newborns

	Total	Before applying our protocol	During application of our protocol	p
Sex†				
Male	107 (51.9)	62 (61.6)	45 (42.1)	0.007¶
Female	99 (48.1)	37 (37.4)	62 (57.9)	
Gestational age (weeks)*	38.84 (± 1.09)	38.82 (± 0.93)	38.85 (± 1.22)	0.850§
Birth weight (grammes)*	3,159.29 (± 425.21)	3,178.34 (± 367.29)	3,141.65 (± 473.60)	0.547§
Discharge weight (grammes)*	2,952.86 (± 361.00)	2,945.80 (± 339.17)	2,959.34 (± 381.37)	0.789§
Weight loss (percentage)*	6.70 (± 3.86)	7.22 (± 3.89)	6.24 (± 3.78)	0.072§
Hospital stay duration in hours (hours)‡	62 (45-69)	62 (45-72)	62 (45-68)	0.393**
APGAR 1 min‡	9 (9-9)	9 (9-9)	9 (9-9)	0.168**
APGAR 5 min‡	10 (10-10)	10 (10-10)	10 (10-10)	0.633**
APGAR 10 min‡	10 (10-10)	10 (10-10)	10 (10-10)	0.608**
Induced labour†	79 (38.5)	40 (40.8)	39 (36.4)	0.567¶
Delivery method†				
Vaginal	31 (15.1)	14 (14.1)	17 (15.9)	0.846¶
Forceps	7 (3.4)	1 (1.0)	6 (5.6)	0.123¶
Suction cup	45 (21.8)	20 (20.2)	25 (23.4)	
Caesarean	123 (59.7)	64 (64.6)	59 (55.1)	
Skin-on-skin contact†	53 (25.9)	25 (25.5%)	28 (26.2%)	0.914¶
Breastfeeding during the first hour of life†	178 (86.4)	87 (87.9%)	91 (85.0%)	0.685¶

*Mean (± standard deviation).
†n (percentage).
‡Median (lower quartile-upper quartile).
§t-test.
¶Pearson's Chi-square test.
**Mann-Whitney U test.

Table 3. Reasons that motivated starting formula milk

	Total, n (%) (n = 102)	Before applying our protocol, n (%) (n = 49)	During application of our protocol, n (%) (n = 53)	p
Mother's choice	52 (51.0)	23 (46.9)	29 (54.7)	0.552*
Newborn weight loss	31 (30.4)	19 (38.8)	12 (22.6)	0.082*
Doctor's prescription	2 (2.0)	1 (2.0)	1 (1.9)	†
Nurse's suggestion	6 (5.9)	6 (12.3)	0 (0.0)	0.014*
Other reasons	11 (10.7)	0 (0.0)	11 (20.8)	0.011*

*Pearson's Chi-square test.
†Assumed p > 005.

Two years later, we contacted all the mothers to ascertain the total duration of exclusive breastfeeding. Regarding duration of exclusive breastfeeding, 115 mothers answered (62 of the control group and 53 of the intervention group), and regarding total duration of breastfeeding, only 140 mothers answered (75 of the control group and 65 of the intervention group).

The median duration of exclusive breastfeeding was six months and that of breastfeeding was 9 months.

No statistically significant differences were found between the groups for these parameters; however, there was a trend towards a longer duration of exclusive breastfeeding with the application of the protocol (6 months vs. 5.5 months; p = 0.057).

Table 4. Type of infant feeding through life time

	Total (n = 200)	Before applying our protocol (n = 93)	During application of our protocol (n = 107)	p
Exclusive breastfeeding‡	124 (62)	60 (64.5)	64 (59.8)	0.025*
Formula milk‡	21 (10.5)	4 (4.3)	17 (15.9)	
Both‡	55 (27.5)	29 (31.2)	26 (24.3)	
Duration of breastfeeding after two years of life				
Exclusive breastfeeding, months§	6.0 (4.0-6.0)	5.5 (4.0-6.0)	6.0 (5.0-6.0)	0.057†
Breastfeeding duration, months§	9.0 (5.0-19.0)	9.0 (5.0-18.0)	10.0 (5.0-23.0)	0.754†

*Pearson's Chi-square test.
†Mann-Whitney U test.
‡n (percentage).
§Median (lower quartile-upper quartile).

Factors related to formula milk intake during the hospital stay of newborns are presented in table 5.

The babies who were supplemented with formula milk stayed in hospital for significantly longer (66.5 hours vs. 50 hours, p < 0.001). The babies who were not breastfed during the first hour of life more frequently had formula milk (78.6% vs. 21% 4, p < 0.001) and babies with skin-on-skin contact were less frequently supplemented with formula milk (69.8% vs. 30.2%, p < 0.001).

Discussion

Among both groups, over 70% of the mothers had completed tertiary education, which is not representative of the Portuguese reality[9]. In developed countries, higher rates of breastfeeding occur among highly educated mothers[10].

Approximately 58% of the mothers had difficulties breastfeeding in previous pregnancies, and the mother's median age when she stopped being breastfed during her childhood was three months of age. This is very representative of the generation of mothers born during the 1980s and 1990s[11].

Caesarean section rates were above average, corresponding to almost 60% of total labours, 59% of which were electively performed. Skin-on-skin contact, which is more difficult to ensure after caesarean section, occurred in 26% of the cases. Newborns that were born after a caesarean section and did not have skin-on-skin had a higher risk of initiating formula milk[12].

There are several reasons to start formula milk, and the mother's choice is one of them. This was the reason in 51% of the cases where formula milk was introduced, with similar rates between both groups. This choice can be made due to lack of information and absence of prenatal education, previous difficulties in breastfeeding, and the fact that the mother was not breastfed at all or only for a short period.

Newborn weight loss as a reason to start formula milk reduced from 61.3% to 38.7% after applying the weight nomogram. In addition, starting formula milk after the nurses' suggestion dropped to zero cases during the protocol application. There was no statistically significant difference regarding the introduction of formula milk, and different aspects other than weight loss justified the introduction of formula milk in the protocol group. This can be explained by the increased awareness among the health team regarding the weight loss criteria to start formula milk and the search for other reasons to justify its introduction. Also, it shows that before the protocol, the introduction of formula milk was probably wrongly attributed to excessive weight loss, in some cases.

In both groups, the duration of hospital stay was longer among the newborns who received formula milk, probably because they had excessive weight loss and needed medical supervision.

After the first month of life follow-up, there were more cases of the introduction of formula milk among the group in which the protocol was applied, 4.3% compared with 15.9%. This probably happened because formula milk was introduced during the first month of follow-up consultations in a primary care setting where this nomogram is unknown among physicians and rarely used. In addition, another probable contributing factor, a prompt follow-up supporting breastfeeding with a lactation specialist, such as an international lactation consultant, was lacking in most cases after discharge from hospital.

Table 5. Factors related to formula milk intake during hospital stay of newborns

	Formula intake		p
	No	Yes	
Breastfeeding difficulties in prior pregnancy†			
Yes	38 (64.4)	21 (35.6)	0.025¶
No	17 (40.5)	25 (59.5)	
Education†			
Basic education	2 (100.0)	0 (0.0)	0.295¶
Secondary education	23 (46.0)	27 (54.0)	
Tertiary education	78 (51.7)	73 (48.3)	
Mother's duration of breastfeeding, months‡	3 (0-60)	3 (0-24)	0.645**
Gestational age, months*	38.94 (± 1.03)	38.73 (± 1.13)	0.160§
Newborn birth weight, grammes*	3,152.22 (± 425.14)	3,166.49 (± 427.27)	0.810§
Newborn discharge weight, grammes*	2,932.29 (± 327.88)	2,973.64 (± 392.15)	0.414§
Weight difference between discharge and birth, grammes*	–219.56 (± 233.52)	–192.85 (± 131.19)	0.315§
Hospital stay duration, hours‡	50.0 (31.0-88.0)	66.5 (36.0-120.0)	< 0.001**
Induced labour†			
Yes	45 (39.8)	68 (60.2)	0.152¶
No	58 (63.0)	34 (37.0)	
Delivery method†			
Vaginal	59 (71.1)	24 (28.9)	0.002¶
Caesarean	45 (36.6)	78 (63.4)	
Skin-on-skin contact†			
Yes	37 (69.8)	16 (30.2)	< 0.001¶
No	66 (43.4)	86 (56.6)	
Breastfeeding during the first hour of life†			
Yes	98 (55.1)	80 (44.9)	< 0.001¶
No	6 (21.4)	22 (78.6)	

*Mean (± standard deviation).
†n (percentage).
‡Median (lower quartile-upper quartile).
§t-test.
¶Pearson's Chi-square test.
**Mann-Whitney U test.

Duration of breastfeeding was longer among the group in which the protocol was applied, without a statistically significant difference. According to WHO recommendations, breastfeeding should be continued up to the age of two years or beyond, as mutually desired by the mother and child, given all its benefits. Although our results are not statistically significant, they are close to this recommendation.

Globally, the rate of introduction of formula milk was similar between both groups, among 49.5% of the newborns. Regardless of application of the nomogram, prompt follow-up with an international lactation consultant in both groups contributed to similar breastfeeding rates. Our intervention was short, and more breastfeeding educational programmes are needed to support healthcare teams. Frequent change among team members could influence the breastfeeding support given to mothers.

Application of the nomogram helps contextualise newborn weight loss and, therefore, introduce formula milk in more selected cases. In the case of excessive weight loss, the newborn-mother dyad should be evaluated, and necessarily means supplementation with formula milk. Given the fact that newborn weight loss is physiologically higher after caesarean section, the use of this nomogram is useful in order to decrease formula supplementation, in a context of high caesarean rates[13].

Our goal was to improve our clinical judgement and provide formula milk in more selected cases. Our results showed that we could introduce formula milk in more selected cases, following more solid criteria.

We consider that our study has several limitations. The fact that the introduction of formula milk during hospital stay, the duration of exclusive breastfeeding and full breastfeeding were not statistically different between groups, can be explained by the small sample and a need to improve our support to mothers and newborns regarding their breastfeeding difficulties.

The study was conducted during July and August, when there is a high rotation of healthcare team members, due to summer holidays. This limits the engagement of the healthcare team members with the study and the regular provision of breastfeeding support and application of the protocol when breastfeeding difficulties arise. This can be illustrated by the fact that the reason to start formula milk was registered in less than 50% of the newborns' clinical files. The poor completion of clinical files is a significant limitation of our study and reminds us of the importance in creating ways to engage healthcare teams to fill in clinical files as part of their daily routine.

This nomogram has not yet been validated in the Portuguese population. However, the nomogram was based on the Californian population, which has some similarities to ours. Further studies are needed with a larger sample of newborns from different health services in different social backgrounds.

We conclude that application of the nomogram appears to increase exclusive breastfeeding rates at the six months of age, and to decrease formula milk supplementation following suggestions from healthcare team members.

Authors' contribution

Carlota Veiga de Macedo: Conception and design of the study, report, review or other type of work or paper. Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. Catarina Schrempp Esteves: Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. José Pedro Pereira: Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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

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ORIGINAL ARTICLE

Impact of COVID-19 lockdown on children with neurodevelopmental disorders

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Abstract

Introduction and objectives: Neurodevelopmental disorders (ND) affect the maturation of the central nervous system, leading to abnormal brain functioning which may affect a child's social, cognitive, and emotional capacities. The coronavirus disease 2019 (COVID-19) pandemic, and particularly the lockdown period, resulted in indisputable changes in the lives of children, especially those with disabilities. The purpose of this study is to determine the impact of the lockdown period on these children and their parents in terms of therapies, mental and physical health, isolation, school performance, and the impact on family dynamics and relationships. **Methods:** A cross-sectional study compared the effect of the COVID-19 pandemic lockdown on the health of children with neurodevelopmental disorders with that of healthy children, using two anonymous surveys. Parents were asked to answer the survey from June 2020 to July 2021. **Results:** Out of 191 questionnaires obtained, 93 referred to parents in the Neurodevelopmental Disorder Group (NDG) and 98 to parents in the Control Group (CG). A total of 50.5% of parents in the NDG believed that their child's school performance improved when compared to the pre-pandemic period vs. 23.5% in the control group ($p < 0.001$). In terms of their overall health, 30.1% of the NDG parents reported that their child had been much better at home, compared to 9.2% of the CG parents ($p = 0.001$). There was a statistically significant improvement in family dynamics and relationships in the NDG, with 31.2% vs. 15.3% in the CG ($p = 0.007$). **Discussion:** This study portrays the impact of the lockdown and its consequences on children with ND. Parents in the NDG reported an improvement in their child's academic performance and in intra-family relationships. We found that most parents believed that access to schooling was insufficient with remote learning as well as access to therapies. There should be more measures and alternative strategies to minimize the impact that a lockdown has on children with special needs, especially among those in need of therapies. This study also emphasizes the importance of parents having an active role in the life of children with ND and achieving work-family balance. Further studies are needed to evaluate the real long-term impact of this period on children with neurodevelopmental disorders.

Keywords: Child. Pediatrics. Growth and development. Coronavirus infections. COVID-19. Health impact assessment.

Impacto do confinamento durante a pandemia COVID-19 em crianças com perturbações do neurodesenvolvimento

Resumo

Introdução e objetivos: As patologias do neurodesenvolvimento afetam a maturação do sistema nervoso central, resultando em alterações da função cerebral que podem comprometer as capacidades sociais, cognitivas e emocionais da criança.

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A pandemia COVID-19 e, principalmente, o período de confinamento resultaram em mudanças indiscutíveis na vida das crianças, especialmente nas crianças com perturbações do neurodesenvolvimento. O objetivo deste estudo é determinar o impacto do período de confinamento nestas crianças relativamente às terapias, saúde mental e física, isolamento, desempenho escolar e impacto na dinâmica familiar e nas suas relações. **Métodos:** Foi realizado um estudo retrospetivo de modo a comparar os efeitos do período de confinamento durante a pandemia COVID-19 entre crianças com perturbações do neurodesenvolvimento e um grupo de controlo de crianças saudáveis, através da aplicação de dois questionários anónimos aos pais. Os questionários foram preenchidos no período compreendido entre junho de 2020 e julho de 2021. **Resultados:** Dos 191 questionários obtidos, 93 foram referentes ao grupo de crianças com Perturbações do Neurodesenvolvimento (NDG) e 98 relativos ao grupo de controlo (CG). 50.5% dos pais das crianças no NDG considerou que o desempenho escolar dos seus filhos melhorou em relação ao período pré-pandémico vs. 23.5% no CG ($p < 0.001$). Relativamente à saúde global das crianças, 30.1% dos pais no NDG afirmou que esta melhorou durante o período de confinamento, comparativamente a 9.2% no CG ($p = 0.001$). Houve uma melhoria estatisticamente significativa na dinâmica familiar e relacionamentos no NDG 31.2% vs. 15.3% no CG ($p = 0.007$). **Discussão:** Este estudo permite avaliar as consequências do impacto do confinamento em crianças com perturbações do neurodesenvolvimento. No NDG, os pais relataram uma melhoria do desempenho escolar dos seus filhos, assim como nas relações intrafamiliares. Constatámos que a maioria dos pais considera que o acesso à escola foi insuficiente no ensino remoto bem como no acesso às terapias. A implementação de medidas futuras para minimizar o impacto que um confinamento tem neste grupo particular de crianças é essencial. Este estudo enfatiza, igualmente, a importância dos pais desempenharem um papel ativo da vida dos seus filhos, encontrando um equilíbrio adequado entre trabalho-família. São necessários estudos adicionais para avaliar o impacto a longo-prazo que o confinamento terá nas crianças com perturbações do neurodesenvolvimento.

Palavras-chave: Criança. Pediatria. Crescimento e desenvolvimento. Infeções por coronavírus. COVID-19. Avaliação impacto na Saúde.

Keypoints

What is known

- Children with neurodevelopment disorders were at high risk of significant emotional and behavioral problems during the COVID-19 pandemic due to school closures.
- During the lockdown period, the family burden was high, especially in families with children with neurodevelopment disorders.
- The lockdown period during the COVID-19 pandemic led to an unavoidable disruption in children's usual dynamics, which was more significant among children with neurodevelopmental pathologies, who frequently need more support and attention.

What is added

- About 30% of the parents in the neurodevelopment group reported an improvement in their child's overall health as well as in intra-family relationships during the lockdown period. When compared with the control group, these results were statistically significant.
- Children with neurodevelopment disorders are more anxious, *per se,* mostly when there is a change of routine, but our results revealed that the perceived anxiety was similar in the control group and in the group with neurodevelopment disorders during the lockdown period.
- Parents of children with neurodevelopmental disorders believed that their child's school performance improved when compared to the pre-pandemic period.

Introduction

Neurodevelopmental disorders (ND) are a group of pathologies that usually manifest early in a child's life, affecting their functional capacity[1]. These disorders affect the maturation of the central nervous system, leading to abnormal brain functioning which may affect a child's social, cognitive, and emotional capacities. Its prevalence is around 15% in the general population aged between three and 17[2-4]. These children were at high risk of significant emotional and behavioral problems, particularly during the coronavirus disease 19 (COVID-19) pandemic and due to school closures[5-7].

On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus SARS-CoV-2 outbreak a global pandemic[8].

Two lockdowns were implemented in Portugal during the pandemic. During these two periods, schools were closed, forcing students to stay at home, some of whom started to take classes through remote technologies, such as videoconferences, email, or television.

Undoubtedly, there were enormous changes in family dynamics and the management of daily activities. In Portugal, there are already some studies that point out the impact of the pandemic on children's health, including psychological, social, and physical consequences[9-11].

Concerning children with ND, some studies focused on children diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD), showing that they encountered significant difficulties regarding their behavior during the lockdowns[12,13]. Based on an online survey aimed at parents of children with Autism Spectrum Disorder (ASD) at the beginning of the pandemic, Colizzi M and colleagues mentioned the increased effort in managing daily activities and more severe behavioral problems[14].

Our study aims to analyze how children with ND and their parents experienced the lockdown period and school closures. We hypothesized that school deprivation could have a remarkably negative impact on these children when compared with children without ND.

Material and methods

We conducted a cross-sectional study in a level II hospital in Portugal. The sample included two groups: the first consisted of children that were followed up at neurodevelopmental appointments with a pre-established ND diagnosis as classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1], whom we designated the Neurodevelopmental Disorder Group (NDG), and the second group consisted of a control group of healthy children with no ND diagnosis, whom we named the Control Group (CG).

Two anonymous surveys were used, which were drafted by the authors. The first one comprised a 45-item questionnaire applied to parents whose children had a pre-established ND diagnosis. The second survey, a 32-item questionnaire, was applied to parents whose children went to the Emergency Department during the selected time period (control group); these children did not present with a ND diagnosis or any chronic pathology that could interfere with the study. Questionnaires that were not fully answered, as well as questionnaires related to children under three years of age or over 17 years and 364 days were excluded.

Parents were asked to answer the survey between June 28, 2020 and July 28, 2021.

We collected information regarding the parents' level of education, whether parents continued to work during the lockdown, who took care of the children during the day, the need and access to therapies during the lockdown period, children's personal background, school characteristics, mental and physical health aspects, anxiety, isolation, and the impact on family dynamics and relationships during this time period. Regarding the impact on their overall health, the impact on physical activity was characterized in the questionnaire as "None" (children maintained pre-lockdown physical activity levels or there was an absence of pre-lockdown physical activity); "Little" (25% decrease in the number of hours spent on physical activity compared to pre-lockdown period); "Some" (50% decrease in the number of hours spent on physical activity compared to the pre-lockdown period); "Significant" (ceased physical activity during lockdown).

Statistical analysis was performed using IBM SPSS© version 26. Since some of the variables under study are categorical, absolute and relative frequencies were used for their characterization. To compare the distribution of responses concerning the CG vs. the NDG, the Chi-square Independence Test and Fischer's Exact Test were used when appropriate. Standardized adjusted residues were also used to identify cells with a frequency higher (> 1.96) and lower than expected (< -1.96) with a significance level of 5%. We used Student's t-Test for independent samples to compare the mean ages of children and parents between the two groups. A significance level of 5% was considered so the associations and differences between groups were considered statistically significant when the significance value was less than 0.05 ($p < 0.05$).

The study was approved by our Institution's Ethics Committee, with a National Registry for Clinical Studies (RNEC) registration number (20170700050) and approval number of 2109.

Results

Our initial sample of 200 questionnaires was reduced to 191, since six were not fully answered and three had more than one answer to unique possibilities. From the 191 questionnaires, 93 refer to children in the NDG and 98 to children in the CG.

The children included in the study had a mean age of 9.8 years (SD = 4.0) ranging from three to 17 years old. The mean age of the children in the CG was 10.2 years (SD = 4.1) and 9.4 years in NDG (SD = 3.7) (Table 1). In both groups, children aged between six and 14 predominated (66.4% in the CG and 71.0% in the NDG) with a greater preponderance of the group aged between 10 and 14 (42.9% in the CG and 40.9% in the NDG). Both groups were homogeneous in terms of age distribution ($p = 0.493$) and average age ($p = 0.177$). The social-demographic characteristics of the participants are demonstrated in table 1.

