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EDITORIAL

Interpreting manuscript rejections

David Lito

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When submitting a manuscript, authors hope to see the results of his scientific production recognized by their peers and add something relevant to scientific knowledge. However, it is not uncommon for a manuscript to be rejected, leading to the authors' frustration and outrage.

There are several reasons why a manuscript is rejected[1]. Firstly, it may be rejected due to the lack of quality of the data, which includes the lack of compliance with legal requirements (indication of authorial responsibility, informed consent, privacy, or plagiarism), the lack of originality, and the lack of quality of the data presented, namely the statistical analysis (when applicable) and the inferences drawn from it (discussion and conclusions).

The editorial board's rejection of manuscripts can have some positive aspects for authors, as it allows them to correct and improve the manuscript for subsequent submission to the same or another journal.

On the other hand, a journal's rejection rate can provide important information to readers and the scientific community about the journal itself. Therefore, journals with the highest rejection rates will be the most demanding as they scrutinize manuscripts more rigorously. At the same time, they have the highest number of submissions, which allows them to select the best ones.

Thus, like most scientific journals, at Portuguese Journal of Pediatrics (PJP), manuscripts can be rejected at various stages of the process: immediately after submission, if they do not comply with the instructions for authors, after preliminary analysis by the editors (first-line rejection), or after analysis by reviewers. Since this editorial team began working in January 2022, 443 manuscripts have been analyzed, of which around 43% were rejected. By comparison, rejection rates can reach 78% in JAMA, or 39% in Parasites & Vectors[2,3]. These numbers honor the PJP because of the number of submissions and because the rejection rate can reflect the rigor that we want to imprint on the scientific journal of the Portuguese Society of Pediatrics.

To facilitate the work of authors, editors, and reviewers, the PJP made it mandatory for each manuscript to indicate "What is added." In response, the author(s) must state what is innovative about the manuscript, even if it is a detail.

I want to express my gratitude to the authors who chose PJP to publish their research and to the associated editors and reviewers who, pro bono, collaborate assiduously and committedly with PJP.

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ORIGINAL ARTICLE

Effects of COVID-19 lockdown on lifestyle behaviours among children living in urban Mysuru – A cross sectional study

Prajwala Hassan-Vasudev, Deepak Anil, Vijaylakshmi Rao-Vadaga, and Jose J. Thomas*

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Abstract

Introduction and Objectives: Getting enough exercise, preventing a sedentary lifestyle, and getting enough sleep all work together to promote healthy childhood growth. Although the COVID-19 outbreak affected children's day-to-day lives, it is unclear how much it may have impacted their development. Therefore, this study aims to gather information regarding the impact of the COVID-19 lockdown on parents and their children. **Methods:** A cross-sectional, online-based survey questionnaire was given to 71 parents aged 21 and above with children aged between three and five, residing in Mysuru. The paired t-test, McNemar's and Wilcoxon signed-rank tests were used to check associations between the selected variables and lockdown-related changes. A p-value of less than 0.05 was considered statistically significant. **Results:** There was a large increase in the consumption of homemade food (90.1%), self-feeding (34.3%) and an improvement in the household practices of cooking, storing, and feeding (95.8%) during the lockdown period. 56.3% of the parents were able to get their children more engaged in physical activities. The time that parents spent with their children increased during the lockdown period. Screen time and sleep duration also increased during the lockdown, which showed statistical significance. **Discussion:** Short-term changes in children's lifestyle habits in response to COVID-19 are concerning because they may raise their risk of obesity, diabetes, and cardiovascular disease. Initiatives to improve physical activity and reduce sedentary behavior in children are needed to prevent long-term health issues.

Keywords: COVID-19. Children. Physical activity. Sedentary lifestyle. Screen time.

Efeitos do confinamento pela COVID-19 no estilo de vida de crianças que vivem em Mysuru urbana – Estudo transversal

Resumo

Introdução e Objetivos: A promoção de um crescimento infantil saudável decorre da prevenção dos estilos de vida sedentários e de um tempo de sono suficiente. Apesar de ter afetado o dia a dia das crianças, desconhece-se o impacto da pandemia COVID-19 no desenvolvimento. Assim, este estudo pretende obter informação sobre o impacto do confinamento decorrente da pandemia COVID-19 nos pais e nas crianças. **Métodos:** Estudo transversal, baseado num questionário online realizado a 71 progenitores (idade superior a 21 anos) de crianças de três a cinco anos, residentes de Mysuru. Foram utilizados os seguintes testes estatísticos: t-test, Mc Nemar e Wilcoxon para as associações entre as variáveis selecionadas e as mudanças relacionadas ao lockdown. As diferenças com valor de $p < 0,05$ foram consideradas estatisticamente significativas. **Resultados**: Durante o confinamento, aumentou significativamente o consumo de alimentos confecionados em casa

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(90,1%), a alimentação individual (34,3%) e os cuidados de higiene durante a confeção, armazenamento e alimentação (95,8%). 56,3% dos pais conseguiram envolver mais seus filhos em atividades físicas. O tempo partilhado entre pais e filhos aumentou durante o período de confinamento. O tempo ecrã e a duração do sono também aumentaram de forma estatisticamente significativa. **Discussão:** As mudanças a curto prazo nos hábitos de vida das crianças em resposta ao confinamento pela COVID-19 preocupam, pois podem aumentar o risco de obesidade, diabetes e doenças cardiovasculares. São necessárias iniciativas para melhorar a atividade física e reduzir o sedentarismo de modo a prevenir problemas de saúde a longo prazo.