During the lockdown period, most children were under their parents' care (58.1%). However, this percentage was significantly higher in the NDG (66.7%) than in the CG (49%) ($p = 0.005$). However, the percentage of children left alone during the day was higher in the CG (11.2%)

Table 1. Characterization of children and comparison by group, in terms of age, gender, household, and other social-demographic characteristics

Characteristics	Total (n = 191)	Control Group (CG) (n = 98)	Neurodevelopment Disorders Group (NDG) (n = 93)	p
Gender				
Female	65 (34.0%)	32 (32.7%)	33 (35.5%)	0.680‡
Male	126 (66.0%)	66 (67.3%)	60 (64.5%)	
Age (years)				
3-5	33 (17.3%)	16 (16.3%)	17 (18.3%)	0.493‡
6-9	51 (26.7%)	23 (23.5%)	28 (30.1%)	
10-14	80 (41.9%)	42 (42.9%)	38 (40.9%)	
15-17	27 (14.1%)	17 (17.3%)	10 (10.8%)	
Median	10.0	11.0	10.0	
Mean (SD)	9.8 (4.0)	10.2 (4.1)	9.4 (3.7)	0.177§
Siblings				
Singleton	85 (44.5%)	45 (45.9%)	40 (43.0%)	0.599‡
1 sibling	82 (42.9%)	43 (43.9%)	39 (41.9%)	
2 siblings	24 (12.6%)	10 (10.2%)	14 (15.1%)	
Type of housing				
Apartment without balcony	94 (49.2%)	44 (44.9%)	50 (53.8%)	0.156‡
Apartment with balcony	62 (32.5%)	31 (31.6%)	31 (33.3%)	
House/villa	35 (18.3%)	23 (23.5%)	12 (12.9%)	
Household				
Nuclear family	142 (74.3%)	75 (76.5%)	67 (72.0%)	0.780¶
Single parent family	30 (15.7%)	14 (14.3%)	16 (17.2%)	
Extended family	16 (8.4%)	7 (7.1%)	9 (9.7%)	
Step-family	3 (1.6%)	2 (2.0%)	1 (1.1%)	
Person responsible for taking care of the child during the day				
Both parents	111 (58.1%)	48 (49.0%)†	63 (67.7%)*	0.005¶
Mother	32 (16.8%)	20 (20.4%)	12 (12.9%)	
Grandparents	22 (11.5%)	13 (13.3%)	9 (9.7%)	
Alone	12 (6.3%)	11 (11.2%)*	1 (1.1%)†	
Aunt	7 (3.7%)	3 (3.1%)	4 (4.3%)	
Father	5 (2.6%)	1 (1.0%)	4 (4.3%)	
Nanny	2 (1.0%)	2 (2.0%)	0 (0.0%)	
Did the child go outside during the lockdown period?				
No	83 (43.5%)	46 (46.9%)	37 (39.8%)	0.319‡
Yes	108 (56.5%)	52 (53.1%)	56 (60.2%)	
Maternal age (years)				
20-30	24 (12.7%)	14 (14.3%)	10 (11.0%)	0.322‡
31-40	91 (48.1%)	45 (45.9%)	46 (50.5%)	
41-50	62 (32.8%)	30 (30.6%)	32 (35.2%)	
51-60	12 (6.3%)	9 (9.2%)	3 (3.3%)	
No information/no response	2	0	2	
Median	39.0	40.0	38.5	
Mean (SD)	38.7 (7.2)	39.2 (7.9)	38.1 (6.4)	0.393§
Paternal age (years)				
20-30	16 (8.8%)	10 (10.9%)	6 (6.7%)	0.042‡
31-40	70 (38.5%)	26 (28.3%)†	44 (48.9%)*	
41-50	78 (42.9%)	45 (48.9%)	33 (36.7%)	
51-60	17 (9.3%)	11 (12.0%)	6 (6.7%)	
60+	1 (0.5%)	0 (0.0%)	1 (1.1%)	
No information/no response	9	6	3	
Median	41.0	43.0	40.0	
Mean (SD)	40.9 (7.8)	41.5 (8.4)	40.3 (7.2)	0.312§
Maternal level of education				
Primary school (1st to 9th grade)	56 (29.6%)	27 (27.6%)	29 (31.9%)	0.496‡

(Continues)

Table 1. Characterization of children and comparison by group, in terms of age, gender, household, and other social-demographic characteristics *(continuation)*

Characteristics	Total (n = 191)	Control Group (CG) (n = 98)	Neurodevelopment Disorders Group (NDG) (n = 93)	p
Secondary school (10th to 12th grade)	82 (43.4%)	41 (41.8%)	41 (45.1%)	
Bachelor's degree or higher	51 (27.0%)	30 (30.6%)	21 (23.1%)	
Paternal level of education				
Primary school (1st to 9th grade)	94 (51.9%)	47 (51.1%)	47 (52.8%)	0.878‡
Secondary school (10th to 12th grade)	58 (32.0%)	31 (33.7%)	27 (30.3%)	
Bachelor's degree or higher	29 (16.0%)	14 (15.2%)	15 (16.9%)	
Parents who continued to work				
Both	96 (50.3%)	63 (64.3%)*	33 (35.5%)†	< 0.001‡
Only one	66 (34.6%)	22 (22.4%)†	44 (47.3%)*	
None	29 (15.2%)	13 (13.3%)	16 (17.2%)	
Maternal workplace**				
Out of home	57 (44.5%)	37 (48.1%)	20 (39.2%)	0.325‡
Teleworking	71 (55.5%)	40 (51.9%)	31 (60.8%)	
Paternal workplace**				
Outside the home	77 (59.2%)	45 (63.4%)	32 (54.2%)	0.291‡
Remote working	53 (40.8%)	26 (36.6%)	27 (45.8%)	

*Standardized adjusted residues > 1.96.
†Standardized adjusted residues < –1.96.
‡Significance value of the Chi-square test.
§Significance value of Student's t-test.
¶Significance value of Fisher's Exact Test.
**Among those who work.

than the NDG (1.1%) (p = 0.005). The only child who was left alone in the NDG was 16 years old, and of the 11 children in the CG (11.2%) who were left alone, 27.3% were 14 years old and 72.7% were ≥ 15 years old.

As for the age of the parents, the same age groups predominated (38.5% from 31 to 40 years and 42.9% from 41 to 50 years) with a mean age of 40.9 years (SD = 7.8). It should be noted that the percentage of parents aged between 31 and 40 years was significantly higher in the NDG (48.9%) than in the CG (28.3%) (p = 0.042). In regard to their work during the lockdown, all the parents worked prior to the lockdown period and the percentage of children whose parents continued to work was significantly higher in the CG (64.3%) compared to the NDG (35.5%) (p < 0.001). Among those who worked, 55.5% of the mothers and 40.8% of the fathers were working remotely (Table 1).

More than half of the children in each group had periods when they went outside regardless of the lockdown, which was not statistically significant between the two groups (Table 1).

Regarding only the NDG (Table 2), the most prevalent diagnoses were Attention-Deficit/Hyperactivity Disorder (ADHD) (44.1%), Specific Learning Disorder (SLD) (36.6%) and Language Disorder (LD) (25.8%), as shown in table 2. Most of the children in the NDG needed therapies (82.8%). Among those, most children required special education (62.4%), speech therapy (54.5%), psychotherapy (28.6%), and occupational therapy (19.5%) (Table 2).

About half had access to therapies during the lockdown period, most of which were online therapies (95%). Among those in need of therapies, most parents believed that not having therapies, or having online therapies, had some negative impact (26%) or a significant negative impact (53.2%) (Table 2).

In the group of 98 children with ND, 31.2% had a development appointment during the lockdown period, most of which were remote-based appointments (82.8%). Among those who had a remote-based appointment, the majority mentioned that they would have preferred to have had a face-to-face appointment (82.8%). It should be noted that nine children (14.3%) had an appointment scheduled but it was canceled by the hospital (Table 3).

About one in four (28.0%) patients were taking medication in relation to their ND, mostly methylphenidate (80.8%). As for the need to taper down or stop medication during the lockdown period, six (23.1%) reported that there was a need to adjust medication (Table 3). No parents said that there was a need to increase the medication.

Table 2. Characterization of children with ND regarding diagnosis and therapy needs (n = 93)

Characteristics	n	%
Neurodevelopmental diagnosis*		
ADHD	41	44.1%
Specific learning disorder	34	36.6%
Language disorder	24	25.8%
ASD	7	7.5%
Intellectual developmental disorder	5	5.4%
Global developmental delay	5	5.4%
Cerebral palsy	4	4.3%
Down syndrome	2	2.2%
Tuberous sclerosis	2	2.2%
Rett syndrome	1	1.1%
Smith-Magenis syndrome	1	1.1%
Noonan syndrome	1	1.1%
Need for therapies		
No	16	17.2%
Yes	77	82.8%
Types of therapies† (among those in need of support)		
Special education	48	62.4%
Speech therapy	42	54.5%
Psychotherapy	22	28.6%
Occupational therapy	15	19.5%
Physical therapy	5	6.5%
Family therapy	5	6.5%
Hippotherapy	1	1.3%
During the lockdown, did the child have access to therapies? (among those in need of support)		
No	37	48.1%
Yes	40	51.9%
Were the therapies online or in-person? (among those who had therapies)		
Online	38	95.0%
In person	2	5.0%
What was the negative impact of not having therapies or therapies having been online? (among those in need of support)		
No impact	12	15.6%
Little impact	4	5.2%
Some impact	20	26.0%
Significant impact	41	53.2%

*Possibility of more than one diagnosis.
†Possibility of more than one type of therapy.
ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder.

Table 3. Characterization of children with ND regarding medical follow-up (n = 93)

Characteristics	n	%
Did your child have scheduled development appointments during the lockdown period?		
No	64	68.8%
Yes	29	31.2%
Why did you not have an appointment? (among those who did not have an appointment)		
It was not scheduled	52	81.2%
It was scheduled but was cancelled	12	18.8%
Type of appointment (among those who had an appointment)		
In-person appointment	5	17.2%
Remote-based appointment	24	82.8%
What kind of appointment would you have preferred? (among those who had a remote-based appointment)		
Remote-based appointment	4	16.7%
Face-to-face appointment	20	83.3%
Does your child take any medication regarding ND?		
No	67	72.0%
Yes	26	28.0%
Type of medication (among those who took medication)		
Methylphenidate	21	80.8%
Risperidone	3	11.5%
Aripiprazole	2	7.7%
Was there a need to adjust the medication? (among those who took medication)		
No	20	76.9%
Yes	6	23.1%

More than three quarters of the children had access to school during the lockdown. The percentage of parents who stated that the access the children had was sufficient for learning was significantly higher in the CG (24.5%) than in the NDG (12.9%) (p = 0.041). Overall, most parents spent more than one hour a day helping their child with schoolwork. It should be noted that the percentage of children who did not need support was significantly higher in the CG (18.4%) than in the NDG (6.5%), and the percentage of parents who spent three to four hours a day supporting their child was significantly higher in the NDG (19.4%) than in the CG (8.2%) (p = 0.030), as shown in table 4. About half of the NDG's parents believed that their child's school performance improved, compared to the pre-pandemic period (50.5%), a percentage that was significantly higher than that registered in the CG (23.5%) (p < 0.001).

Regarding the impact on physical activity, more than 50% of the parents stated that the pandemic had some (34.7%) or a significant negative impact (24.2%) on their child's physical activity. It should be noted that the perceived impact on physical activity was higher in the CG than in the NDG (p = 0.010): 15.3% of the CG answered "no impact" (vs 33.7% in NDG) and 30.6% of the CG answered, "a significant impact" (vs. 17.4% in NDG) (Table 5).

In regard to overall health, parents were asked to consider the child's state of physical, mental, social, and emotional well-being overall, compared to the pre-lockdown period. The percentage of those who reported

Table 4. Characterization of children and comparison by group regarding school data

Characteristics	Total (n = 191)	Control Group (CG) (n = 98)	Neurodevelopment Disorders Group (NDG) (n = 93)	p
Education level				
Kindergarten	36 (18.8%)	16 (16.3%)	20 (21.5%)	0.125‡
1st to 4th grade	60 (31.4%)	27 (27.6%)	33 (35.5%)	
5th to 6th grade	38 (19.9%)	22 (22.4%)	16 (17.2%)	
7th to 9th grade	45 (23.6%)	23 (23.5%)	22 (23.7%)	
Secondary school (10th to 12th grade)	12 (6.3%)	10 (10.2%)	2 (2.2%)	
Access to school during lockdown				
No	40 (20.9%)	24 (24.5%)	16 (17.2%)	0.216‡
Yes (TV, e-mail, SMS or videocalls)	151 (79.1%)	74 (75.5%)	77 (82.8%)	
Was the access to school sufficient for learning?				
No	155 (81.2%)	74 (75.5%)†	81 (87.1%)*	0.041‡
Yes	36 (18.8%)	24 (24.5%)†	12 (12.9%)†	
Hours per day in need of parental support (school-related)	24 (12.6%)	18 (18.4%)*	6 (6.5%)†	0.030‡
No need for support	21 (11.0%)	9 (9.2%)	12 (12.9%)	
< 1 hour per day	99 (51.8%)	53 (54.1%)	46 (49.5%)	
1-2 hours per day	26 (13.6%)	8 (8.2%)†	18 (19.4%)*	
3-4 hours per day	21 (11.0%)	10 (10.2%)	11 (11.8%)	
≥ 5 hours per day				
School performance compared to the pre-lockdown period	28 (14.7%)	15 (15.3%)	13 (14.0%)	< 0.001‡
Worsened	93 (48.7%)	60 (61.2%)*	33 (35.5%)†	
Remained the same as before	70 (36.6%)	23 (23.5%)†	47 (50.5%)*	
Improved				

*Standardized adjusted residues > 1.96.
†Standardized adjusted residues < –1.96.
‡Significance value of the Chi-square test.

that they had been much better at home was significantly higher in the NDG (30.1%) than in the CG (9.2%) (p = 0.001). In contrast, the percentage of those who said that their overall health was the same was higher in the CG (59.2%) than in the NDG (44.1%). The percentage of those who stated that their overall health got worse was similar in the two groups: 31.6% in the CG and 25.8% in the NDG (Table 5).

As for anxiety, overall, 61.3% stated that their child was more anxious than usual, which was similar in both groups. Regarding difficulty in imposing rules, 44% said it was more difficult than usual, 49.2% said it was the same as usual, and 6.8% said it was easier than usual. Half of the CG parents stated that their children were more isolated than usual (50.0%), a percentage that is significantly higher than that registered in the NDG (22.6%) (p < 0.001). There were no differences between groups concerning levels of anxiety (p = 0.123) or parents' difficulty in imposing rules (p = 0.560) (Table 5).

More than half of the caregivers stated that the family burden was higher than usual during lockdown, with no significant differences between the two groups (p > 0.05). The influence of the lockdown period on family dynamics and relationships is shown in table 5. There was a statistically significant improvement on family dynamics and relationships in the NDG (31.2% answered "relationships improved significantly") than in the CG (15.3%) (p = 0.007), and the impact on family relationships was more negative in the CG than in the NDG, as shown in table 5. The percentage of those who answered that they "remained as usual" was similar in both groups (42.9% in the CG and 45.2% in the NDG) (Table 5).

Discussion

Our study aimed to describe and understand the consequences of the lockdown period imposed by the COVID-19 pandemic on children with ND. This is one of the first studies in Portugal to compare children with ND to healthy children, concerning this issue.

The changes that the COVID-19 pandemic brought about worldwide were massive and the measures taken

Table 5. Characterization of children and comparison by group concerning data on overall health data and family environment

Characteristics	Total (n = 191)	Control Group (CG) (n = 98)	Neurodevelopment Disorders Group (NDG) (n = 93)	p
Negative impact on physical activity				
None	46 (24.2%)	15 (15.3%)†	31 (33.7%)*	0.010‡
Little	32 (16.8%)	15 (15.3%)	17 (18.5%)	
Some	66 (34.7%)	38 (38.8%)	28 (30.4%)	
Significant	46 (24.2%)	30 (30.6%)*	16 (17.4%)†	
How were the child's anxiety levels during the lockdown?				
Less than usual	15 (7.9%)	4 (4.1%)	11 (11.8%)	0.123‡
Same as usual	59 (30.9%)	30 (30.6%)	29 (31.2%)	
More than usual	117 (61.3%)	64 (65.3%)	53 (57.0%)	
Was it more difficult to impose rules than before the lockdown?				
Less than usual	13 (6.8%)	8 8.2% ()	5 (5.4%)	0.560‡
Same as usual	94 (49.2%)	45 (45.9%)	49 (52.7%)	
More than usual	84 (44.0%)	45 (45.9%)	39 (41.9%)	
Did your child become more isolated than before the lockdown?				
Less than usual	17 (8.9%)	6 (6.1%)	11 (11.8%)	< 0.001‡
Same as usual	104 (54.5%)	43 (43.9%)†	61 (65.6%)*	
More than usual	70 (36.6%)	49 (50.0%)*	21 (22.6%)†	
Influence on child's overall health				
Worsened	55 (28.8%)	31 (31.6%)	24 (25.8%)	0.001‡
Remained the same	99 (51.8%)	58 (59.2%)*	41 (44.1%)†	
Since he/she has been at home, he/she is much better	37 (19.4%)	9 (9.2%)†	28 (30.1%)*	
Family burden				
Less than usual	5 (2.6%)	3 (3.1%)	2 (2.2%)	0.314‡
Same as usual	28 (14.7%)	12 (12.2%)	16 (17.2%)	
Some days more, others unchanged	46 (24.1%)	24 (24.5%)	22 (23.7%)	
Higher than usual	112 (60.2%)	59 (60.2%)	53 (57.0%)	
Impact of COVID 19 on family dynamics and relationships				
Negative impact	63 (33.0%)	41 (41.8%)*	22 (23.7%)†	0.007‡
Remained the same	84 (44.0%)	42 (42.9%)	42 (45.2%)	
Relationships have improved a lot	44 (23.0%)	15 (15.3%)†	29 (31.2%)*	

*Standardized adjusted residues > 1.96.
†Standardized adjusted residues < –1.96.
‡Significance value of the Chi-square test.

to prevent the dissemination of the virus, namely remote working, school closures, and the prohibition of going outside for great distances, had a significant mental impact on families worldwide[15-18].

During this period, most children had to completely change their routines and habits. They had to respect new rules that were being implemented, often without understanding them. This led to an inevitable disruption of their usual dynamics, which was more significant for children with neurodevelopmental pathologies who frequently need more support and attention[15,19,20].

In our study, we identified that during the lockdown period ND children were in the care of their parents during the day more than the CG. Since the age distribution was similar in the two groups, the ND group probably needed more support given the overall difficulties and lack of autonomy[21]. Despite the lockdown requirements, both groups had periods when they went out, regardless of the type of housing, as shown by Amorim R[20]. In the NDG, at least one parent did not work, which was statistically significant compared to the CG, in which most parents continued to work. Parents had to reorganize their family dynamics, and given the inherent needs of children with ND, it was frequently impossible for both parents to work.

As for access to therapies, similarly to other studies, about half of the children in the NDG did not have access to these during the lockdown period[22]. Among those who had, the vast majority could only have access to online therapies. More than half of the

parents felt that this lack of access had a major impact on their child's overall functioning. In fact, maintaining the child's regular therapies and special education routines creates a daily strategy and improves learning, along with cognitive and adaptive development[21,23,24].

Of the children in the NDG who had scheduled appointments during the lockdown periods, 19% had the appointment canceled and the rest had mostly remote-based appointments. Most parents (83.3%) said that they would have preferred to have had a face-to-face appointment, which demonstrates the importance of implementing a guidance plan for these children, as parents often felt unaccompanied without the option for face-to-face interaction. This demonstrates the importance of the doctor-patient relationship and the need for a more humanized interaction in supporting families during these times[25,26].

When we analyzed the impact on learning, despite most children in both groups maintaining online school activities, most parents considered the support provided was insufficient for learning. This negative impact was significantly higher in the NDG.

However, and surprisingly, in the NDG, even though parents thought that access to school and tools necessary for learning were insufficient, these parents believed that their child's school performance improved compared to the pre-lockdown period, which allows us to infer that parental support was essential to fill these gaps. Time was not scarce and according to the child's needs, they could assist them by revising school content, helping them focus, and they could also guide them with their home assignments and in acquiring new learning skills. These are children who, regardless of the diagnosis, have greater educational needs and to whom face-to-face and individualized support is essential for favorable development[27]. This is corroborated by international studies that show how individualized education plans for children with special needs are crucial[20,21,28,29]. Online school lacks face-to-face interaction, it is more difficult to remain motivated, and sometimes there are technical problems. Moreover, caretaking responsibilities provided only by the family can be overwhelming and have a negative impact on remote learning in this group[30,31]. Parental support for school learning was more necessary in the NDG, which would be expected, given the inherent needs of this group with lower cognitive abilities, less autonomy, and more inattention. We can speculate that the presence and involvement of parents in school tasks may have been an important factor in the empowerment and academic performance improvement of children as well as the reduction in school-related anxiety. As already demonstrated in other studies, parental involvement could be a significant predictor of a child's academic performance, as a higher parental involvement contributed to an increase in a child's perceived level of competence[32]. Parents also noticed minor learning improvements that otherwise would not have been perceived by caregivers in a normal daily routine.

When we evaluated the impact of the lockdown on physical activity, we found that the group without ND reported a statistically significant negative impact, similarly to what was observed in other studies[10,33,34]. This may likely have an impact on obesity in future studies. The COVID-19 pandemic disrupted eating behaviors, as many children rely on school meals to ensure adequate nutrition and these meals came to an end during the lockdown period[35,36]. A study conducted by the Center for Disease Control in a population between two and 19 years of age showed that the body mass index ratio doubled from pre-pandemic to pandemic periods, with a greater increase in children with pre-pandemic obesity or overweight than in healthy children[37]. The group without pathologies may have had more investment in pre-lockdown physical activity, making parents feel a major impact, which corroborates the studies that describe the caregivers' perceptions of new acute-onset obesity[38].

Concerning changes in behavior during the lockdown, we found that the CG was more isolated compared to the group with pathologies. In children with ND, there are often socializing problems that lead to isolation[39]. We could consider different features of the NDG to explain this result. For example, children with ADHD may have difficulties in socialization *a priori*[40], given that one of the main consequences of ADHD is inattention that ends up causing poor school results, difficulties in maintaining friendships, and being neglected or ignored, resulting in isolation. Therefore, the perception that parents had of isolation was no different from usual. Children with ASD have persistent deficits in social communication and social interaction[41], which could enlighten us as to why having less contact with peers did not make them more isolated, since these children have a lower interest in maintaining relationships[31].

The COVID-19 pandemic drastically changed the routines of both the children and their parents. Undoubtedly, the lockdown period contributed to increased parental anxiety and disruption in family relationships[42-45]. However, this time of adversity could also be seen as a way to create new opportunities, strengthen relationships, and have positive effects on children and adolescents.

Contrary to what we initially believed, our results revealed that, despite the unfavorable conditions

expected from the lockdown, about 30% of the parents in the NDG reported an improvement in the child's overall health, as well as in intra-family relationships. When compared with the CG's results, these were statistically significant. These results differed from those of another study, regarding the impact of the first lockdown on healthy children aged one to three, which stated that 95.4% of parents claimed that their child's overall health improved or remained the same as in the pre-lockdown period[46]. Another study, regarding the impact on relationships in families with children with ASD found that 44.2% of the parents reported a positive impact on family relationships, compared to 18.6% who perceived a negative impact[20]. One could hypothesize that being a child with a ND requires more attention, and being able to spend more time with a parent could have improved the relationship. A recently published study compared psychological distress caused by COVID-19 in parents of children with normal developmental progress with that in parents of children with ASD, and the latter group revealed more symptoms of depression and anxiety during the pandemic period[47]. However, as our study showed, some parents stated that, in some cases, a lockdown period could be perceived as a positive experience from which conclusions could be drawn to lessen the impact on mental wellbeing[48]. Parents could identify more rewarding aspects versus challenging or negative aspects of the lockdown, improving their resilience, and thus protecting against the potential negative psychological impact of the lockdown. If the caregiver had psychological flexibility, he or she would be able to cope better with the stressful events of the pandemic and this attitude would improve their capacity to recognize positive feelings in the "minor things"[48].

A pandemic may increase parents' risk for stress, social distancing, and loss of assurance[49]. Similarly to our results that stated that there was a negative impact on family dynamics and relationships in the CG, other published studies showed that, due to the lockdown, there was an increase in depressive symptoms and a high prevalence of emotional disturbance, stress, low mood, irritability, and insomnia in parents, which could negatively influence family dynamics[50-52]. In addition, unemployment or a change of work organization, the inability to cope with new routines, and online teaching without adequate equipment or learning tools can trigger stressful events and worsen family relationships and create emotional disturbances.

Although children with ND are more anxious *per se*, especially when there is a break in routine[21,41], our results revealed that the perceived anxiety was similar in both groups. These results were somewhat surprising. Some studies, one of which took place in Portugal, showed that children with ASD revealed statistically significant higher anxiety levels compared to those of a control group, which also had a direct impact on their behavior[20].

As expected, our results showed that the family burden was high in both groups during the lockdown period and it may reflect external family stress, as well as financial difficulties, lack of external support, mental health issues, increased everyday responsibilities, and these results were similar to what some studies stated[21,53,54]. Therefore, better guidance about suitable and supportive practices, medical care, and school services could be needed in order to improve coping strategies and to manage a lockdown situation[23].

Our findings will hopefully help improve further strategies implemented in a hypothetical future lockdown period. They will also be important in understanding the potential consequences of the pandemic in this vulnerable group.

Nonetheless, our study also presented some limitations. The data collected was answered by parents rather than reported by children directly, which can be biased because there is always a subjective perception. Moreover, during the implementation of our questionnaire, there were two lockdown periods, and the questionnaires did not specify which period the parents were responding to. Also, we did not evaluate each neurodevelopmental disorder separately, but rather as a group, despite the large heterogeneity between ND. Furthermore, when we assessed the impact of the lockdown period on therapies, we did not individualize each type of therapy, but approached therapies in general because our objective was to assess the impact from therapies having been online instead of face-to-face.

Conclusion

This study provided evidence of the impact of the lockdown period and its consequences on children with ND. A pandemic can create unexpected problems but also unforeseen solutions.

The COVID-19 pandemic caused unparalleled health and humanitarian crises, affecting all aspects of everyday life. In short, our study showed it was the group of children with ND that needed more parental care, and in which at least one parent did not work, becoming fully available for overall care. Although access to face-to-face therapeutic intervention was deficient and had an impact on general functioning, parental involvement in supporting children with pathologies was perceived

as positive and decisive for the child's overall health. We can speculate that the opportunity for family involvement had a positive effect on overall functional performance and on intra-family relationships, particularly on children with pathologies, which emphasizes the need to rethink the organization of family working time. There should be more measures in place to minimize the impact that a lockdown has on children with special needs, especially among those in need of therapies.

Further studies are needed to evaluate the real long-term impact of the lockdown period on children with ND.

Authors' contribution

For all: Idea behind, and design of, the study, report, review or other type of paper. Data acquisition from patients, research studies, or literature. Analysis or interpretation of data from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be held accountable for the accuracy or integrity of the paper.

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

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

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ORIGINAL ARTICLE

Birth month influences the likelihood of attention-deficit/hyperactivity disorder diagnosis in young boys – Evidence from Portugal

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Abstract

Introduction and objectives: Studies carried out worldwide concluded that children born in the last months of the school year are more likely to be diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD), in what is known as the relative age effect. The likeliest explanation for this phenomenon is that these children are the youngest in their class and therefore exhibit relative immaturity when compared to their older classmates, which might be misinterpreted as inattention and hyperactivity-impulsivity. Our aim is to find evidence of this phenomenon in the Portuguese population. We hypothesize that children born in the second semester of the year have an increased prevalence of ADHD diagnosis. **Methods:** Retrospective cohort study of patients followed in a child and adolescent psychiatry outpatient clinic between December 2011 and December 2021. **Results:** The relative risk of ADHD diagnosis under the age of 11 for patients born in the second semester of the year was only significantly elevated in boys (RR = 1.280, 95% CI of 1.007 – 1.628, p = 0.044). **Discussion:** The results demonstrate the relative age effect in the diagnosis of ADHD in the male subset of a Portuguese population sample. Differences in gender may be attributable to the small size of the female population sample. This is the first evidence of the relative age effect in the diagnosis of ADHD in Portugal in young boys. Clinicians should be mindful of this phenomenon when performing this diagnosis.

Keywords: ADHD. Diagnosis. Child development.

O mês de nascimento influencia a probabilidade de diagnóstico de perturbação de hiperatividade e défice de atenção em crianças do sexo masculino – Evidência em Portugal

Resumo

Introdução e objetivos: Estudos realizados em vários países concluíram que as crianças nascidas nos últimos meses do ano escolar têm uma maior probabilidade de serem diagnosticadas com perturbação de hiperatividade e défice de atenção, de acordo com o chamado efeito de idade relativa. A explicação mais provável para este fenómeno é que essas crianças são as mais novas da sua turma e por esse motivo exibem imaturidade relativa quando comparadas com os seus colegas mais velhos, o que pode ser erradamente interpretado como desatenção e hiperatividade/impulsividade. O nosso objetivo é encontrar evidência deste fenómeno na população portuguesa. A nossa hipótese é que crianças nascidas no segundo semestre

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do ano têm uma prevalência aumentada de diagnóstico de PHDA. **Métodos:** Estudo restrospetivo de coorte de pacientes seguidos num serviço de consulta externa de Psiquiatria da Infância e da Adolescência entre dezembro de 2011 e dezembro de 2021. **Resultados:** O risco relativo de ter um diagnóstico de PHDA antes dos 11 anos de idade para pacientes nascidos no segundo semestre do ano é significativamente elevado apenas em rapazes (RR = 1.280, 95% CI of 1.007-1.628, p = 0,044). **Discussão:** Os resultados demonstram o efeito de idade relativa no diagnóstico de perturbação de hiperatividade e défice de atenção no subconjunto masculino de uma amostra da população portuguesa. As diferenças de género observadas poderão ser atribuíveis à pequena dimensão da amostra de população feminina. Esta é a primeira evidência do efeito de idade relativa no diagnóstico de perturbação de hiperatividade e défice de atenção em crianças do sexo masculino em Portugal. Este fenómeno deve ser tido em conta na realização deste diagnóstico.

Palavras-chave: PHDA. Diagnóstico. Desenvolvimento infantil.

Keypoints

What is known
- Younger children in a classroom are more likely to be diagnosed with ADHD (a phenomenon known as "relative age effect").
- Clinicians should be mindful of this phenomenon when diagnosing ADHD.

What is added
- First evidence of the relative age effect for the diagnosis of ADHD in young boys in Portugal.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity, and impulsivity that interferes with functioning or development[1]. Clinicians rely on the observation of the child or adolescent as well as on reports and rating scales completed by parents and teachers to diagnose ADHD[2]. The diagnostic process and its accuracy has been a subject of debate[3,4], and systematic reviews of studies conducted around the world concluded that the youngest children within a class are more likely to be diagnosed with ADHD, in what is known as the relative age effect[5-7]. The most accepted explanation for this phenomenon is that teacher ratings of ADHD symptoms rely on the comparisons of children within the classroom, where relative younger age and thus relative immaturity may be misinterpreted as inattention or hyperactivity-impulsivity, suggesting that classroom comparisons drive the relative age effect[8,9]. In an effort to quantify the increased likelihood of relatively younger children to receive an ADHD diagnosis, a recent meta-analysis yielded a relative risk (RR) of 1.34 for children born in the last four months of the school year[5].

To the best of our knowledge, the relative age effect in ADHD diagnosis has never been studied in Portugal. Our hypothesis is that children born in the second semester of the year have an increased likelihood of having an ADHD diagnosis.

The aim of this study was to find evidence of the relative age effect in ADHD diagnosis in a cohort of patients followed in a child and adolescent psychiatry outpatient clinic in Portugal.

Methods

We conducted a retrospective cohort study of all the children and adolescents up to 18 years of age followed in a child and adolescent psychiatry outpatient clinic between December 2011 and December 2021 with at least one electronically-recorded diagnosis of a mental and behavioral disorder, defined as diagnostic codes 290-319 in the International Classification of Diseases, 9th Revision [ICD-9] and codes F00-F99 in the International Classification of Diseases, 10th Revision [ICD-10] (n = 1876).

We collected data regarding the birth month and clinical diagnosis. ADHD cases were defined as having a diagnosis of 314 (Hyperkinetic syndrome of childhood) in ICD-9 or F90 (attention-deficit/hyperactivity disorders) in ICD-10. ICD-9 was used in this medical institution from the beginning of the study period until June 2020 and ICD-10 was used from July 2020 onwards. All data was collected from the patients' electronic medical records.

Because the birth month is more relevant to the age difference between younger children than between older children or adolescents, we restricted our analysis to children who received an ADHD diagnosis before they completed 11 years of age (the term "ADHD<11y"

Table 1. Descriptive statistics and relative risk of ADHD diagnosis under the age of 11 for patients born in the second semester of the year and for male patients born between August and October

Date of birth	Total	ADHD<11y (%)	RR (95% CI)	p-value
First semester	845	113 (13.4%)		
Male	500	87 (17.4%)		
Female	345	26 (7.5%)		
Second semester	1031	170 (16.5%)	1.233 (0.990-1.536)	0.069
Male	633	141 (22.2%)	1.280 (1.007-1.628)	0.044
Female	398	29 (7.3%)	0.983 (0.590-1.635)	0.528
August-October	546	97 (17.7%)		
Male	330	82 (24.8%)	1.347 (1.092-1.731)	0.021
Female	216	15 (6.9%)		
Total	1876	283 (15.1%)		

RR: relative risk; CI: confidence interval.

is used from this point onwards for simplicity). We grouped patients into two categories: those born in the first semester (relatively older) and those born in the second semester (relatively younger) and calculated the relative risk of ADHD<11y diagnosis for the relatively younger patients. No patients were excluded from the analysis on account of other medical diagnoses.

We also calculated the proportion of patients with a diagnosis of ADHD<11y for each birth month.

All data analysis was conducted in IBM SPSS Statistics Version 28.0.0.0. Associations were tested for significance using the chi-square test of independence. Statistical significance was set at $p < 0.05$.

The study was approved by the institution's ethics committee and board.

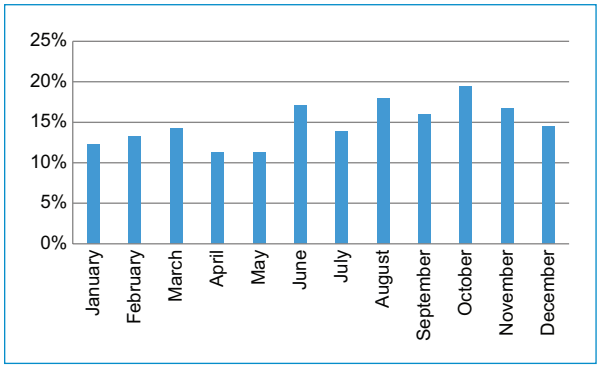

Figure 1. Percentage of patients with an ADHD<11y diagnosis by birth month.

Results

The clinical sample consisted of 1876 patients, 283 of which had a diagnosis of ADHD<11y (Table 1).

The relative risk of ADHD<11y diagnosis for patients born in the second semester of the year was not significantly elevated (RR = 1.233 with a 95% confidence interval [CI] of 0.990 – 1.536, p = 0.069). However, a stratified analysis by gender revealed a significantly elevated relative risk for male patients (RR = 1.280, 95% CI of 1.007 - 1.628, p = 0.044) but not for female patients (RR = 0.983, 95% CI of 0.590 - 1.635, p = 0.528) (Table 1).

Figure 1 shows the rate of ADHD<11y diagnosis by birth month for the total study sample, while figures 2 and 3 show the diagnosis rate for male and female patients, respectively.

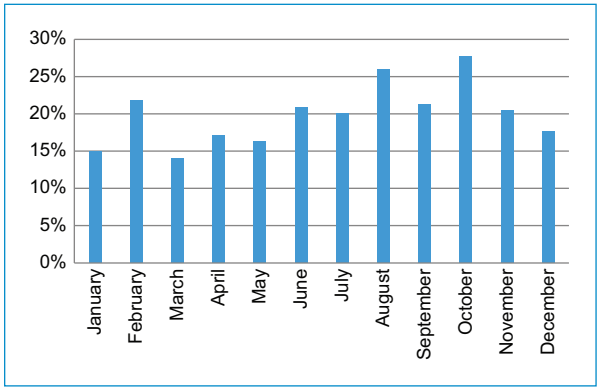

Figure 2. Percentage of male patients with an ADHD<11y diagnosis by birth month.

The three-month period between August and October revealed a particularly high ADHD<11y diagnosis rate for boys (24.8%) (Fig. 2 and Table 1). The relative risk of ADHD<11y diagnosis for boys was also calculated for the period between August and October (RR = 1.347, 95% CI 1.092-1.731, p = 0.021).

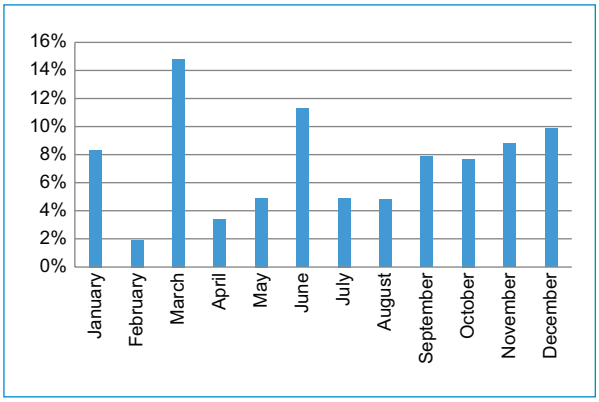

Figure 3. Percentage of female patients with an ADHD<11y diagnosis by birth month.

Discussion

The relative age effect in ADHD diagnosis has been extensively studied and reviewed[5-7]. Our goal was to study and quantify this effect in a clinical sample from a Portuguese child and adolescent psychiatry outpatient clinic.

Although we could not find any evidence for a significantly elevated relative risk of ADHD diagnosis under the age of 11 in patients born in the second semester of the year when both male and female patients were included, a stratified analysis by gender revealed a significantly elevated relative risk for male patients, with a RR of 1.28, which is similar to the relative risks found in two recent meta-analyses (RR = 1.34 and RR = 1.27)[5,6].

These results could raise the hypothesis that the relative age effect is more pronounced in boys than in girls due to developmental differences, but both meta-analyses mentioned above[5,6] found no difference between male and female populations in regards to the relative age effect, leading us to believe that these differential results regarding gender are more likely to be explained by the low number of female patients with an ADHD<11y diagnosis in our study population (n = 55, representing just 19% of all ADHD<11y patients), which may limit the statistical power of the analysis.

Analyzing ADHD<11y diagnosis rates by birth month revealed high diagnosis rates in boys born between August and October (Fig. 2 and Table 1). This prompted further analysis by calculating the relative risk of having an ADHD<11y diagnosis for boys born in this three-month period, which yielded a RR of 1.347 (95% CI 1.092-1.731, p = 0.021) (Table 1), which is even higher than the RR for boys born in the second semester of the year. One possible explanation is that parents may request early enrollment for children who complete six years of age between September 15 (the national school-entry cut-off date) and December 31, and these children would therefore be some of the youngest in their class. We suspect that the likelihood of opting for early enrollment decreases the further the child's birth date is from the September 15 cut-off date, despite having no data to support this. This could, however, help explain the lower diagnosis rates of ADHD<11y observed in the months of November and December, as boys who were born in these months and did not opt for early enrollment would be the oldest in class. In fact, Whitely and colleagues argue that the practice of "redshirting" (i.e. delaying school entry for children judged as immature, such as those born in the last months of the year) might disguise late birthdate effects[7].

Our study design has some limitations. We gathered data from a clinical sample, which may not be representative of the general population. All data refers to a single child and adolescent psychiatry outpatient clinic and may not be representative of other regions in the country. In addition, the female population sample was relatively small, which may have limited the statistical power of the analysis. The fact that parents may opt for early school enrollment for children born between September 15 and December 31 means that there is some flexibility in school entry, and we could not find data regarding the prevalence of early enrollment.

Our findings have relevant clinical implications. The relative age effect implies that some relatively younger children are being misdiagnosed and offered unnecessary medication. Clinicians should therefore be mindful of the relative age effect when diagnosing children who are relatively younger than their classmates, particularly with regards to young boys, by checking their birth month and whether they enrolled in school before they turned six years of age. Clinicians should also be mindful of this effect when analyzing teacher ratings of ADHD.

There are also educational implications to our study. When it comes to deciding whether or not to opt for early school enrollment, both parents and teachers should consider whether each particular child is sufficiently mature to face the academic challenges ahead, and whether they will stand out among their classmates as relatively immature, increasing the risk of an ADHD misdiagnosis.

To the best of our knowledge, this is the first evidence of the relative age effect for ADHD diagnosis in male children in Portugal.

In conclusion, clinicians should be mindful of the relative age effect when diagnosing ADHD in young boys and when analyzing teacher ratings of ADHD behavior. Parents and teachers should also consider the relative age effect when deciding whether or not a child should enroll in school ahead of schedule.

Further research on the relative age effect for ADHD diagnosis is needed, namely with studies conducted with samples from the general population and from across the country rather than limited to clinically-referred individuals to a single clinic.

Authors' contribution

Rui Sampaio: Idea behind, and design of, the study, report, review or other type of paper. Data acquisition from patients, research studies, or literature. Analysis or interpretation of data from patients, research studies, or literature. Drafting the article. Final approval of the version to be published. Agreement to be held accountable for the accuracy or integrity of the paper. João Caseiro: Idea behind, and design of, the study, report, review or other type of paper. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be held accountable for the accuracy or integrity of the paper.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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

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ORIGINAL ARTICLE

Timing of intervention in posthemorrhagic ventricular dilatation in preterm infants

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Abstract

Introduction and objectives: There is still significant variation in the management of post-hemorrhagic ventricular dilatation (PHVD). Recent evidence recommends cerebrospinal fluid (CSF) drainage as soon as Levene's Ventricular Index (LVI) surpasses the 97th centile, which was shown to improve neurodevelopmental outcomes and reduce the need for a ventriculoperitoneal (VP) shunt. This study aimed to assess the timing of intervention in PHVD in a level 3 Neonatal Intensive Care Unit (NICU), its impact on the need for a VP shunt, and the presence of neurological sequelae at two years of age. **Methods:** A retrospective, single-center study was conducted, comprising preterm infants who developed PHVD. Ventricular dilatation was quantified in cerebral ultrasounds and details of interventions were obtained from clinical records. Infants were categorized into three groups depending on the neurological sequelae present at two years: surviving without sequelae, surviving with sequelae, and death. **Results:** Among the 22 infants diagnosed with PHVD, 59% required CSF drainage, and all the patients received initial intervention after LVI crossed the p 97 + 4 mm line (mean 7.5 mm above the 97th centile), at a mean postmenstrual age (PMA) of 30.6 weeks (± 2.7). Ventricular stabilization occurred after lumbar punctures (LPs) in 23% (3/13); 15% (2/13) died after temporizing neurosurgical procedures; 62% (8/13) required a VP shunt, at a median PMA of 38.9 weeks (IQR 37.0-41.3). Neurological sequelae (delayed motor development, cerebral palsy, epilepsy, and/or visual impairment) were less likely to occur in infants not requiring CSF drainage ($p < 0.05$), although no significant difference was found between ventricular width at first intervention and the need for a VP shunt or outcomes. **Discussion:** This cohort, treated before international guidelines were revised, received intervention later than what is now recommended. Infants who received intervention were more likely to have neurological sequelae than those that did not require intervention. Actively considering intervention as soon as the Ventricular Index (VI) surpasses the 97th centile will certainly make it possible to lower the intervention threshold to not more than p 97 + 4 mm, as currently recommended.

Keywords: Premature infant. Intraventricular hemorrhage. Hydrocephalus. Outcomes.

Intervenção na dilatação ventricular pós-hemorrágica da prematuridade

Resumo

Introdução e objetivos: O tratamento da Dilatação Ventricular Pós-hemorrágica (DVPH) ainda é muito variável. A última revisão das recomendações internacionais sugere iniciar a drenagem de líquido cefalorraquidiano assim que o índice ventricular de Levene (IVL) ultrapassa o percentil 97, o que mostrou melhorar o neurodesenvolvimento e reduzir a necessidade

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sistemas de derivação ventrículo-peritoneal (SDVP). Este estudo teve como objetivo avaliar o momento da intervenção na DVPH numa UCIN de nível III e o seu impacto na necessidade de SDVP e na presença de sequelas neurológicas aos 2 anos de idade. **Métodos:** Foi realizado um estudo retrospetivo unicêntrico, incluindo recém-nascidos prematuros que desenvolveram DVPH. A dilatação ventricular foi quantificada em ecografias cerebrais seriadas e os detalhes relativos às intervenções foram obtidos a partir dos registos clínicos. De acordo com as sequelas neurológicas presentes aos 2 anos de idade, as crianças foram categorizadas em 3 grupos: sobrevivência sem sequelas, sobrevivência com sequelas e morte. **Resultados:** Vinte e dois recém-nascidos foram diagnosticados com DVPH, dos quais 59% (n = 13) foram intervencionados, todos após ultrapassarem o p97 + 4 mm, com uma idade pós-menstrual média de 30,6 semanas (± 2,7). Vinte e três porcento (3/13) tiveram estabilização ventricular após punção lombar; 15% (2/13) morreram após intervenções neurocirúrgicas temporizadoras; 62% (8/13) precisaram de SDVP, com uma idade pós-menstrual mediana de 38,9 semanas (AIQ 37,0-41,3). A probabilidade de ter sequelas neurológicas (atraso no desenvolvimento motor, paralisia cerebral, epilepsia, alterações visuais) foi inferior nas crianças que não precisaram de intervenção ($p < 0,05$), apesar de não haver diferença significativa entre a dilatação ventricular antes da primeira intervenção e a necessidade de SDVP ou o outcome. **Discussão:** Esta coorte foi tratada previamente à revisão das recomendações internacionais e, consequentemente, mais tarde do que é atualmente recomendado. Os recém-nascidos intervencionados revelaram ter uma maior probabilidade de ter sequelas neurológicas comparativamente aos não intervencionados. Futuramente, iniciar a drenagem de LCR assim que o IVL ultrapasse o p97 permitirá reduzir o limiar de intervenção para valores inferiores ao p97 + 4 mm, como é atualmente recomendado.

Palavras-chave: Prematuridade. Hemorragia intraventricular. Hidrocefalia. Desfechos.

Keypoints

What is known
- Posthemorrhagic ventricular dilatation in premature infants is an important cause of impaired neurodevelopment and long-term disability.
- Early intervention reduces the need for a ventriculoperitoneal shunt and neurodevelopment.

What is added
- An analysis of the management of posthemorrhagic ventricular dilatation in a renowned Portuguese neonatal care center.
- Outborn infants are at increased risk of delayed intervention for posthemorrhagic ventricular dilatation.
- Intervention in posthemorrhagic ventricular dilatation should occur earlier and early referral to specialized centers can contribute to improved outcomes.

Introduction

Posthemorrhagic ventricular dilatation (PHVD) is a major complication of preterm birth that occurs after periventricular-intraventricular hemorrhage (PIVH), and is an important cause of impaired neurodevelopment and long-term disability, increasing the risk of cognitive, motor, and sensory deficits[1,2]. PHVD is diagnosed on cerebral ultrasound (cUS) once Levene's Ventricular Index (LVI) crosses the 97th percentile for the gestational age, and is usually combined with additional ventricular measurements, including the anterior horn width (AHW)[1,3].

Various treatment modalities have been investigated[4-6], and the therapeutic approach for PHVD varies greatly across neonatal care centres[7,8]. Currently, management focuses on cerebrospinal fluid (CSF) drainage, usually starting with temporizing lumbar punctures (LPs), followed by temporary ventricular drainage devices, and lastly by implanting a ventriculoperitoneal (VP) shunt[1]. In recent years, several observational studies[8-11] and, more recently, the Early versus Late Ventricular Intervention Study (ELVIS) trial[11], have associated an early cUS-based intervention, before LVI crosses the 97th centile + 4 mm and the onset of clinical signs, with lower rates of death and need for a VP shunt, as well as better neurodevelopmental outcomes.

The aim of our study is to assess the outcomes of the need for a VP shunt and neurological sequelae at two years of corrected age in preterm neonates who required CSF drainage due to PHVD, according to the timing of the initial intervention.

Methods

Patients

This retrospective, single-center study, comprised the preterm infants (gestational age of 32 weeks and

below) born between January 2014 and December 2020, admitted to a level 3 Neonatal Intensive Care Unit (NICU), and diagnosed with periventricular-intraventricular hemorrhage, who subsequently developed PHVD, making them eligible for this study.

Patients were selected from the NICU's database of very low birth weight infants, which records babies born at less than 1,500 g, using the diagnosis of PIVH as the search criterion for the abovementioned period. Demographic and clinical data were collected both from the database and from the discharge clinical records of the eligible patients. Demographic characteristics included gestational age, birth weight, being inborn or outborn, the type of delivery, and whether it was a single or multiple birth. Complications during the neonatal period that have been reported as risk factors for the development of PIVH or PHVD were registered, namely, respiratory distress syndrome, use of inotropes, early- and late-onset sepsis, meningitis, bronchopulmonary dysplasia, patent ductus arteriosus, and necrotizing enterocolitis requiring treatment.

Cerebral ultrasound (cUS)

Serial cUS scans of eligible patients performed during their hospital stay, registered at the NICU's workstation, were reanalyzed by a single observer to assess the progression of PHVD. Ventricular measurements, including LVI and AHW were obtained, along with the date and postmenstrual age (PMA) at each scan. When cUS were not available at the workstation, LVI values were obtained from the patients' clinical records, where AHW was not recorded.

Intervention

To assess the management of PHVD, the details of the interventions performed were obtained. The number, date, and PMA at each LP were obtained from the discharge clinical records of each patient. For those with further progression of ventricular dilatation who required neurosurgical treatment, the respective date, PMA, and type of intervention were obtained from the database maintained by the Neurosurgery division. The most frequent neurosurgical procedures included ventricular reservoir (VR) and VP shunt implantation and, exceptionally, direct ventricular puncture, insertion of an external ventricular drain (EVD), and endoscopic third ventriculostomy (ETV). Complications relating to a VP shunt that required a shunt review were also recorded.

Neurological sequelae

To assess the outcomes of eligible patients, the clinical records of follow-up pediatric appointments at two years of corrected age were consulted. Owing to the retrospective nature of this study, only the presence of cerebral palsy, delayed motor development, visual impairment, and epilepsy were recorded. According to the information available on the clinical records, cerebral palsy (CP) was further classified into spastic (hemiplegia/hemiparesis, diplegia/diparesis, or quadriplegia/quadriparesis), dyskinetic, ataxic, or mixed, and the maximal locomotor function of the infant was graded using the Gross Motor Function Classification System (GMFCS)[12]. Patients were subsequently categorized into three groups according to the presence of any of the abovementioned deficits, namely 1) Surviving without neurological sequelae, 2) Surviving with neurological sequelae, and 3) Death.

Statistical analysis

The collected data was analyzed using the Statistical Package for Social Sciences® software (SPSS, version 29.0). To compare the means of continuous variables with normal distribution, the Independent-samples T-test was used, and the Mann Whitney test for non-parametric variables. Categorical variables were compared using the χ^2 test. Statistical significance was considered as p-value < 0.05.

Ethical considerations

This project was approved by our center's Ethics Committee.

Results

Between January 2014 and December 2020, among the 370 preterm infants admitted to our NICU with a gestational age of 32 weeks or less, 30% (110 out of 370) were diagnosed with PIVH of any grade, of whom 20% (22 out of 110) went on to develop PHVD. Fifty-nine percent (13 out of 22) of these also required CSF drainage interventions due to progressive ventricular dilatation. The demographic and clinical characteristics of the infants diagnosed with PHVD, as well as the information according to the need for intervention, are presented in table 1.

Both groups were comparable for all demographic and clinical characteristics. Five of the 22 infants were outborn. Of the 22 infants who developed PHVD, 23%

Table 1. Demographic and clinical characteristics of the study population

	Overall (n = 22)	No intervention (n = 9)	Intervention (n = 13)
Male, n (%)	10 (45.5)	3 (33.3)	7 (53.8)
Gestational age (weeks), mean (± SD)	27.1 (± 2.7)	26,8 (± 2.7)	27.4 (± 2.7)
Birth weight (grams), mean (± SD)	1017.5 (± 420.9)	993 (± 345.4)	1031.4 (± 470.5)
Type of delivery, n (%) Vaginal Caesarean section	 12 (54.5) 10 (45.5)	 6 (66.7) 2 (22.2)	 6 (46.1) 8 (61.5)
Multiple birth, n (%)	8 (36.4)	3 (33.3)	5 (38.5)
Outborn, n (%)	5 (22.7)	2 (22.2)	3 (23.1)
PIVH, n (%) Grade II Grade III	 5 (22.7) 17 (72.3)	 2 (22.2) 6 (66.7)	 3 (23.1) 11 (84.6)
PVHI, n (%)	6 (27.3)	1 (11.1)	5 (38.5)
Inotropes, n (%)	4 (18.2)	2 (22.2)	2 (15.4)
Early-onset sepsis, n (%)	6 (27.3)	2 (22.2)	4 (30.8)
Late-onset sepsis, n (%)	12 (54.5)	3 (33.3)	9 (69.2)
Meningitis, n (%)	1 (4.5)	0	1 (7.7)
BPD > grade 2, n (%)	8 (36.4)	1 (11.1)	7 (53.8)
Treated for NEC, n (%)	4 (18.2)	0	4 (30.8)
Treated for PDA, n (%)	12 (54.5)	5 (55.6)	7 (53.8)

PIVH: periventricular-intraventricular hemorrhage; PVHI: periventricular hemorrhagic infarction; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus.

had grade II PIVH and 77% had grade III, of whom 27% also developed PVHI (according to Papile's classification system, later adapted by Volpe)[1,13].

Cerebral ultrasound scans were available at the workstation for 91% (20 out of 22) of infants diagnosed with PHVD and were unavailable for one patient who did not receive intervention and one patient who did receive intervention.

In patients who did not receive intervention, although some newborns showed transient increases in LVI over the 97th centile and AHW over 6 mm, towards the 97th centile + 4 mm and 10 mm, respectively, there was a spontaneous reversion in ventricular size without CSF drainage, before crossing these limits.

Among the group of patients who did receive intervention, the left and right LVI of 11 patients are presented in figure 1. Four patients did not have cUS prior to their initial intervention at the workstation, and the Ventricular Index (VI) was obtained from clinical records. One patient had unreliable measurements due to a large cyst coalescing with the lateral ventricle. All of the patients were subject to the first CSF drainage procedure after crossing Levene's line of 97th centile + 4 mm, at a mean PMA of 30.6 weeks (± 2.6), with a mean VI of 7.54 mm (± 3.0 mm) above the 97th centile, and a mean AHW of 7.16 mm (± 1.9) above 6 mm.

Three of the infants who received intervention were outborn and transferred in order to be treated for PHVD: 1) Was not subject to temporizing LP in the hospital of origin due to thrombocytopenia, and was transferred to insert a ventricular reservoir (VR); 2) Had significant ventricular dilatation with concomitant ventriculitis and was transferred to insert an external ventricular drain (EVD) after a LP was performed at the hospital of birth; and 3) Was transferred after surpassing the 97th centile + 4 mm to be treated for PHVD. These patients had a significantly higher LVI at the first intervention when compared to inborn infants (Fig. 2).

Among the infants who required intervention, LP was the most common initial temporizing procedure, performed in 77% (10 out of 13) of patients who received intervention, at a mean PMA of 30.8 weeks (± 2.7); the number of LPs ranged from one to three. The ventricular size stabilized in three of these infants and they did not

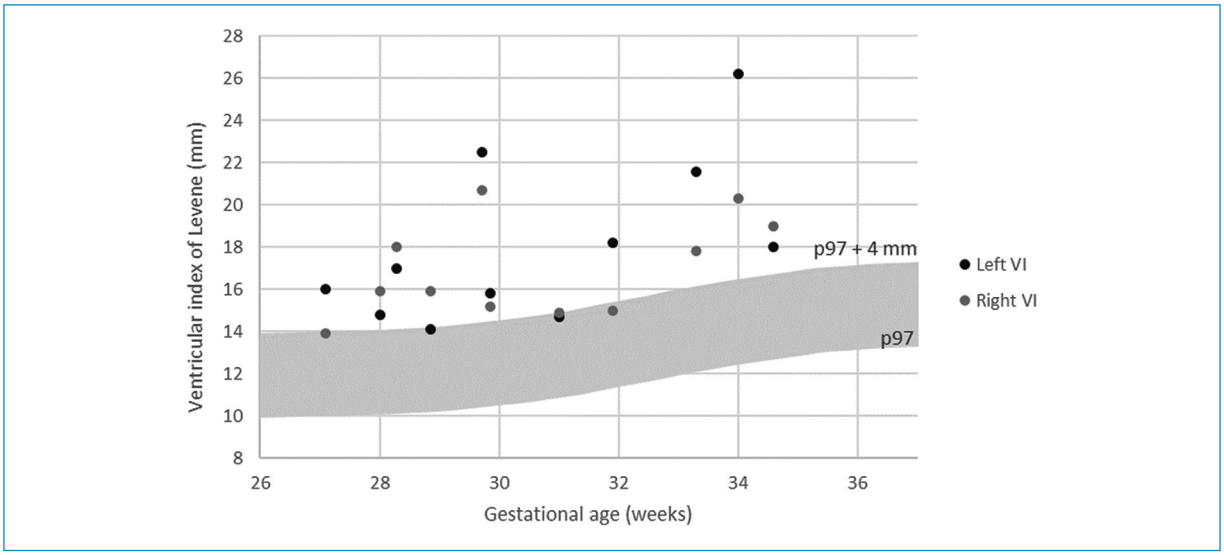

Figure 1. Left and right ventricular index of infants who received intervention, before the first procedure.

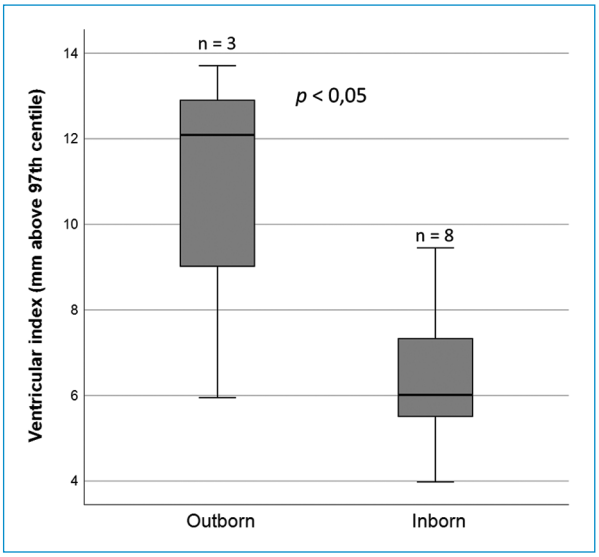

Figure 2. Ventricular index before the first intervention in outborn versus inborn patients.

require further intervention. Among the remaining seven patients, five underwent additional neurosurgical temporizing procedures (three had a VR inserted, one patient underwent an ultrasound-guided ventricular puncture due to clinical instability, and another had an EVD implanted due to refractory meningitis), and two infants had a VP shunt implanted.

Among the remaining 23% (three out of 13), a VR was inserted as an initial temporizing procedure in two patients (at a PMA of 29.7 and 29.9 weeks), one of whom also underwent an ETV, and both required a VP shunt. One infant initially underwent an ETV (at 40.7 weeks) and later required a VP shunt placement (Fig. 3).

Overall, 62% (eight out of 13) of patients who received intervention required the implantation of a VP shunt, at a median PMA of 38.9 weeks (IQR 370 – 41.3), and 23% (three out of 13) died. No significant difference was found between LVI before the first intervention and both the need for VP shunt implantation and death (Fig. 4). Two infants subsequently required VP shunt revision, one due to meningitis and the other due to peritonitis.

Follow-up clinical records were available for 91% (20 out of 22) of patients diagnosed with PHVD. Thirty-five percent (seven out of 20) of the infants died, six during their hospital stay, between one and 11 weeks of birth, one due to respiratory failure, and five owing to systemic illness. One patient was transferred and subsequently died at a PMA of 37 weeks because of refractory *Aspergillus* meningitis.

Of the patients who did not receive intervention, none of the followed-up survivors (four out of nine) had neurological sequelae at two years of corrected age. In contrast, among the survivors of the intervention group with follow-up data (nine out of 13), 78% (n = 7) had sequelae at this age, including delayed motor development (n = 1), visual impairment (n = 1), epilepsy (n = 3), and cerebral palsy (n = 5), of whom four had spastic hemiparesis and one had spastic quadriparesis. Among patients who developed CP, three had a GMFCS grade

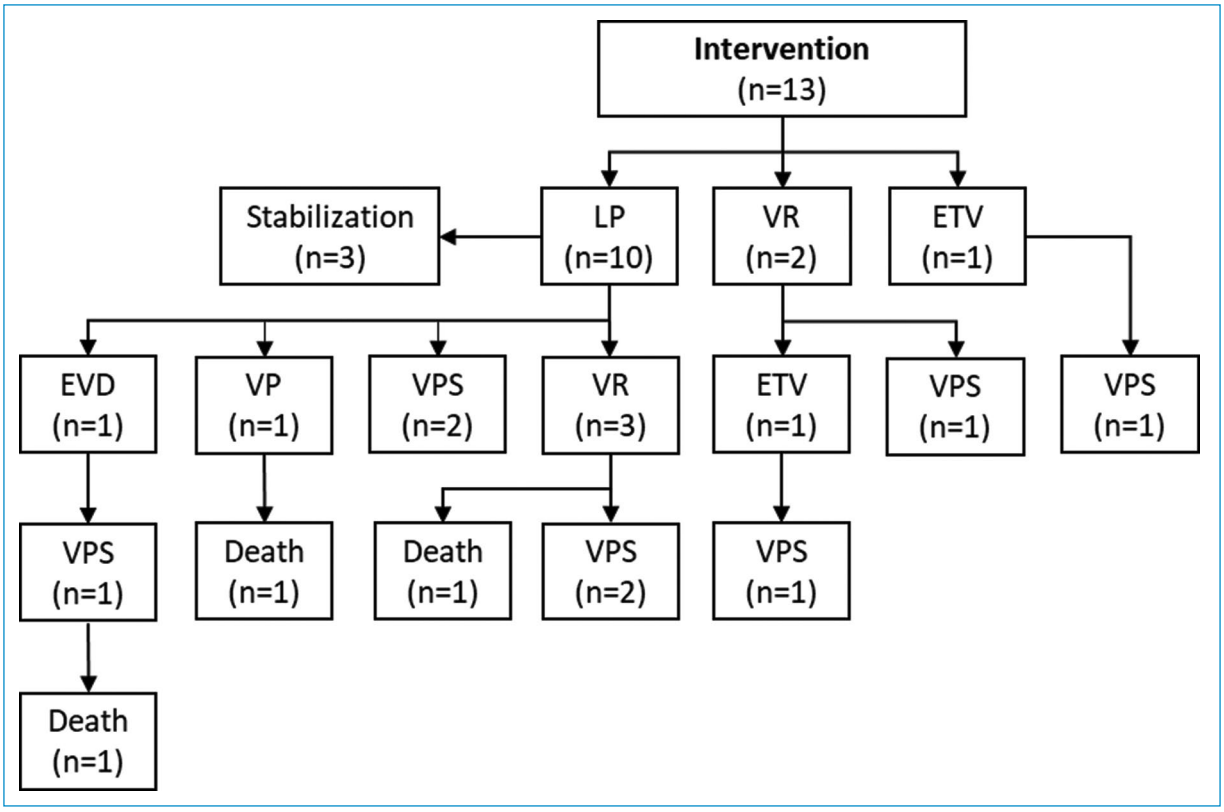

Figure 3. Flowchart of cerebrospinal fluid drainage interventions performed.
LP: lumbar puncture; ETV: endoscopic third ventriculostomy; EVD: external ventricular drain; VPS: ventriculoperitoneal shunt; VP: ventricular puncture; VR: ventricular reservoir.

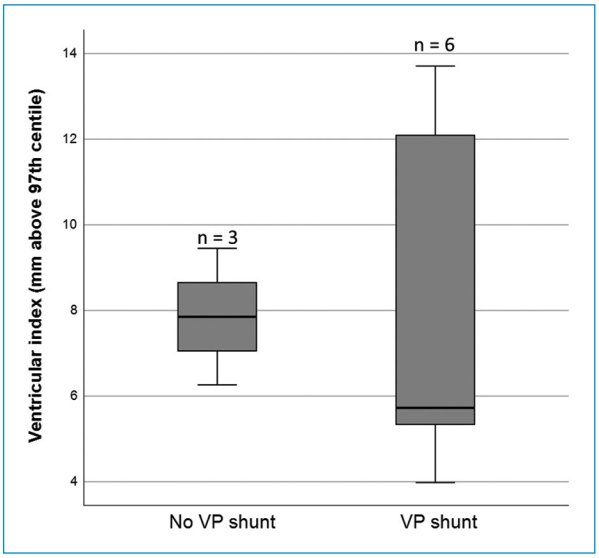

Figure 4. Ventricular index before the first intervention in infants who did and did not require ventriculoperitoneal (VP) shunt implantation.

greater than two. There was a trend towards a higher incidence of CP in infants who received intervention, although it did not reach statistical significance ($p = 0.057$). Overall, significantly more children who required CSF drainage had neurological sequelae, compared to those who did not ($p < 0.05$). VP shunt placement was not associated with an increased probability of adverse outcomes.

Considering the impact of the timing of intervention in the neurological outcome, no significant difference was found between LVI before the first intervention in infants with a favorable outcome, adverse outcome, and death (Fig. 5).

Discussion

This retrospective study aimed to assess the effect of the timing of intervention in the need for a VP shunt and the presence of neurological sequelae at two years of corrected age. It is important to note that this cohort was treated between 2014 and 2020, before the recent review of the international guidelines, which recommend an early approach to PHVD, based on the increasing evidence of its beneficial effect on the need

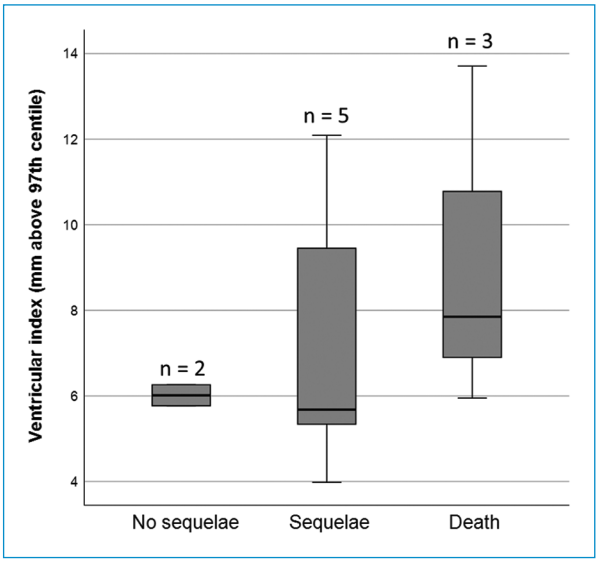

Figure 5. Ventricular index before the first intervention according to neurodevelop-mental outcome at two years of corrected age.

for a VP shunt and on the neurodevelopmental outcomes. Thus, all the infants included in this study received intervention after crossing the threshold of the 97th centile + 4 mm of LVI and 10 mm of AHW, which is later than what is currently recommended.

Among the group of infants who required CSF drainage, no differences were found between ventricular size at the initial intervention and the VP shunt implantation rate or neurodevelopmental outcome, as opposed to what had been reported in previous studies[9-11]. In fact, all the patients included in this study started intervention after surpassing 97th centile + 4 mm, contrasting with studies that compared early and late management groups, with a greater difference in ventricular size at the initial intervention.

In the group that did not receive intervention, a subset of patients showed a transient increase in ventricular size above the 97th centile that later reverted without intervention, which could support the rationale that, with early management, some infants are subject to unnecessary temporizing procedures with associated risks. Although the low threshold group in the ELVIS trial had a higher number of procedures and need for VR and VP shunt revision, severe neurodevelopmental outcomes were reported to be reduced in these patients[11].

Among patients who received intervention, 62% required the implantation of a VP shunt, which is comparable to the rate reported in the previous Ventriculomegaly Study RCT (62%)[6], where repeated lumbar punctures were performed when LVI had crossed the 97th centile + 4 mm, as well as the rate of VP shunt requirement in the late intervention group of the retrospective study conducted by De Vries et al. (62%)[9], that received intervention with a similar timing. In contrast, the VP shunt placement rate of the late approach group reported by Leijser et al.[8] was significantly higher (92%), since initial procedures were guided by the development of clinical signs of raised intracranial pressure, rather than ventricular measurements on cUS. Compared to the results of the ELVIS trial[11], this study's VP shunt rate was higher than reported for the late intervention group of the trial (23%), which may be explained by the additional aim of reducing LVI below the 97th centile, rather than solely preventing further ventricular dilatation.

Regarding outcomes at two years, Leijser et al.[8] reported that infants who received intervention after the development of clinical signs were more likely to have adverse cognitive and motor neurodevelopmental outcomes (88% vs. 27%, respectively) and cerebral palsy (94% vs. 27%) than those who did not receive intervention, as opposed to patients with an early approach, whose outcomes were identical regardless of the need for intervention. In our NICU, although the decision to initiate intervention was based on cUS measurements, with a mean LVI at the first intervention of 7.5 mm over the 97th centile, compared to 11 mm of the late approach group reported in the aforementioned study, patients who received intervention were more likely to have neurological sequelae at two years, namely delayed motor development, cerebral palsy, epilepsy, and/or visual impairment, compared to those who did not receive intervention (78% vs. none). Thirty-three percent of the patients in our study group who required CSF drainage developed CP, compared to 25% of the late intervention group (who received intervention after crossing the 97th centile + 4 mm) reported in the ELVIS trial[11]. Although there was a trend towards a higher probability of developing CP in the group of patients who received intervention, it was not statistically significant, as reported by Leijser et al.[8].

Concerning the timing of intervention in outborn patients, and although this cohort included only three outborn infants, their mean ventricular sizes at the time of the first procedure was significantly higher than that of inborn infants. Indeed, when specialized neurosurgical treatment is required, in addition to the delay in the procedure that may be imposed by the hospital's restrictions, the process of hospital transfer may further delay timely intervention. Thus, owing to the unpredictability of disease progression and the need for

neurosurgical treatment, referring these patients at the time of diagnosis would allow for timely detection and treatment of progressive ventricular dilatation.

The retrospective nature of this study limited data collection, including missing cUS and consequently ventricular measurements at relevant timings, as well as a thorough analysis of outcomes, owing to the unavailability of standardized assessments. Additionally, involving a single center and addressing an infrequent pathology resulted in a reduced study population, and consequently a lack of significant conclusions.

Conclusions

The best way to manage PHVD has been a matter of debate for several years, and different approaches have been used across different countries and units. Despite not confirming that a LVI 97th threshold is better than the + 4 mm threshold, the ELVIS trial did suggest that the 97th + 4 mm threshold should never be surpassed. This concept was translated into the current international guidelines.

We believe that sharing our experience may be of importance to improve the care for these infants, especially in avoiding very late treatment thresholds and bringing forward the referral to experienced centers that can provide full care for these infants.

Authors' contribution

Luísa Carneiro da Silva: Idea behind, and design of, the study, report, review or other type of paper; Acquisition of data from patients, research studies, or literature; Analysis or interpretation of data from patients, research studies, or literature; Drafting the article; Final approval of the version to be published. Agrees to be held accountable for the accuracy or integrity of the paper. Cláudia Coelho Faria: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Critical review of the article for important intellectual content; Final approval of the version to be published (mandatory for all authors); Agreement to be accountable for the accuracy or integrity of the work (mandatory for all authors). André Mendes da Graça: Idea behind, and design of, the study, report, review or other type of paper; Acquisition of data from patients, research studies, or literature; Analysis or interpretation of data from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published. Agrees to be held accountable for the accuracy or integrity of the paper.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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

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SYSTEMATIC REVIEW

Is eight-plate more effective than reconstruction plate in pediatric guided growth? A systematic review and meta-analysis

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Abstract

Introduction and objectives: Pediatric angular deformities in the lower limb need surgeries that are less invasive to correct deformities and prevent premature degenerative changes in the knee. Partial growth arrest, also known as hemiepiphysiodesis, relies on the growth potential of the unaffected side of the physis to facilitate gradual angular correction. Although recognized as an effective implant for this procedure, eight-plate is an expensive device that increases the economic burden for developing countries. There has been some debate about whether a cheaper implant, reconstruction-plate, is comparable in terms of its efficacy in children with angular deformities. **Methods:** A systematic search was conducted in line with the PRISMA guideline to identify relevant studies through the PubMed, Google Scholar, and Cochrane databases. A total of three studies (181 patients, 339 knees) were included, divided into five meta-analyses, which were processed using Review Manager 5.3. **Results:** Eight-plate and reconstruction-plate offer comparable efficacy in terms of lateral distal femur angle (LDFA) correction ($p = 0.30$, $I^2 = 99\%$, MD 3.38), medial proximal tibial angle (MPTA) correction ($p = 0.27$, $I^2 = 94\%$, MD 4.39), the implant failure rate ($p = 0.28$, $I^2 = 0\%$, OR 0.36), rebound rate ($p = 0.44$, $I^2 = 0\%$, OR 0.44), and complication rate ($p = 0.36$, $I^2 = 0\%$, OR 0.47). **Discussion:** Both internal and external factors should be monitored closely in hemiepiphysiodesis, as they may play a role in the success of the surgery. Internal factors include being overweight and physeal conditions. External factors include plate positioning, screw placement, and the screw tightening technique. Regular follow-up should also be given, as this may minimize the risk of overcorrection and the rebound rate. Reconstruction-plate resulted in comparable efficacy to eight-plate in terms of angular correction, implant failure rate, rebound rate, and complication rate.

Keywords: Eight-plate. Guided growth. Meta-analysis. Reconstruction-plate.

É a placa de oito mais eficaz do que a placa de reconstrução no crescimento guiado pediátrico? Uma revisão sistemática e meta-análise

Resumo

Introdução e objetivos: Deformidades angulares pediátricas nos membros inferiores necessitam de cirurgias menos invasivas para corrigir deformidades e prevenir alterações degenerativas prematuras no joelho. A parada parcial de crescimento, também conhecida como hemiepifisiodese, baseia-se no potencial de crescimento do lado não afetado da fise para facilitar a correção angular gradual. Embora reconhecida como um implante eficaz para este procedimento, a placa de oito é um dispositivo caro que aumenta o ônus econômico para países em desenvolvimento. Tem havido algum debate sobre se um

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implante mais barato, a placa de reconstrução, é comparável em termos de eficácia em crianças com deformidades angulares. **Métodos:** Uma busca sistemática foi conduzida de acordo com a diretriz PRISMA para identificar estudos relevantes através das bases de dados PubMed, Google Scholar e Cochrane. Um total de três estudos (181 pacientes, 339 joelhos) foram incluídos, divididos em cinco meta-análises, processadas usando o Review Manager 5.3. **Resultados:** A placa de oito e a placa de reconstrução oferecem eficácia comparável em termos de correção do ângulo distal lateral do fêmur (LDFA) (p = 0,30, I2 = 99%, MD 3,38), correção do ângulo tibial proximal medial (MPTA) (p = 0,27, I2 = 94%, MD 4,39), taxa de falha do implante (p = 0,28, I2 = 0%, OR 0,36), taxa de rebote (p = 0,44, I2 = 0%, OR 0,44) e taxa de complicações (p = 0,36, I2 = 0%, OR 0,47). **Discussão:** Tanto fatores internos quanto externos devem ser monitorados de perto na hemiepifisiodese, pois podem influenciar no sucesso da cirurgia. Fatores internos incluem sobrepeso e condições da fise. Fatores externos incluem posicionamento da placa, colocação dos parafusos e técnica de aperto dos parafusos. Acompanhamento regular também deve ser realizado, pois isso pode minimizar o risco de supercorreção e a taxa de rebote. A placa de reconstrução apresentou eficácia comparável à placa de oito em termos de correção angular, taxa de falha do implante, taxa de rebote e taxa de complicações.

Palavras-chave: Placa de oito. Crescimento guiado. Meta-análise. Placa de reconstrução.

Keypoints

What is known
- Pediatric angular deformities in the lower limb need surgeries that are less invasive to correct deformities and prevent premature degenerative changes.
- Hemiepiphysiodesis is a well-known procedure for this condition, often with the use of an eight-plate.
- There has been some debate about whether a cheaper implant, reconstruction-plate, is comparable in terms of its efficacy.

What is added
- This is the first meta-analysis to objectively compare the two implants for this condition.
- Reconstruction-plate had comparable efficacy to eight-plate in terms of angular correction, implant failure rate, rebound rate, and complication rate.
- Internal and external factors, as well as perioperative monitoring, are important for treatment success.

Introduction

The most common angular deformities of the lower limbs in children, genu varum and genu valgum, need surgeries that are less invasive to correct deformities and prevent premature degenerative changes in the knee. Surgical treatment depends on the degree of the deformity and the patient's skeletal maturity. Early diagnosis and an accurate choice of treatment is important to prevent the need for more invasive procedures, as osteotomy is linked to a higher risk of complications and a longer recovery. Deformity correction in skeletally immature patients can be achieved through temporary or permanent hemiepiphysiodesis, commonly known as guided growth. In guided growth, deformity correction is achieved by tethering the physis on the convex side of the deformity, while allowing the physis on the concave side of the deformity to continue to grow. The anticipated degree of correction depends on the patient's age and the location of the physis[1,2].

Stapling and transphyseal screws were introduced earlier as a treatment for pediatric angular deformity. However, this has been linked to iatrogenic physeal arrest, implant migration, and irreversibility[3]. Later, a newer treatment, tension-band plates, commonly known as the eight-plate, were adopted by many orthopedic surgeons. The eight-plate is a two-hole plate that is fixed to the deformed bone at the physis, with screws inserted proximal and distal to it. Although recognized as an effective implant for this procedure, the eight-plate is an expensive device that increases the economic burden for developing countries. The price of an eight-plate can reach up to 20 times the price of a reconstruction-plate, making reconstruction-plate use an appealing alternative for healthcare fund providers[3]. There has been some debate about whether the cheaper implant, reconstruction-plate, is comparable in terms of its efficacy in children with angular deformities[4].

To date, there have not been many studies comparing the efficacy of both implants. Through this study, we aim to objectively compare the efficacy and complications of pediatric angular correction using the eight-plate and reconstruction-plate.

Materials and methods

This study was registered in PROSPERO (CRD42023410685). The study design was a meta-analysis of randomized controlled trial and a non-randomized comparative study. A systematic search was conducted based on the PRISMA (Preferred Reporting Items for Systematic

Table 1. PICO table describing inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Pediatric angular deformity of the knee, diagnosed through clinical and radiological studies	Non-human studies Less than six months of follow up
Intervention and comparison	Operative treatment of hemiepiphysiodesis using eight-plate or reconstruction-plate	Non-operative treatment Hemiepiphysiodesis with other types of implant
Outcome	LDFA correction MPTA correction Implant failure rate Rebound rate Complication rate	No outcome mentioned or different outcomes
Publication	Primary research published in English in a peer-reviewed journal	Abstracts, editorials, letters Duplicate publications of the same study/cohort that do not report on different outcomes Conference presentations or proceedings
Design	Randomized controlled trials Cohort studies	Case reports or series Review articles

PICO: population, intervention, comparison, and outcome.

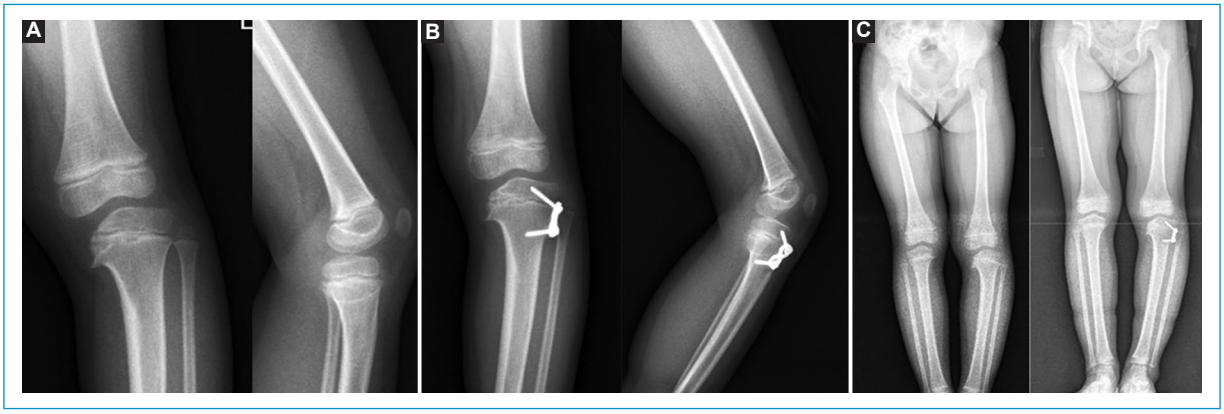

Figure 1. Plain knee X-Ray of a patient with blount disease, treated with emiepiphysiodesis using reconstruction-plate. **A:** before surgery. **B:** at seven months follow-up. **C:** comparative scanogram *(courtesy of Maharjana MA)*.

Reviews and Meta-Analyses) guideline from September 2022 to March 2023 to identify relevant studies through the PubMed, Google Scholar, and Cochrane databases. The following keywords were used: "eight-plate" AND "reconstruction plate" AND "guided-growth" AND "outcome".

The titles and abstracts of the articles found were then manually scanned and reviewed by each of the authors. The full text of relevant articles was subsequently extracted and carefully selected according to the following inclusion criteria: (1) studies including a comparative design for eight-plate versus reconstruction-plate in pediatric angular deformity of the knee, whether in retrospective, prospective, as well as randomized controlled and observational studies; (2) studies reporting a clinically and/or radiologically desirable outcome with either continuous or dichotomous variables; (3) studies in English with any publication year. Exclusion criteria were adult patients, patients with trauma, malignancy, a history of previous surgery, and patients receiving other treatment methods. Duplicate publications, noncomparative studies, non-human in vivo and in vitro studies, and articles in languages other than English were also excluded. The inclusion and exclusion criteria are described in the Population, Intervention, Comparison, and Outcome (PICO) table below (Table 1). Critical appraisal was then performed on potential studies based on the

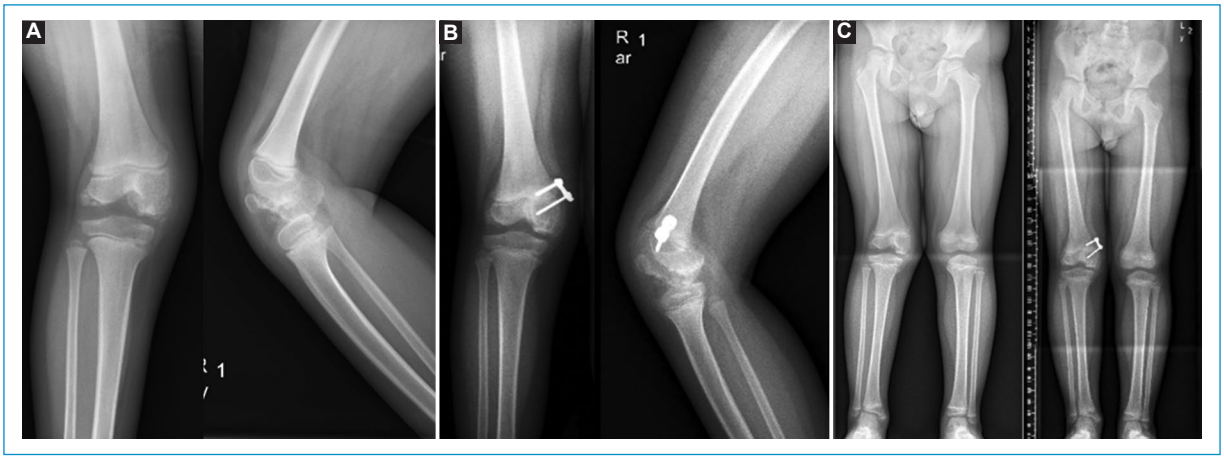

Figure 2. Plain knee X-Ray of a patient with post-traumatic genu valgum, treated with hemiepiphysiodesis using reconstruction-plate. **A:** before surgery. **B:** at nine months follow-up. **C:** comparative scanogram *(courtesy of Maharjana MA).*

Table 2. Studies included in the analysis

No.	Reference	Journal	Study design	Level of evidence
1	Jamil et al. (2021)	Malaysian Orthopaedic Journal	Cohort Retrospective	III
2	Ghaznavi et al. (2022)	The Archives of Bone and Joint Surgery	Cohort Retrospective	III
3	Park et al. (2017)	Journal of Orthopaedic Science	Cohort Retrospective	III

Joanna Briggs Institute (JBI) Checklist for Systematic Reviews and Research Syntheses.

Extracted data was collected under the basic characteristics and outcomes using designated tables in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) for all of the studies identified and included. When the data was available, a quantitative analysis was performed using Review Manager (RevMan, computer program ver. 5.3, the Cochrane Collaboration, 2014; The Nordic Cochrane Center, Copenhagen, Denmark). Outcomes were presented in the form of forest plots. The mean difference for continuous outcomes and an odds ratio (OR) for dichotomous outcomes with a 95% confidence interval (CI) was calculated in each study. A fixed-effects model was used when heterogeneity (I^2) was < 50%, whereas a random-effects model was used when heterogeneity was > 50%.

Results

A total of three studies (181 patients, 339 knees) were included, divided into five forest-plot analyses. All of the studies used have a retrospective study design (Level III evidence) (Table 2). Critical appraisal based on the Joanna Briggs Institute Scoring System showed that none of the studies had more than four invalidity criteria.

The sample age ranged from three to 16 years old, with males comprising most of the study population (male: female = 54.7%:45.3%). Eight-plate was used in 153 knees (45.13%), while 186 knees were treated with reconstruction-plate (54.87%). Syndromic as well as idiopathic genu valgum and genu varus were included in the analysis. The distal femur was the most common region for plate application (281 knees/82.89%). The time to implant removal varies from five to 68.5 months, and the follow-up time ranged from seven to 104 months after implant removal. Body Mass Index (BMI) ranged from 18.7 – 28 in both groups (Tables 3 and 4).

For lateral distal femur angle (LDFA) correction, two studies were included in the analysis, with a total of 93 patients treated with eight-plate and 123 patients treated with reconstruction-plate. Eight-plate and reconstruction-plate offer comparable efficacy in terms of

Table 3. General characteristics of the studies included in the analysis

No.	References	Sample size	Implant selection		Pathology	Mean age (years)		Sex		Region	Time to implant removal	Follow up
			8-plate	Recon plate		8-plate	Recon plate	8-plate	Recon plate			
1	Jamil et al. (2021)	17 patients (27 knees)	24	3	Down's syndrome: 2 Idiopathic genu valgus: 2 Tibia vara: 23	4 (3-6)		F = 5 (29.4%) M = 12 (70.6%)		Distal femur: 4 Proximal tibia: 23	20.5 months (13.75-25.5 months)	12-104 months after implant removal
2	Ghaznavi et al. (2022)	109 patients (212 knees)	90	122	Idiopathic genu valgum in all patients	11.9 ± 5 (9-16)		F = 58 (53.2%) M = 51 (46.8%)		Distal femur in all patients	11.3 + 3 months (5-18 months)	32.9 + 15.1 months (7-74 months)
3	Park et al. (2017)	55 patients (100 knees)	39	61	Idiopathic genu valgum: 15 Rickets: 14 Multiple osteochondromatosis: 11 Blount disease: 8 Post-traumatic: 6 Others: 7	7.5	8.6	F = 9 (45%) M = 11 (55%)	F = 10 (28.6%) M = 25 (71.4%)	Distal femur: 65 Proximal tibia: 35	Time to angular correction: 13.7 months (12.7-31.3 months) in 8-plate and 19.7 (11.4-68.5 months) in Recon plate	14 months (12-20 months) after implant removal

Table 4. Characteristics of study outcomes

No.	References	Mean BMI (kg/m^2)		Outcome measurements									
				LDFA correction		MPTA correction		Failure rate		Rebound rate		Complication rate	
		8-plate	Recon plate	8-plate	Recon plate	8-plate	Recon plate	8-plate	Recon plate	8-plate	Recon plate	8-plate	Recon plate
1	Jamil et al. (2021)	26 (25-28)		0.67°/month		0.71° / month		8.3%	33.3%	8.3%	0%	-	
2	Ghaznavi et al. (2022)	22.4 ± 1.8		8° ± 3.7°	7.9° ± 3.5°	2.7° ± 3.7°	2.1° ± 3.4°	0%	0.8%	-		1.1%	3.3%
3	Park et al. (2017)	18.7	22.7	9° (1.03°/month)	9.9° (0.77°/month)	7.1°	9°	0%	1.6%	0%	3.3%	2.6%	3.3%

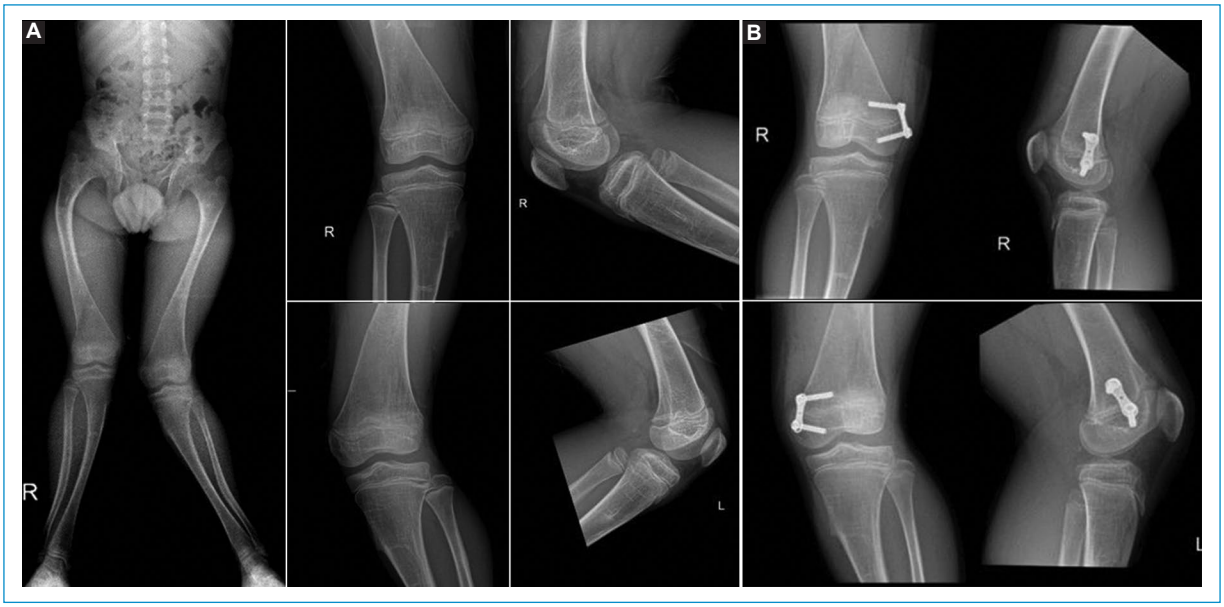

Figure 3. Plain scanogram and knee X-Ray of a patient with rachitic genu valgum, treated with bilateral hemiepiphysiodesis using eight-plate. **A:** before surgery. **B:** after surgery *(courtesy of Maharjana MA).*

Figure 4. Plain post-operative scanogram and knee X-Ray of a patient with idiopathic genu valgum, treated with distal femur and proximal tibia hemiepiphysiodesis using eight-plate *(courtesy of Maharjana MA).*

LDFA correction (I^2 = 99%; weighted mean difference (WMD) 3.38; 95% CI, –3.06 to 9.82; p = 0.30). In the analysis for medial proximal tibial angle (MPTA) correction in 235 patients, both implants also showed comparable efficacy (I^2 = 94%; WMD 4.39; 95% CI, –3.47 to 12.26; p = 0.27).

Dichotomous variables were also analyzed, where a fixed effects model was used in three forest plots. For implant failure rate, three studies were included in the analysis, comprising 153 patients in the eight-plate group and 186 patients in the reconstruction-plate group. Both implants were proved to have a comparable implant failure rate (I^2 = 0%; OR 0.36; 95% CI, 0.06 to 2.28; p = 0.28).

The rebound rate of angular deformity was analyzed through a total of 63 patients treated with the eight-plate and 64 patients treated with the reconstruction-plate. There are two patients in the eight-plate group with rebound and two patients in the reconstruction-plate group with rebound. The forest plot analysis showed a comparable rebound rate between the two procedures (I^2 = 0%; OR 0.44; 95% CI, 0.05 to 3.58; p = 0.44).

The last analysis differentiates the rate of complications between patients treated with the eight-plate and the reconstruction-plate. Through 129 patients treated with the eight-plate and 183 patients treated with the reconstruction-plate, it was found that the rate of complications did not vary significantly (I^2 = 0%, OR 0.47; 95% CI, 0.09 to 2.36; p = 0.36). Park et al. (2017), found one implant failure (screw breakage) in his study of the reconstruction-plate group, and one superficial infection in both groups. Ghaznavi et al. (2022) recorded five complications in total, where the eight-plate group had a case of screw loosening, and the reconstruction-plate group had a screw loosening, two overcorrections, and one screw breakage.

Discussion

The use of reconstruction-plate in the treatment of pediatric angular deformity of the knee is recognized (Figs. 1 and 2). However, research comparing it with the widely-recognized eight-plate has not been discussed often. The use of reconstruction-plates has been acknowledged to be an innovative surgical implant compared to older osteotomy techniques in terms of surgical duration, complications, and the invasiveness of the procedure[6]. The successfulness of the reconstruction-plate was also addressed in another study by Ghaffari (2020), where a modulated growth of eight degrees bilateral genu valgum without previous intervention was treated with a distal femoral and proximal tibial two-hole reconstruction-plate and achieved complete correction at eight months, when the implant was removed[7]. Another study also mentioned the successful correction of 86% of angular deformity using reconstruction-plate with a failure rate in 10% of the subjects, with screw failure or plate failure[8]. In another study with a bigger sample, it was found that 61.5% of varus knees and 85.2% of valgus knees were able to be corrected with a two-hole reconstruction-plate. Correction failure in the study was bigger in varus knees compared to valgus knees (38.5% vs. 14.8%). This study divided the physis of the patients into normal physes and sick physes, and the complication rate was significantly higher in sick physes (81.8% vs. 18.2%), where rebound and implant failure were only found in the sick physis group[3].

Various factors are attributed to the hardware failure, patients' factor, and technical factors. Suggested patients' factors may include obesity combined with sick physis, which may cause abnormal growth motion of the physis. This suggested factor was shown in the Jamil et al. (2021) study where the screw failure happened in a 13-year-old boy with a BMI of 32. Technical factors may include the small screw diameter and poor plate contouring. To prevent against hardware failure, the author suggests a three-hole plate instead of two-hole to increase screw divergence. Proper screw tightening by alternating tightening may provide better plate attachment to the bone. To avoid rebound, a proposed technique of 3°-5° overcorrection with the eight-plate may be used[1]. In regard to the complications for both methods, Park et al. (2017) recorded one patient with a BMI of 37.8 kg/m^2. A research paper by Burghardt et al. reported that the eight-plate implant failure consisted of a screw breakage and a combination of Blount disease with high BMI as the suspected cause. Multiple studies suggested that cannulated screws were reported to be weaker than a solid cortical screw. However, in his study, the screw that was broken was the cortical screw, which had the same diameter as the cannulated screw. Hence, the strength of the cortical screw and cannulated screw need to be studied in more detail to decide which one is better for applying hemiepiphysiodesis[2,9].

Soft tissue infection is another complication described in literature, where Park et al. suggested that soft tissue infection was caused by the thickness of the reconstruction-plate impacting patients' knee motion. Certain measures can be taken to prevent soft tissue problems, such as proper tightening of the screws and optimal contouring of the plate to provide proper plate to bone contact[2].

It is true that in a large study comparing the eight-plate (tension-band plate) with other more conventional methods, such as percutaneous screws, stapling, and osteotomies, the efficacy of the tension-band plate has been proven[10]. Jamil et al. (2021) stated that the eight-plate is less invasive, reversible,

easily inserted, and removed with minimal damage to the physis and periosteum (Figs. 3 and 4). In a patient with a sick physis, such as skeletal dysplasia or Blount disease, the correction rate of hemiepiphyiodesis with the eight-plate may be slower, but the rate of hardware failure is no different when compared to the reconstruction-plate[10]. The rate of correction in patients treated with an eight-plate shows an auspicious result where the average MPTA and LDFA correction is 8.6° while the studies included in this meta-analysis only correct MPTA and LDFA at 7.6 and 8-9, respectively[11]. Furthermore, a study by Boero et al. (2011) mentioned that the rate of correction might be slower in pathological physis due to physeal compromise (e.g. in dysplasias and endocrinopathies), resulting in the need for early intervention and possible repeated treatment procedures[12]. In a larger study of 135 physes, the success rate reached 94.06% with no rebound complications or risk factors[13]. In a study by Martinez et al., the eight-plate was proven to provide better correction compared to screw and suture (0.54° vs 0.45° per month, p = 0.33)[14].

Despite its advantages, the eight-plate is five times more expensive than the reconstruction-plate. Patient satisfaction combined with cost-effective treatments will lead to a well-organized and effective environment for every aspect of the healthcare industry, from patients, healthcare providers, and governments, who play a significant role in funding treatments[1]. Our findings suggest that the reconstruction-plate offers similar efficacy in angular correction as well as a comparable rebound, complication, and implant failure rate. This study has several limitations: (1) All three studies included in the analysis were of level III evidence. However, we have ensured that these studies were of high quality and eligible to be included in this meta-analysis; (2) The heterogeneity of some analysis was > 50%, and this may contribute to analysis bias. This issue may be the result of the different patient characteristics in the two studies involved, where Jamil et al. (2021) also included syndromic conditions with more correction-resistant sick physes whereas the sample in Ghaznavi et al. (2022) was exclusive to idiopathic conditions. The mean age also varies, where Jamil et al. (2021) included younger patients up to three years of age, while the youngest sample in the study by Ghaznavi et al. (2022) had a mean age of 11.9 years old. This leads to our recommendation to apply these results with caution, especially in young patients with syndromic deformities. However, this study also has several advantages: (1) To our knowledge, this is the first meta-analysis to objectively compare eight-plate and reconstruction-plate for pediatric guided growth; (2) Outcomes were thoroughly assessed, in terms of several outcome measures, aiming to describe as many aspects as possible to be considered in treating such cases. It is hoped that this study could serve as an influential bridge to future research with larger sample sizes and some cost analysis, as well as a clinical guideline for choosing surgical therapeutic approaches for pediatric patients receiving guided growth treatment.

Conclusion

Reconstruction-plate offers comparable efficacy to eight-plate in terms of angular correction, implant failure rate, rebound rate, and complication rate.

Authors' contribution

Anak Dwipayana and Sherly Desnita Savio: Performed the selection of literature to be included in the study, performed systematic and meta-analysis, and discussed with the other authors about how to formulate the discussion and conclusion. Read and approved the final manuscript.

Made Agus Maharjana: Supervision of the literature selection, discussed with the other authors about how to formulate the discussion and conclusion. Read and approved the final manuscript.

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Conflicts of interest

None.

Ethical disclosures

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

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

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

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

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PERSPECTIVE

Ethics and the "do not attempt resuscitation" order

Ética e a decisão de não tentar reanimar

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Keypoints

What is known

– Ethics and the "do not attempt resuscitation" order has been discussed in medical literature.

What is added

– We review this subject and add our perspective from the field of Pediatrics and Neurology.

Progress in science, technology, and medicine has created a strong belief in the omnipotence of medical care: every problem must have a solution, every disease must have a cure, death is (almost) always avoidable.

Pediatrics is a very special area of medicine because of the enormous emotional investment in children from families and society in general.

Robinson states that the death of a child is always considered a premature death and the acceptance of tragedy is clearly not the state of mind that parents have when a serious, life-threatening disease affects their child[1].

In the practice of pediatrics, the number of patients with advanced and terminal diseases is increasing and physicians and patient representatives have to discuss and agree on difficult topics such as resorting to expensive and potentially harmful pharmacologic interventions, complex surgery with a marginal likelihood of benefit, intubation and mechanical ventilation, and of course what to do in the event of cardiorespiratory arrest.

Physicians have been practicing resuscitation techniques for centuries. The modern era of cardiopulmonary resuscitation (CPR) is mainly founded on the work of cardiologists throughout the 20th century. In 1960, Dr. Kouwenhoven published a landmark paper on the technique of external cardiac massage in the Journal of the American Medical Association[2]. Increasingly sophisticated medical interventions with the aim of restoring vital signs and supporting life are now blurring the dividing line between life and death.

CPR is not always successful and may eventually leave the patient with profound impairments. Also, cardiopulmonary arrest often occurs in patients that already have a severe, chronic, and advanced disease that may seriously and irreversibly compromise their quality of life.

If resuscitation is unlikely to be successful, or if it is successful and the patient's handicap is likely to worsen, can we narrow down the treatment options? On what basis?

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Some considerations must be made:

– Applying the "low quality of life" standard if CPR successfully restores vital signs is often inappropriate because patients or their families may have a different view on what would be a "good quality of life" or their thoughts on this subject may fall within the framework of a religious belief in the sanctity of life (every human life is intrinsically valuable for most religions worldwide).
– The patient or his/her representatives may be willing to accept a low risk of success in a medical intervention.
– Children have a limited ability to evaluate and decide because of their young age (and sometimes also because of clinical reasons, like advanced neurologic disease). So, healthcare-related decisions fall to a surrogate. Parental autonomy in decision-making about a child's health is not without limits: parents must always consider the best interests of their child. The child has the inherent right to be cared for and to have decisions about their healthcare made on the basis of his/her best interests. The divergence between physicians and parents can result in a conflict between the physician's decisions and physician integrity and parental autonomy. However, a discussion between the medical team and the family on what is in the patient's best interest will, in many instances, not solve the problem and parents may insist on medical interventions that the physician believes to be inadequate and not "evidence-based". Gillam proposes the concept of a "zone of parental discretion" whereby the parents would have the right to make a decision about a specific intervention even if this intervention has a low probability of success (as long as their decision is not malicious and is not harmful to the child). By doing so, the focus on the issue of "the child's best interest" is removed[3]. In the past, cases of disagreement between physicians, institutions, and parents have consistently shown that courts generally recommend that the parents' demand for advanced interventions should be very seriously considered and not easily dismissed as "unrealistic"[4].
– Are moral rules universal and inherent to human nature or do they differ in different times and places? The debate on moral relativism is a major issue today because immigration and cultural changes in indigenous populations have promoted interindividual diversity to an extent that we have never seen before. The beliefs and moral values of physicians and institutions may well differ from those of patients or families from very different ethnic, cultural, socioeconomic, and religious backgrounds.
– In Western societies, unlimited belief in the progress of science and medicine clearly coexists with patients' distrust of physicians' decisions about their healthcare. Moreover, the ability of physicians to prognosticate accurately is notoriously limited.
– Much has been written on the issue of futile intervention[5-8] (with arguments for and against). Some argue that if an intervention is truly futile there is no reason to implement it, so there is always a dividing line between what should be done and what should not. Others say that in extreme cases, a morally-valid agreement may be reached by using the concept of futility: the balance between beneficence, non-maleficence, and the preservation of respect and dignity may favor setting limits for medical intervention. In extreme circumstances, CPR may be successful at restoring vital signs but only temporarily, for a short period of time, and will have no effect on the inexorable course of the underlying disease. In these cases, CPR and other interventions may be considered futile. The concept of futility may therefore be the background for the "do not attempt CPR" decision. It is also very likely that "yes to basic CPR" and "no to advanced CPR" may be a more appropriate option than "no CPR".
– There is also debate surrounding the validity of giving a patient unlimited, advanced, and costly medical treatment that may only bring marginal benefit, perhaps compromising society's healthcare expenses in general. Utilitarian ethics are generally invoked by politicians and economists: a decision is morally valid if it promotes equality in the distribution of resources or, in other words, when it provides "the greatest benefit for the greatest number of people". In opposition to this consequentialist view, deontological ethics states that a morally-valid action is justified in itself and not by its consequences (the right has priority over the Good). In the context of the physician-patient relationship, deontological ethics is of course very compelling.

Our own experience and the literature on this topic[4] suggest that the unilateral decision to not attempt CPR against the will of the parents may create a conflict that entails many legal and ethical problems and must be avoided.

Families of patients with chronic and serious diseases that may experience hyperacute events leading to death are never prepared to discuss with the physician about whether or not to perform CPR in the acute and very stressful situation of cardiorespiratory arrest. Likewise, the physician in charge of the acute event is very unlikely to be the usual caregiver and will have

more limited knowledge of the disease itself and on the specific characteristics of the individual patient. Discussion should therefore anticipate the acute event. It is also advisable to have a written, signed document that can provide proof of the discussion and this should include a clear statement that the review of any decision made should always be considered.

Authors' contribution

José P. Vieira: Conception and design of the study, report, review or other type of work or paper. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

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

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

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CASE REPORT

Acute myocardial infarction in a previously healthy child: case report

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Abstract

Introduction: Acute myocardial infarction is a rare life-threatening event in children. Although more frequent in those with congenital heart disease and/or abnormal coronary anatomy, it can occur in otherwise healthy children. **Case report:** We present the case of a previously healthy seven-year-old boy evaluated because of chest pain. An ECG revealed major repolarization abnormalities in the inferior and left precordial leads and an echocardiogram showed mild global left ventriclar dysfunction and a dyskinetic apical interventricular septum. Laboratory testing showed an isolated, but significant, elevation of cardiac markers. He underwent cardiac catheterization that confirmed an occlusion of the distal segment of the left descending artery. Cardiovascular magnetic resonance findings indicated a recent transmural infarction of the apical septal segment. **Discussion:** Despite being an uncommon entity in the pediatric population, myocardial ischemia and infarction can be the reason behind plain chest pain. The diagnosis warrants a high index of suspicion and should prompt meticulous cardiac testing.

Keywords: Chest pain. Myocardial infarction. Pediatrics. Cardiology. Case report

Enfarte agudo do miocárdio em criança previamente saudável: caso clínico

Resumo

Introdução: O enfarte agudo do miocárdico é um evento ameaçador da vida raro em crianças. Apesar de ser mais frequente em doentes com cardiopatia congénita e/ou alterações da anatomia coronária, pode ocorrer em crianças previamente saudáveis. **Relato de caso:** Os autores descrevem o caso de um menino de 7 anos, previamente saudável, avaliado por dor torácica. O ECG revelou alterações da repolarização nas derivações pré-cordiais inferiores e esquerdas e o ecocardiograma mostrou disfunção ligeira do ventrículo esquerdo e discinésia da porção apical do septo interventricular. O estudo analítico demonstrou uma elevação isolada e significativa dos marcadores de necrose miocárdica. O paciente foi submetido a cateterismo cardíaco que confirmou a oclusão do segmento distal da artéria descendente anterior esquerda. Os achados da ressonância magnética cardíaca indicaram enfarte transmural recente do segmento apical. **Discussão:** Ainda que seja uma entidade incomum na população pediátrica, a isquemia do miocárdio pode ser a razão por detrás de uma simples dor torácica. Por este motivo, o diagnóstico de um enfarte agudo do miocárdio pediátrico requer um alto índice de suspeição e deve ser acompanhado de uma investigação cardíaca meticulosa.

Palavras-chave: Dor torácica. Enfarte do miocárdio. pediatria. Cardiologia. Caso clínico.

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Keypoints

What is known
- Myocardial infarction is a rare, life-threatening condition in healthy children.
- Chest pain is a frequent cause of emergency department visits in the pediatric population.
- Chest pain associated with cardiac causes is rare.

What is added
- Description of a rare case of myocardial infarction in a child.
- Importance of prompt and meticulous cardiac testing and invasive coronary angiography to establish diagnosis if there is a high index of suspicion.

Introduction

Acute myocardial infarction (AMI) is a life-threatening condition resulting from a sudden reduction or interruption in the blood flow of the vessels supplying the heart[1]. This clinical entity is well known in adult patients, though very rare in children. Chest pain, however, is a frequent cause of emergency department visits in the pediatric population, although for the large majority, it is not associated with cardiac causes[2]. Myocardial ischemia leading to AMI in childhood is more common in those with congenital heart disease (CHD) and abnormal coronary anatomy. Nevertheless, it can have different etiologies requiring different management approaches. AMI etiologies in children include Kawasaki disease, myocarditis, cardiomyopathy, substance abuse, trauma, complications from CHD surgery, and other rare conditions[3]. In this report we present an AMI case of a previously healthy child that presented with chest pain after minor chest trauma.

Case report

A seven-year-old boy was transferred from a private hospital to the emergency department of a tertiary hospital due to abnormal findings in a chest radiography and echocardiogram. On the day before admission, he suffered a minor chest compression while playing and subsequently presented retrosternal chest pain and discomfort with low tolerance in supine position and trouble sleeping. He had no palpitations, syncope, gastric or respiratory symptoms. He was previously healthy and had no family history of cardiovascular disease. He had a COVID-19 infection six weeks before.

On examination, the patient looked unwell and pale, denying any chest pain at the time. He was afebrile, with a normal respiratory rate and oxygen saturation, a heart rate of 116 beats per minute and blood pressure of 108/75 mmHg (50th percentile) in the upper right arm. There were no visible chest abnormalities or contusion marks. Cardiac auscultation revealed tachycardia, normal heart sounds and no murmurs, rubs or gallop. No peripheral edemas were observed and no other clinical alterations were found upon physical examination.

The 12-lead electrocardiography (ECG) showed sinus tachycardia with ST segment elevation in leads DI, aVL and V2 to V6 and ST segment depression in leads DIII, aVR and V1 (Fig. 1). A 2D echocardiogram revealed a segmental dysfunction of the left ventricle with a dyskinetic/akinetic interventricular septum and apex, a foramen ovale with left-to-right shunt, a small posterior pericardial effusion next to the right ventricle apex, with hyper-refringence of the pericardium and minor left pleural effusion. Cardiac morphology and the origin and initial course of the coronary arteries were normal. Laboratory tests revealed elevated levels of troponin-I (6908.4 ng/L, reference range: < 34.0 ng/L), CK-MB (59.7 ng/mL, reference range: 0.00-6.40 ng/mL) and BNP (746.8 pg/mL, reference range: < 100.0 pg/mL). A computed tomography (CT) angiography scan confirmed the pericardial and left pleural effusion and raised suspicions about a small segment of myocardial bridging in the mid/distal left anterior descending artery. No other coronary abnormalities were found. In view of the patient's clinical presentation, laboratory test results and imaging findings, cardiac catheterization was performed promptly. The examination showed an occlusion of the distal segment of the left descending artery and no significant lesions in the remaining coronary arteries (Fig. 2). After the procedure, the patient was transferred to the pediatric intermediate care unit for clinical surveillance, under anti-aggregation with acetylsalicylic acid (150 mg/day).

On the first day of hospitalization, due to clinical deterioration, he was transferred to the pediatric intensive care unit (PICU) and started high-flow oxygen therapy and furosemide perfusion for two days. He presented a favorable clinical evolution and was discharged from the PICU after six days. At the pediatric cardiology ward, he remained hemodynamically stable. A cardiovascular magnetic resonance (CMR) was performed on the seventh day of hospitalization and revealed an akinetic apical segment of the cardiac septum with relative

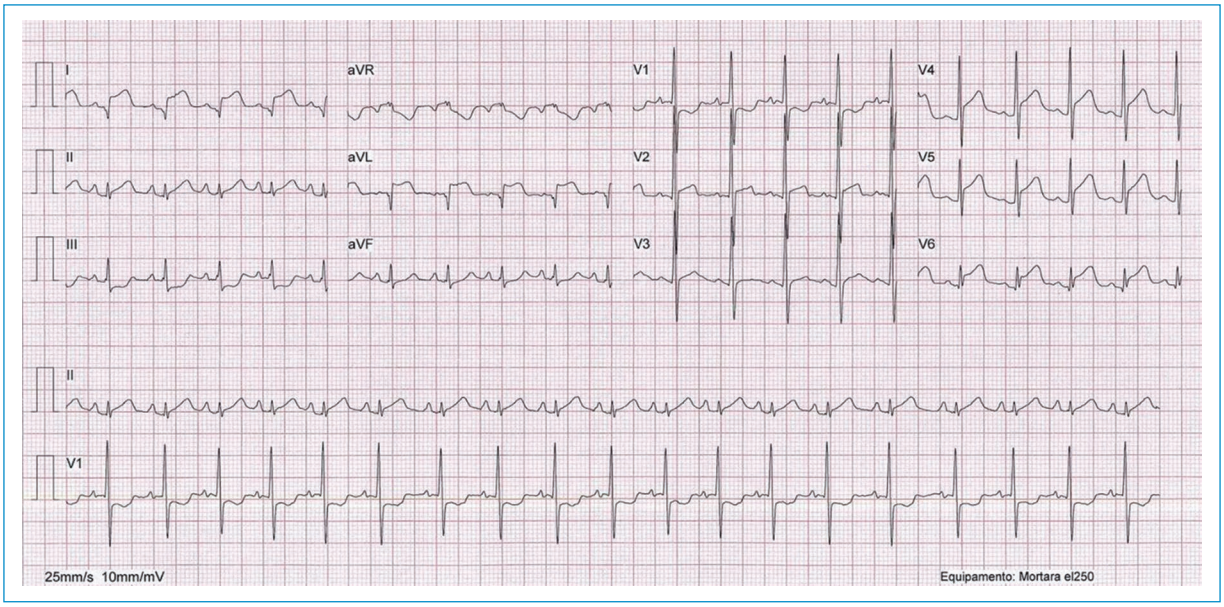

Figure 1. ECG showing sinus tachycardia with ST segment elevation in leads DI, aVL and V2 to V6 and ST segment depression in leads DIII, aVR and V1.

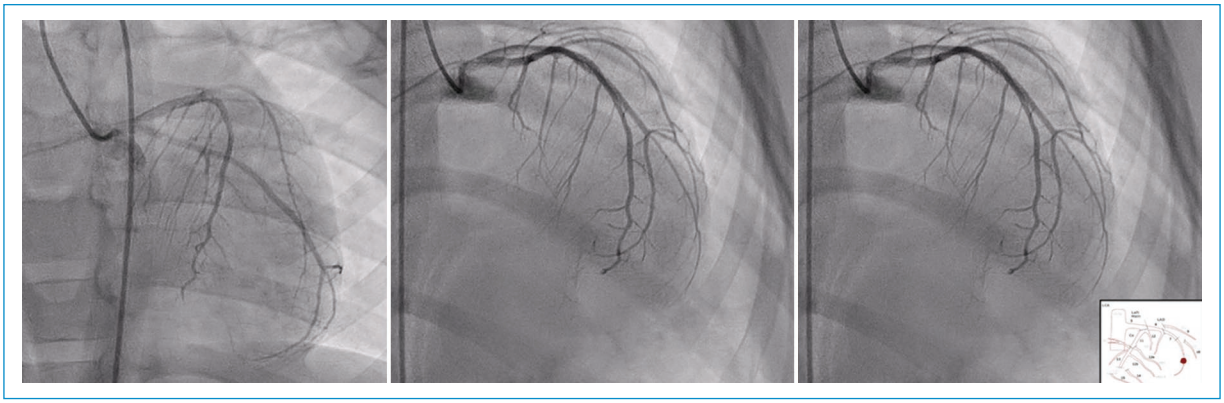

Figure 2. Cardiac catheterization examination showed an occlusion of the distal segment of the left descending artery.

parietal thickening. No alterations to the other segments were found. T2-weighted imaging showed transmural myocardial edema in the apical segment with a hypointense core, suggestive of intramyocardial hemorrhage. Post-contrast enhancement of the apical septal segment evincing microvascular obstruction was identified. He presented normal biventricular volumes and good global systolic function. There was no evidence of intracardiac thrombi or masses, or pericardial or pleural effusions. Findings were indicative of a recent transmural infarction of the apical septal segment (Fig. 3), compatible with an AMI. Serial laboratory measurements of cardiac biomarkers showed progressive normalization: troponin-I 302.6 ng/L (reference range: < 34.0 ng/L), CK-MB 0.9 ng/mL (reference range: 0.00-6.40 ng/mL), myoglobin 36.3 ng/mL (reference range: < 146.9 ng/mL) and BNP 219.7 pg/mL (reference range: < 100.0 pg/mL) at the last evaluation. Further investigations were negative, namely coagulation, prothrombotic, and infection screening. An echocardiography prior to discharge evinced a discrete dilatation of the ventricle apex and normal ventricular function with no pericardial or pleural effusion. An ECG showed a sinus rhythm, poor R-wave progression and

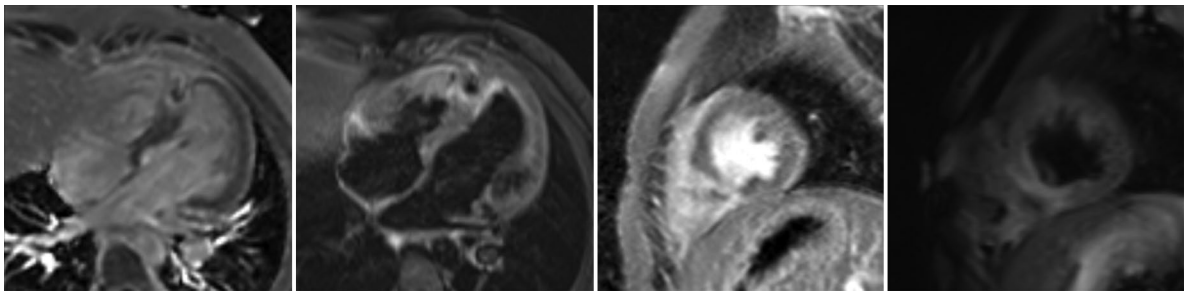

Figure 3. CMR revealing transmural myocardial edema in the apical segment with a hypointense core suggestive of intramyocardial hemorrhage. Post-contrast enhancement of the apical septal segment evincing microvascular obstruction was identified.

normal repolarization in the precordial leads. He was discharged on furosemide and bisoprolol. He remained asymptomatic one month later and, on his last visit, the ECG showed changes in repolarization that were compatible with a subacute myocardial infarction. The echocardiogram showed hyper-refringence of the distal part of the septum and right ventricle apex, as well as a slight dilatation of the left ventricle apex.

Discussion

Myocardial ischemia and infarction are uncommon in children with normal coronary anatomy. Nevertheless, when dealing with acute typical chest pain in a child, this etiology must not be forgotten. A clear protocol workup is needed, and these children may require hospital admission for further investigation, monitoring and treatment, whenever clinical and laboratory findings are indicative. Here we report the occurrence of an AMI caused by an occlusion of the left anterior descending artery in a patient presenting primarily with chest pain after a minor chest injury. Although an AMI in the context of chest trauma is extremely rare, particularly in this age group, no other causative factor was found, despite exhaustive investigation. The mechanisms of coronary occlusion following chest trauma could be the result of intraluminal thrombosis caused by a tear in the intimal layer due to the shear force impacting the coronary artery, embolism to the coronary arteries, vascular rupture, or a vascular spasm at the site of the injury. The left anterior descending artery is the most frequently injured vessel[4]. This patient had no prior artery disease, yet the ECG and echocardiogram were consistent with myocardial infarction confirmed by cardiac catheterization. Catheter-directed thrombolysis was not a management option for this child and conservative treatment with long-term anti-aggregation was the main treatment option. There are no controlled trials to guide early treatment of AMI in the pediatric population and long-term follow-up is necessary[5]. To conclude, AMI in not a common entity in children and its diagnosis requires a high index of suspicion. It may occur as a result of different causes that require different management approaches. However, once the hypothesis is raised, there needs to be prompt and meticulous cardiac testing (including an ECG, echocardiography, and cardiac enzyme levels). Invasive coronary angiography will establish the diagnosis.

Authors' contribution

Catarina Maria Almeida, Sofia Granja and Jorge Moreira: Conception and design of the study, report, review or other type of work or paper. Acquisition of data either from patients, re-search studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. Marisa Pereira: Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. João Carlos Silva: Analysis or interpretation of data either from patients, research studies, or literature. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

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Ethical disclosures

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

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

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

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CASE REPORT

Adolescent with groin pain: case report

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Abstract

Introduction: Avulsion fractures are common in skeletally immature athletes and occur more often in the proximal femur and in the iliac bone. An avulsion fracture of the lesser trochanter is a rare pathology, and it results from a sudden and violent muscle contraction of the iliopsoas muscle during sports practice. Radiography is important for the diagnosis and exclusion of other pathologies. In most cases, symptomatic treatment is recommended, and surgery is reserved for specific situations. **Case report:** We report a clinical case of an adolescent with groin and right thigh pain and impaired gait after kicking a ball during a football match. **Discussion:** The patient underwent a radiographic study, and an avulsion fracture of the lesser trochanter was diagnosed. He was successfully treated with a conservative approach and no sequelae were documented.

Keywords: Adolescent. Avulsion. Femur. Fractures.

Adolescente com dor inguinal: um caso clínico

Resumo

Introdução: fraturas avulsão são comuns em atletas esqueleticamente imaturos e ocorrem mais frequentemente no fémur proximal e osso ilíaco. A fratura avulsão do pequeno trocânter é uma patologia rara e resulta da contração muscular súbita e violenta do músculo iliopsoas durante a prática desportiva. É importante a realização de radiografia para o diagnóstico e exclusão de outras patologias. Na maioria dos casos, o tratamento é conservador e a cirurgia está reservada para casos específicos. **Relato de caso:** Apresentamos um caso clínico de um adolescente com fratura avulsão do pequeno trocânter que iniciou quadro de dor na região inguinal e coxa direita e claudicação da marcha após um remate num jogo de futebol. **Discussão:** O adolescente foi tratado conservadoramente, com boa evolução clínica e sem sequelas.

Palavras-chave: Adolescente. Avulsão. Fémur. Fraturas.

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Keypoints

What is known

– An avulsion fracture of the lesser trochanter is an uncommon injury that should be suspected when a skeletally immature patient presents with painful limping after sports activity requiring forceful hip flexion.

What is added

– This injury can be misdiagnosed, so it is important to perform a complete history and examination to provide the correct diagnosis and treatment.
– Although some patients require surgery, the conservative approach showed excellent results.

Introduction

Avulsion fractures in the proximal femur and iliac bone (at the ischial tuberosity, anterior superior iliac spine, and anterior inferior iliac spine) are relatively common in young athletes. An isolated fracture of the lesser trochanter is rare, especially compared to other fracture sites[1,2].

This pathology affects mostly young male athletes between the ages of eight and 16 years old. Patients usually manifest groin pain, thigh pain, or referred knee pain that is linked to a reduction in strength and range of motion[1,3]. An avulsion fracture of the lesser trochanter should be suspected when a skeletally immature patient presents with painful limping after sports activity requiring forceful hip flexion.

We describe the clinical case of an adolescent with an avulsion fracture of the lesser trochanter, presenting pain in the groin and right thigh and impaired gait.

Case report

A 13-year-old male with prior medical consultations due to lower limb asymmetry and isthmic spondylolysis was observed at a Pediatric Orthopedics consultation. He presented pain and functional limitation of the right lower limb after kicking a ball during a football match two days prior to the evaluation. At the physical examination, he displayed intense tenderness of the groin and right thigh linked to a limitation of active and passive flexion of the right hip. In a sitting position, pain was elicited with further flexion of the right hip (positive Ludloff sign). No edema or deformities were evident. There were no neurological or vascular deficits.

A standard radiograph of the pelvis showed an avulsion of the right lesser trochanter with a deviation of approximately 0.75 cm (Fig. 1) and an avulsion of the right anterior inferior iliac spine was suspected. Nuclear Magnetic Resonance Imaging (MRI) of the hip confirmed the avulsion of the right lesser trochanter and showed a modest degree of apophysitis and traction of the anterior inferior iliac spine, but with no detachment (Fig. 2).

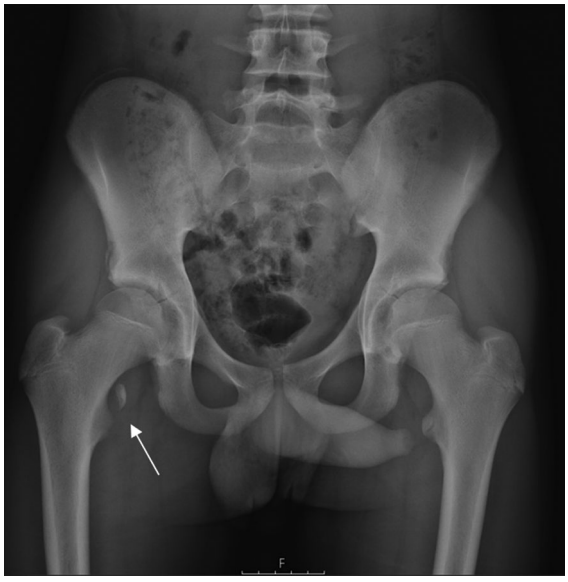

Figure 1. Standard radiograph of the pelvis showed the avulsion fracture of the right lesser trochanter with displacement.

The patient was treated with a conservative approach including analgesics and non-weight-bearing activity followed by partial weight-bearing activity as tolerated, associated with a functional rehabilitation program.

He was re-evaluated at six weeks, with good clinical progression, no pain, normal gait, and symmetrical muscle strength in both lower limbs. A hip radiography was repeated and showed full union of the fracture (Fig. 3).

At this time, the patient returned to sports practice with no restrictions and no sequelae of the lesion were documented.

Discussion

Avulsion fractures occur at points where tendons, ligaments, or muscles are attached to bone. The soft tissue is pulled away from the anchoring site (usually an apophysis), ripping a fragment out of the bone.

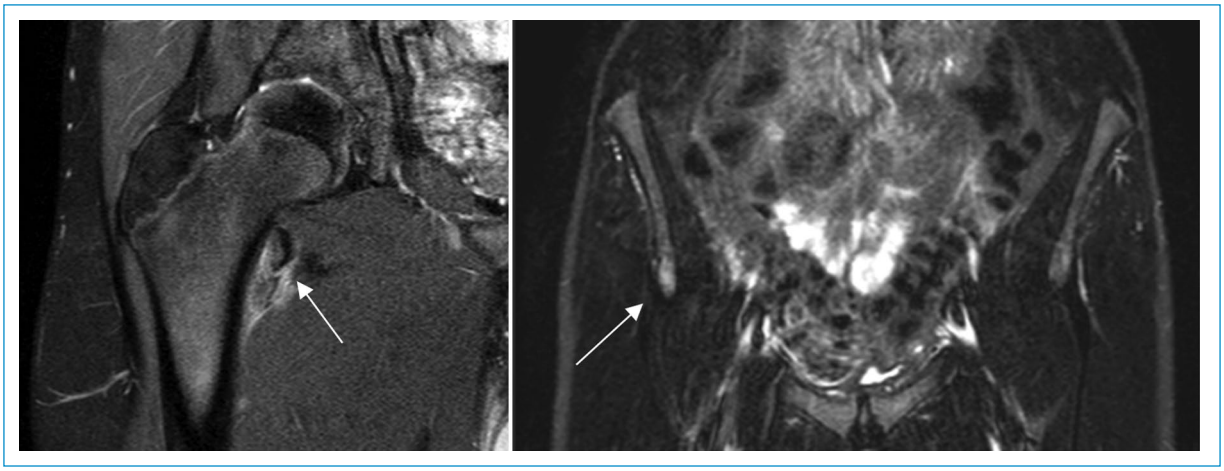

Figure 2. Nuclear Magnetic Resonance Imaging (MRI) of the hip showed the avulsion fracture of the right lesser trochanter and a modest degree of apophysitis of the ante-rior inferior iliac spine, but with no detachment.

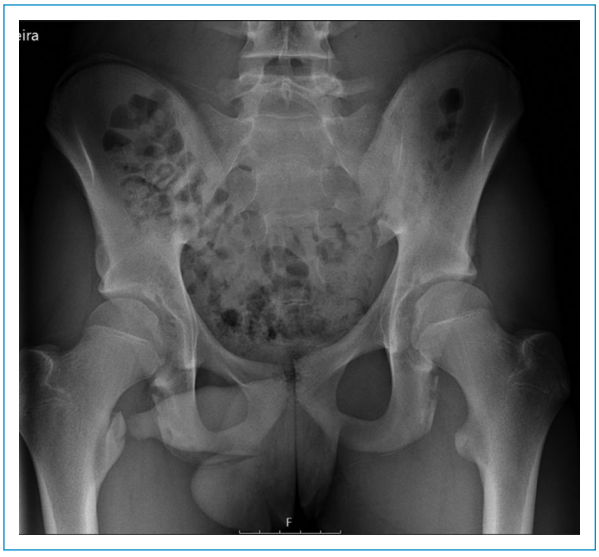

Figure 3. Standard radiograph of the pelvis of same patient at six weeks after the injury, demonstrating full union of the fracture.

Apophyses usually have secondary ossification centers and, therefore, are a vulnerable place for these injuries during the period of skeletal growth. In the pediatric age, the muscle is connected to the apophysis by Sharpey's fibers that are more resistant to tensile force than the junction of cells between the calcified and uncalcified apophysis[4,5]. After skeletal maturity, due to the complete ossification of the growth plates, tendon, ligament, and muscle ruptures are more common than avulsion[1].

Avulsion fractures typically involve the proximal femur and the iliac bone, namely the ischial tuberosity, anterior superior iliac spine, and anterior inferior iliac spine[1,2]. Acute trauma is the most common cause of these injuries. However, some authors reported that avulsion fractures may also be associated with repetitive movements of the lower limb with the hip and knee in flexion. These movements cause tension forces on the distal insertion of the iliopsoas muscle, encouraging fractures of the small trochanter[6,7,8].

An avulsion fracture of the lesser trochanter is a rare injury representing < 1% of hip injuries[2]. It affects mostly young males between the ages of eight and 16 years and is associated with sports activity, usually involving running and jumping[1,2,3]. It is caused by sudden and forceful tensile force applied through a powerful muscle contraction of the iliopsoas during flexion of the thigh[7]. Patients may present with groin pain, posterior thigh, or referred knee pain and reduced strength and range of motion[1]. Physical examination reveals tenderness over the hip and patients are unable to flex the hip in a sitting position (Ludloff sign)[2].

An anteroposterior radiography is essential not only to make the diagnosis, but also to exclude other pathologies, such as Legg-Calvé-Perthes disease or Slipped Capital Femoral Epiphysis. If there is uncertainty, other imaging techniques such has ultrasound or an MRI may be necessary[9,10].

Groin pain is common in adolescents and may have several causes in addition to orthopedic pathology. The child's age, gender, location, and intensity of the pain and associated symptoms may help clarify the diagnosis. In pediatric age, it is important to rule out the presence of genitourinary disorders such as ovarian cyst,

pelvic inflammatory disease, urinary tract infection, nephrolithiasis, testicular torsion, and varicocele. Intra-abdominal pathologies (inguinal hernia, appendicitis, lymphadenitis, and inflammatory bowel disease) may also cause groin pain[11].

With an avulsion fracture of the lesser trochanter, symptomatic treatment is recommended with pain control, non-weight-bearing activity, and a rehabilitation program. Ruffing T et al.[2] showed excellent results with non-operative treatment with all patients returning to competitive sports.

In contrast, many authors have described significant displacement (≥ 2 cm) and late-onset painful sequelae as indications for surgery[1,2]. For example, Khemka A et al.[4] established that surgical treatment of these injuries minimizes the chances of a non-union, secondary loss of muscle strength, and potentially of ischiofemoral impingement.

Physical activity can be resumed within two to three months after the injury, and most athletes return to their original activity levels[1,2].

With a growing participation of adolescents in competitive sports, timely diagnosis and treatment of avulsion fractures is essential to allow a quick return to sports and to avoid long-term disability. Patients should be followed up in consultation to identify possible complications, such as symptomatic pseudoarthrosis or painful exostosis that may require surgical treatment[6].

Authors' contribution

Daniela da Rocha Couto: Bibliographical search, study design, drafting of the article. José Ricardo Oliveira, Bárbara Angélica Choupina de Melo e Sousa, and Mafalda Santos: Critical review of the content of the article.

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

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CASE REPORT

Recurrent infections and short stature – Listening may be the key. A Bloom syndrome case report

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Abstract

Introduction: Bloom syndrome is a rare autosomal recessive disorder characterized by chromosomal instability caused by mutations in the BLM gene that increase the risk of developing neoplasia, particularly at an early age. Bloom syndrome is typically characterized by short stature, photosensitivity, telangiectatic erythema, learning difficulties, immunodeficiency, and malignancy. **Case report:** We report a case of an adolescent girl with short stature and recurrent infections, who does not present typical erythematous sun-sensitive skin lesions to the face and whose high-pitched voice led to the diagnosis of BS caused by a novel L753X mutation. **Discussion:** To date, she has not presented with any malignancy or characteristic malar rash.

Keywords: Bloom syndrome. Chromosomal instability. Sister chromatid exchange. Novel mutation. Case report

Infeções recorrentes e baixa estatura – Ouvir pode ser a chave. Um caso de síndrome de Bloom

Resumo

Introdução: A síndrome de Bloom é uma doença autossómica recessiva, caracterizada por instabilidade cromossómica resultante de mutações no gene BLM, que aumentam o risco de desenvolver neoplasia, sobretudo, em idade precoce. **Relato de caso:** A síndrome de Bloom é caracterizada habitualmente por baixa estatura, fotossensibilidade, eritema telangiectásico, dificuldades de aprendizagem, imunodeficiência e neoplasia. Descrevemos um caso de uma adolescente com baixa estatura e infeções recorrentes, mas sem lesões clássicas eritematosas faciais associadas a fotossensibilidade e cuja voz aguda levou ao diagnóstico de síndrome de Bloom, resultante de uma mutação não descrita previamente, L753X. **Discussão:** Atualmente, a doente não apresenta evidência de neoplasia nem de eritema malar clássico.

Palavras-chave: Síndrome de Bloom. Instabilidade cromossómica. Troca cromatídea irmã. Mutação *de novo*. Caso clínico.

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Keypoints

What is known

- Bloom syndrome is a rare autosomal recessive disorder, characterized by chromosomal instability caused by mutations in the BLM gene.
- Diagnosing Bloom syndrome is challenging because it is a rare condition, but also because of the variations in the severity of its hallmark features.

What is added

- Classic, sun-sensitive facial skin rash features of Bloom syndrome may be absent.
- Awareness of this phenotypic variability without the "hallmark" feature of Bloom syndrome could prevent a diagnostic delay.
- A novel private homozygous variant in BLM (p.L753X) was identified in our patient, which led to the diagnosis of Bloom syndrome.

Introduction

Bloom syndrome (BS; MIM #210900) is a rare autosomal recessive disorder. Ever since the first time it was reported, more than half a century ago[1], fewer than 300 cases are known to the Bloom syndrome registry (BSR)[2]. It has been reported to be more prevalent in populations where the rate of parental consanguinity is higher. In particular, it is more common in the Eastern European Ashkenazi Jewish population, which constitutes about one quarter of the affected families in the BS registry, with a 1% carrier rate[2-5].

BS is characterized by chromosomal instability caused by mutations in the BLM gene, one of the so-called "guardians of the genome"[6], which encodes a RecQ helicase, the BLM helicase (RECQL3)[7]. The BLM helicase is essential to maintaining the structure and integrity of DNA[8], contributing to the preservation of genomic stability[6]. Defects in the BLM gene and the absence of a functional BLM protein lead to chromosome instability, excessive homologous recombination, and a markedly increased rate of sister chromatid exchange (SCE) that is pathognomonic of BS[4]. BS cells are characterized by a SCE rate that is ten times higher than average[9]. The main clinical features of BS include pre- and post-natal growth deficiency, a sun-sensitive erythematous face rash, high-pitched voice, dysmorphic features, varying degrees of immunodeficiency manifested by recurrent respiratory and gastrointestinal tract infections, a predisposition to developing a wide variety of malignancies at an early age, and early-onset type 2 diabetes[2,5,10].

Diagnosing BS is challenging because it is rare, but also because its hallmark features may vary in severity.

We report the case of an adolescent girl of short stature with recurrent infections, who does not present the classic erythematous sun-sensitive skin lesions to the face and whose high-pitched voice led to the diagnosis of BS caused by a novel L753X mutation.

Case report

A 15-year-old girl, the second child of a non-consanguineous non-Jewish family, was born prematurely at 27 weeks of gestation due to severe intrauterine growth restriction and oligohydramnios.

She had a mild cognitive delay, low weight, and symmetric short stature, with normal IGF1 and IGF1-BP3. She reported having recurrent respiratory infections, leading to conductive hearing impairment. She had a long, narrow face (Fig. 1) and a high-pitched voice was noted. She had no skin lesions or sun-sensitive rash. Her neurological and cardiac examinations were unremarkable.

She presented 3-lineage hypogammaglobulinemia and impaired vaccine responses, as well as CD4 and CD8 naïve lymphopenia, but preserved class-switched B cells. Autoimmunity screening was negative (Table 1).

The combination of her extremely short stature, recurrent infections, and high-pitched voice led to the clinical hypothesis of BS and genetic testing revealed a novel private homozygous variant in BLM (p.L753X), inherited from her healthy parents. The nonsense mutation causes a stop gain in the BLM DNA helicase domain and is predicted to be pathogenic by *in silico* prediction methods (CADD score 38). SCE frequency was elevated, thereby confirming the diagnosis (Fig. 2).

She recently developed diabetes mellitus with negative autoantibodies (anti- insulin, anti-tyrosine phosphatase, and anti-glutamic decarboxylase).

Currently, at the age of 19, she is under multi-disciplinary monitoring with no signs of malignancy.

Discussion

In rare diseases, a possible phenotype-genotype correlation is hard to establish due to the limited number of cases and its potential range of manifestations.

Figure 1. Facial features of the patient.

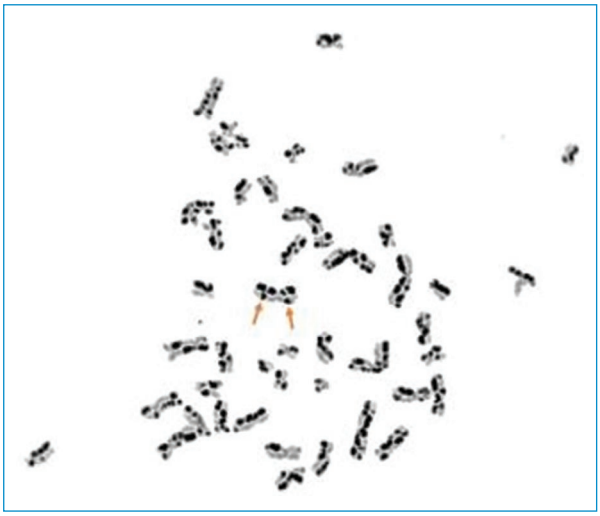

Figure 2. Karyotype of the patient highlighting the increased proportion of sister chromatid exchanges (arrows pointing to examples).

Although BS was first described in 1954, there are currently no clinical diagnostic criteria for BS. The only up-to-date BS patient cohort indicates a likely genetic heterogeneity[3].

In this case report, we describe a 15-year-old adolescent girl with BS. She presented with typical features of this condition, but without the classic feature of erythematous sun-sensitive skin lesions to the face. The clinical features that fit with BS are her pre-natal and post-natal growth deficiency, facial dysmorphism (long, narrow face), high-pitched voice, and recurrent infections. According to the BSR, type 2 diabetes mellitus was identified in 16% of patients, with onset prior to the age of 20 in more than 25% of these[2,7], which resembles our case report.

However, it is surprising that our patient has not reported any symptoms of sun sensitivity or malignancy by the age of 19.

The first symptom described by dermatologist Dr. David Bloom was a face eruption resembling lupus erythematous in addition to bullous eruptions on the lips related to sunlight hypersensitivity[1]. Pigmentation disorders are also frequent, with both hypo- and hyper-pigmented lesions coexisting, mainly on the torso and extremities, leading to the appearance of *café-au-lait* spots[2,7].

However, this "hallmark" feature of BS may not always be present. Indeed, there have been six case reports describing a total of thirteen BS patients, twelve of them in pediatric age, who did not suffer from any facial skin lesions at all[11-16]. Boduroglu et al.[11] reported two siblings, both with BS, where the boy did not show sun-sensitive facial skin lesions but the sister experienced severe sun-related facial skin lesions. There has been some debate about the possible role of environmental factors and gender[11,12]. Conversely, skin lesions are usually milder among female and dark-skin phototypes of BS patients[15,17,18].

A predisposition to developing a wide range of malignancies at an abnormally early age is well described in BS, making it the most serious medical complication seen and the leading cause of death in BS patients[2,4,5,10]. Cancers of virtually any type at any location have been reported[9].

Of particular note, four case reports regarding five pediatric BS patients have no findings suggestive of any malignancy[13,15,19,20], although none had yet reached adulthood. Due to its wide variations and non-specific clinical features, BS diagnosis requires a cytogenetic and/or molecular confirmation.

BS results from mutations in both copies of the BLM gene, which is located on chromosome 15 (band 15q26.1)[21]. German et al.[3] identified multiple recurrent mutations in the BLM gene. To date, 151 different BLM mutations have been described all over the world in different ethnicities, most of them missense/nonsense

Table 1. Laboratory testing

	Patient value	Reference value
Hemoglobin	13.6 x 10 g/L	12.0-16.0
Leukocytes	7.07 x 10 g/L	4.5-13.0
Lymphocytes	2.22 x 10 g/L	1.0-5.3
CD3+T cells	1584.83/µL	1000-2200
CD4+T cells	795.94/µL	330-920
CD8+T cells	756.94/µL	330-920
CD3+CD4+CD45RA T cells	27% ↓	40-95%
CD3+CD8+CD45RA T cells	30% ↓	40-95%
CD19+B cells	343.69/µL	110-570
CD19+CD27+IgD B cells	9.9%	5-120%
CD3- CD16+CD56+NK cells	358.43/µL	70-480
Platelets	405×10 g/L	150-450
IgG	4.17 g/L ↓	6.50-18.50
IgA	0.29 g/L ↓	0.70-4.00
IgM	0.19 g/L ↓	0.40-2.30
Growth hormone	0.166 ng/mL	0.010-3.607
Insulin-like growth factor 1 (IGF1)	522.00 ng/mL	143-693
Insulin-like growth factor binding protein-3 (IGFBP-3)	5.80 ng/mL	2.4-8.4
Anti-diphtheria toxin antibodies (IgG)	0.06 UI/mL ↓	> 0.10: vaccine protection
Anti-tetanus toxin antibodies (IgG)	0.01 UI/mL ↓	> 0.10: vaccine protection
Thyroid peroxidase antibodies (TPO)	< 1.00 UI/mL	< 5.61
Antithyroglobulin antibodies (ATG)	< 1.00 UI/mL	< 4.11
Anti-insulin antibodies (AIA)	Negative	-
Anti-tyrosine phosphatase antibodies (IA2)	Negative < 1	Positive > 2
Anti-glutamic acid decarboxylase (GAD) antibodies	Negative	-
IgA antigliadin antibodies (AGAs)	Negative < 5.2 UQ	< 30
IgG antigliadin antibodies (AGAs)	Negative < 3 UQ	< 30
IgA anti-tissue transglutaminase antibodies (tTG)	Negative < 1.90 UQ	< 30
IgG anti-tissue transglutaminase antibodies (tTG)	Negative < 3.80 UQ	< 30
Anti-smooth muscle antibody (ASMA)	Negative	-
Anti-mitochondrial M2 antibody (AMA-M2)	Negative	-
Liver kidney microsome type 1 (anti-LKM-1) antibodies	Negative	-
Liver cytosol specific antibody type 1 (anti-LC1)	Negative	-

NK: natural killer.

mutations[5]. A common founder mutation (a 6-bp deletion and 7-bp insertion at nucleotide position 2281 in the *BLM* cDNA, commonly known as *blm*Ash) is present in about 1/100 in the Eastern European Jewish population and it is the most common of the BLM mutations. A prevalence of 1:48,000 is estimated for BS in Ashkenazi Jews[3].

BLM is a protein that temporarily links to other compounds to form a complex with the Topoisomerase IIIα (Topo IIIα), RecQ-mediated genome instability protein 1 (RMI1) and 2 (RMI2) and single-stranded DNA (ssDNA)-binding protein.

RPA[22]. This complex (BTR complex or BLM dissolvasome) also has a role in DNA replication repair[23].

In addition to BLM mutations, loss of function mutations in the BTR complex (Topo IIIα, RM1 and RM2) have been implicated in BS-like disorders[3,24,25].

The phenotypic features of patients with biallelic Topo IIIα mutations were identical to those of patients with homozygous BLM mutations in terms of pre-natal growth retardation, microcephaly, and *café-au-lait* spots[24]. However, dilated cardiomyopathy was also reported[24], which is not a typical feature of BS. Interestingly, elevated SCE were also identified but facial malar rash, cancer, and diabetes were not present[24].

Hudson et al.[25] described a milder phenotypic feature in two siblings with a homozygous deletion in the RMI2 gene, who presented a mild growth retardation and *café-au-lait* spots. Similarly to BS, increased SCE were identified. However, both siblings showed no evidence of photosensitivity, recurrent infections, cancer, or diabetes.

Recently, Gönenc[16] demonstrated that pathogenic variants in the different members of the BTRR complex may have a fluctuating impact on phenotype significance, especially when comparing BLM and RM1 associated phenotypes. Patients with pathogenic BLM variants had a major BS phenotype when compared to patients carrying RM1 pathogenic variants. Indeed, none of the patients with RM[1] pathogenic variants presented signs of skin lesions, *café-au-lait* spots, or recurrent infections.

A novel private homozygous variant in BLM (p.L753X) was identified in our patient which led us to the diagnosis of BS. We are not aware of the existence of specific BLM mutations associated with a mild, or even absent, skin facial rash phenotype. Hence, we can only speculate about a possible phenotype-genotype correlation that would have explained the phenotypic variability that is present among BS patients.

There are no evidence-based guidelines for the treatment of BS patients[4,5]. Management consists of monitoring and treating complications. Although most BS patients survive to adulthood, the average age of death is 26[2], usually from cancer. This highlights the importance of early diagnosis and appropriate cancer screening.

Although it was first described more than 60 years ago, there is still little that is known about the clinical and molecular aspects of BS. Indeed, the wide spectrum of clinical manifestations, together with this rarely-remembered entity, contribute towards the underdiagnosis of this disorder worldwide.

Given the high risk of malignancy, close multi-disciplinary monitoring focused on early detection and appropriate cancer treatment are the cornerstones of BS management.

This case report proves that BS does not always present with a sun-sensitive facial skin rash. Awareness of this phenotypic variability without the “hallmark” feature of BS could prevent a delay in diagnosis.

Authors’ contribution

Margarida Almendra: Conceived and designed the study; acquired data from patients, research studies, or literature; analyzed and interpreted data; drafted the article; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. Rosa Pina and Conceição Neves: Critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. João Farela Neves: Conceived and designed the study; acquired data from patients, research studies, or literature; analyzed and interpreted data; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work. Ana Isabel Cordeiro and Catarina Martins: Acquired data from patients, research studies, or literature; analyzed and interpreted data; critically reviewed the article for important intellectual content; gave final approval of the version to be published; agreed to be accountable for the accuracy or integrity of the work.

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CASE REPORT

Bilateral functional ptosis in adolescence: a case report

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Abstract

Introduction: Bilateral eyelid ptosis is an extremely rare form of functional neurological disorder (FND). FNDs are a group of disorders that have in common the absence of a structural pathology of the nervous system and the presence of common neurological symptoms, and can be somewhat challenging in regard to diagnosis, approach, and treatment. **Case report:** We present the case of an adolescent diagnosed with sudden asymmetric ptosis. To consider the different potential diagnoses (cranial polyneuropathy, mitochondrial disease, and neuromuscular junction disorder), the patient underwent several complementary diagnostic tests, which gave inconclusive results. Although there had been no recent stressful events, the observed inconsistency and incongruity, as well as the observation of certain details in the neurological exam, led to a diagnosis of FND. Six days after clinical discharge, the patient recovered suddenly and spontaneously from all neurological problems. **Discussion:** Relevant symptoms and an accurate assessment of psychological factors are fundamental to ensuring a correct diagnosis and positive prognosis.

Keywords: Functional neurological disorder. Functional eyelid ptosis. Child and adolescence psychiatry. Neuropediatrics. Case report.

Ptose funcional bilateral na adolescência: um reporte de caso

Resumo

Introdução: As perturbações neurológicas funcionais (PNF) são um grupo de doenças que têm em comum a ausência de patologia "estrutural" do sistema nervoso e a presença de manifestações neurológicas comuns, constituindo um desafio no que concerne ao diagnóstico, abordagem e tratamento. **Relato de caso:** Apresenta-se o caso clínico de um adolescente com ptose assimétrica de início súbito. Tendo em conta os diagnósticos diferenciais considerados (polineuropatia craniana, doença da placa motora e doença mitocondrial), realizou vários exames complementares que foram inconclusivos. Apesar de não se identificarem eventos stressores recentes, a inconsistência e incongruência observadas, e o reconhecimento de detalhes no exame neurológico permitiu o diagnóstico de PNF. Seis dias após alta, o doente recuperou súbita e espontaneamente de todos os défices neurológicos. A ptose palpebral bilateral é uma apresentação extremamente rara de PNF. **Discussão:** A fenomenologia clínica e a correta avaliação de fatores psicológicos são aspetos essenciais para estabelecer o diagnóstico e para um bom prognóstico.

Palavras-chave: Perturbação neurológica funcional. Ptose palpebral funcional. Pedopsiquiatria. Neuropediatria. Adolescência.

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Keypoints

What is known

- Functional neurological disorders (FNDs) are a highly prevalent group of disorders that present certain challenges in terms of diagnosis, approach, and treatment.
- Eyelid ptosis is a rare form of FND, with only a few cases of functional unilateral ptosis reported.

What is added

- Until this article was published, no cases of bilateral functional ptosis during childhood had been published; this is a unique case.
- Diagnosis of FND without an identified recent stressful event or associated psychopathology – factors that increase the difficulty in correct diagnosis and management.
- Clear and complete description of the clinical judgement behind the evaluation and diagnosis of this case report, enabling the reader to acquire knowledge about functional ptosis and its differential diagnosis.

Introduction

Functional neurological disorders (FNDs) are a group of disorders that have in common the absence of a "structural" pathology of the nervous system and the presence of often persistent and disabling neurological manifestations[1]. These are a group of highly prevalent disorders, representing 16% of the total number of referrals for Neurology consultations[2]. They can be somewhat challenging in terms of diagnosis, approach, and treatment[3], which can result in an excessive consumption of time and resources.

In the last decade, there has been a paradigm shift, recommending a positive approach to FND diagnosis, through the recognition of clinical patterns, rather than a diagnosis based on exclusion or the bizarre and/or unusual character of the semiology[4]. A better understanding of the pathophysiological and neurobiological mechanisms associated with FND[5], such as the identification of alterations in cerebral perfusion or metabolism in associated areas[4], has led to a lesser appreciation of psychological factors as a single and causal explanation. The terms 'conversion' and 'psychogenic' have been replaced by the term 'functional'[6,5], and the presence of psychopathology or the identification of a precipitating stressor is not currently required for diagnosis[7].

The most common manifestations of FND in the field of neuro-ophthalmology are blindness, diplopia, and ophthalmoparesis[8]. Eyelid ptosis is a rare form of FND, with only a few cases of functional unilateral ptosis reported and, until this article was published, no cases of bilateral functional ptosis during childhood had been reported. We present the case of a 14-year-old boy admitted to the Emergency Unit with asymmetric palpebral ptosis.

Clinical case

A 14-year-old male adolescent was admitted to the Emergency Unit with a sudden onset of asymmetric palpebral ptosis, frontal headache, and generalized asthenia. There was no fatigability, appendicular weakness, fever, or symptoms suggesting increased intracranial pressure. Four episodes of right eyelid ptosis in the previous two years were reported, in the context of a respiratory infection of the upper tract, from which he completely recovered following a cycle of antibiotic therapy. No personal history of head or face trauma was reported. The young man lived with his mother and father and was undergoing his 9th year of schooling, displaying medium-low school performance, with several changes in the educational establishment in the last year being described, and periods of school absenteeism.

The neurological examination carried out during admission showed bilateral eyelid ptosis, almost complete closure of the right eye and the left eye had coverage of about one third ptosis of the right eyebrow and elevation of the left eyebrow, more pronounced eyelid creases on the right side, absence of folds on the right in the contraction of the frontalis muscle, and hypoesthesia of the right hemiface including the angle of the mandible. The remaining neurological examination displayed no further changes.

The young man was admitted to the Adolescents Unit and underwent several complementary diagnostic tests, including orbital and cranioencephalic CT and MRI, electromyographic study, and laboratory evaluations (anti-acetylcholine receptor antibodies, ACE measurement, and study of mitochondrial DNA deletions) that were considered unaltered. He underwent a therapeutic test with pyridostigmine (15 mg, 4 id, in one day) that come out negative. During hospitalization, in addition to slight fluctuations, a single episode of total ptosis reversal was observed after the eyelid was forcedly closed and subsequently opened, lasting a few seconds. The Child and Adolescence Psychiatry and Psychology departments followed up his development, and no recent stressful events were identified.

Six days after discharge, in the context of a Neuropediatric Appointment, a sudden and spontaneous recovery of all

neurological deficits was observed. The patient is now accompanied by a district hospital, with no recurrence, as evaluated by telephone interview.

Discussion

Bilateral eyelid ptosis is an extremely rare manifestation of FND[8], especially during childhood[9]. The differential diagnosis of bilateral eyelid ptosis is extensive[10], including cranial polyneuropathy (inflammatory, infectious, or autoimmune), motor end plate disorder, and mitochondrial disorder.

In the clinical case presented, despite not having identified recent stressful events, the inconsistencies and incongruities observed, the recognition of details in the neurological examination, including spasm of the orbicularis muscle, the existence of folds in the upper and lower eyelids, the position of the eyebrows (ptosis and elevation of the left eyebrow), and hypoesthesia of the right hemiface with no anatomical relation to innervation of the trigeminal nerve, as well as the involvement of different specialties, made it possible to establish a diagnosis.

There are some diagnostic clues that make it possible to differentiate functional ptosis from other causes of ptosis, including: (1) the one-sidedness of symptoms, as the bilaterality of the symptoms in the clinical case presented prolonged the etiological investigation and made the final diagnosis difficult; (2) the exposure to stress factors or adverse life events that, though not necessary for a diagnosis, constitute an important clue[11]; (3) the presence of details in the neurological examination, including (a) the position of the eyebrows: on the ptosis side, there may be ptosis of the eyebrow[10], while on the contralateral side, the eyebrow is higher, which is due to the spasm of the frontal muscle to compensate for the decreased activity of the levator palpebrae muscle on the same side; (b) the existence of folds in the upper and lower eyelids due to the spasm of the orbicularis oculi muscle[10]; (c) inverse lower eyelid ptosis[9]; (d) no attempt by the patient to open the eye using the fingers or tilt the chin[8].

FNDs are a very heterogeneous group of pathologies, requiring careful assessment and holistic discussion, involving collaboration between several specialties[3]. An error or delay in establishing a diagnosis can bring harm to the patient, namely by subjecting him/her to unnecessary diagnostic and therapeutic methods, affecting the prognosis. Reliable knowledge about the expected manifestations of a given clinical syndrome, associated with the recognition of clinical patterns, will pave the way for a positive approach to diagnosing FNDs.

Authors' contribution

Sofia Vaz Pinto: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Analysis or interpretation of data either from patients, research studies, or literature; Drafting the article; Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work. Ana Isabel Gonçalves and Inês de Oliveira: Conception and design of the study, report, review or other type of work or paper; Acquisition of data either from patients, research studies, or literature; Final approval of the version to be published; agreement to be accountable for the accuracy or integrity of the work. Andreia Pereira: Critical review of the article for important intellectual content; Final approval of the version to be published; Agreement to be accountable for the accuracy or integrity of the work.

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Conflicts of interest

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

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

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Hyperpigmentation in toes resembling ischemia: a challenging diagnosis

Hiperpigmentação nos dedos dos pés assemelhando-se a isquemia: um diagnóstico desafiante

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Keypoints

What is known

- Some insects, such as beetles, release vesicant and irritating substances when threatened.
- Skin lesions due to human contact with these substances occur mostly in tropical regions and are rarely found in literature.

What is added

- A differential diagnosis can be challenging as the skin lesions can resemble potentially more serious pathologies, such as tissue necrosis.
- It is important to be aware of, and able to recognize, this entity in order to prevent misdiagnosis.

A healthy six-year-old male child was seen at the emergency department for ischemic-appearing dark macules on the extremities of the first two toes on his left foot (Fig. 1). The lesions appeared about 30 minutes after removing his shoes and noticing an insect inside his footwear (Fig. 2). He did not complain of pain, itching, stinging sensation, or any other symptoms. On examination, the child appeared well, had normal vital signs, and no obvious portal of entry or signs of inflammation were seen. Pedal pulses were palpable and symmetrical, and the sensory examination of the extremities was normal. The picture taken by the parents revealed a beetle, which led to the hypothesis that the lesions originated from contact with a substance released by the insect. The area was irrigated with a saline solution and skin hydration was recommended for the following days. The lesions resolved completely within two weeks, with no complications or further symptoms.

Similar cases are rarely found in literature, occurring mostly in tropical regions. These substances have vesicant and irritating properties and are released when the insect feels threatened. They can cause lesions that range from vesicles and blisters, resembling other pathologies such as contact dermatitis and herpetic infection, to hyperpigmented spots, as in this case, simulating tissue necrosis and that can persist for months. There is a risk of secondary infection as well as the possibility of systemic symptoms, such as fever, nausea, and vomiting. It is recommended to disinfect and clean the skin with soap. In some cases, treatment with corticosteroids is advised[1,2].

The authors emphasize the importance of recognizing this entity which, despite the favorable outcome of this case, provides a differential diagnosis with potentially more serious pathologies. Both the anamnesis and physical examination were essential to the differential diagnosis, therapeutic approach, and reassurance given by caregivers.

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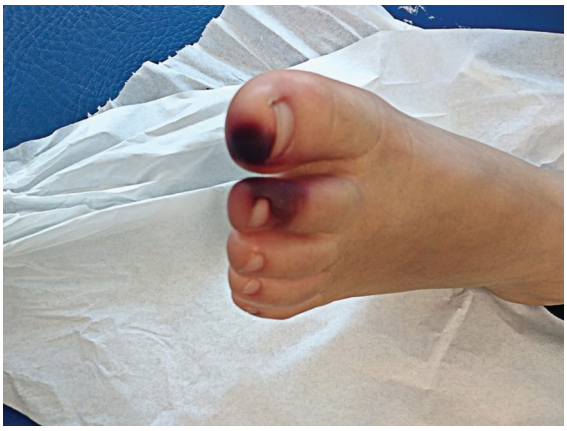

Figure 1. Dark purple macules resembling ischemia on the left foot, namely on the tip of the first toe, interdigital surface and the second toe, with no plantar involvement.

Figure 2. Picture of the beetle removed from the child's shoe.

Authors' contribution

Maria Miguel Resende and Tomás Ferrão: Conception and design of the study, report, review or other type of work or paper. Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Drafting the article. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work. Manuel Cordeiro and Inês Sobreira: Conception and design of the study, report, review or other type of work or paper. Acquisition of data either from patients, research studies, or literature. Analysis or interpretation of data either from patients, research studies, or literature. Critical review of the article for important intellectual content. Final approval of the version to be published. Agreement to be accountable for the accuracy or integrity of the work.

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