Palavras-chave: COVID-19. Crianças. Atividade física. Estilo de vida sedentário. Tempo de tela.

Keypoints

What is known
- COVID-19 has resulted in considerable modifications to daily life.
- Getting enough exercise, preventing a sedentary lifestyle, and getting enough sleep promote healthy childhood growth.
- During the time of COVID-19, physical activity decreased, sleep patterns were disrupted, and sedentary behavior and screen time also increased.

What is added
- Parents made new dishes of nutritional value which increased consumption of homemade foods and reduced the consumption of junk food.
- Parents were able to get their children more engaged in physical activities.
- Parents became more frequently involved in their children's activities such as storytelling/singing during bathing, feeding, etc. during the lockdown period.

Introduction

The COVID-19 outbreak was declared a global pandemic by WHO on January 30, 2020, and as of January 12, 2022, over 312,173,462 confirmed cases had been diagnosed in over 130 countries, resulting in about 5,501,000 deaths. In India, there were 35,875,790 confirmed cases and more than 450,000 deaths as of January 3, 2022[1]. COVID-19 is highly contagious and can be transmitted from person to person through direct contact or droplets from an infected person's coughing or sneezing. Fever, headache, dry cough, and diarrhea are some of the primary symptoms while respiratory symptoms include rhinorrhea, sore throat, sneezing, pneumonia, and acute respiratory distress syndrome[2,3]. This led to over 100 countries mandating social distancing, often known as 'lockdown', to minimize the rate of COVID-19 transmission. As a result of these lockdowns, jobs, education, travel, and recreation were disrupted, as were levels of physical activity, leading to a rise in sedentary behavior[4].

The COVID-19 pandemic poses a direct threat to human health, but the controlled lockdown may also have had an indirect impact on health. The Indian government implemented one of the world's largest lockdowns on March 25, 2020, consisting of non-pharmaceutical interventions (NPIs) such as physical separation and limits on non-essential travel to slow the spread of the virus and minimize peak incidence[5,6]. Even though children appear to have a lower risk of severe infection, these actions may have had a significant impact on their lifestyle. The controlled lockdown may have had an impact on children's levels of physical activity. Even though indoor physical activity can help with overall levels, the advantages of playing outside and in nature are obvious. Physical activity decreased, sedentary behavior and screen time increased, and sleep patterns were disrupted as a result of this pandemic. There is strong evidence that spending time outside and in nature promotes healthy movement habits in children and adolescents, allowing them to get more daily physical exercise, engage in less sedentary behavior, and sleep better[7,8]. Given the enormous and ongoing changes in child and family lifestyles throughout the pandemic, there is a growing feeling that the COVID-19 virus epidemic and accompanying restrictions will have major long-term physical and mental health repercussions for young people and their families[9].

The COVID-19 virus outbreak has resulted in considerable changes to children's, young people's, and families' daily lives, with precise suggestions and restrictions varying from country to country. Most children and teenagers were being home-schooled or learning through online activities, which replaced school attendance. Families were seeking guidance and solutions to maintain healthy routines, including healthy movement behavior and opportunities to spend time outdoors, during the initial response to the COVID-19 outbreak and guidelines for physical distancing, behavior restrictions, and overall instructions to stay home[10,11].

Therefore, it is essential to understand the change in physical inactivity and sedentary lifestyle due to the lockdown among both children and their parents. This study, therefore, aims to gather information regarding the impact of lockdown due to COVID-19 on physical activity, sleep, and lifestyle changes associated with the COVID-19 lockdown.

Methodology

A cross-sectional study was conducted after the COVID-19 lockdown period from March to May 2022. A purposive sampling method was used for recruiting parents from the general population living in urban Mysuru. Data were collected using a web-based E-survey link that was shared among the participants. The inclusion criteria were parents aged 21 or above, living in Mysuru, and with a child aged between three and five. Professionals who were unable to fill out the questionnaire due to a lack of a Facebook/WhatsApp/Instagram account or lack of a smartphone were excluded from the study. The study was approved by the institutional ethics committee. The survey's purpose and procedure were added to the web-based E-survey. The participant's consent was deemed to be given when they completed the survey and submitted it successfully. Within the survey questionnaire, there was no separate declaration seeking consent.

The required sample size for this online survey was calculated using the formula for estimating proportions:

$$\text{Sample size, } n = \frac{Z^2PQ}{L^2}$$

where Z = 1.96; P = 90% for the online survey response rate, Q = (100-P) and d = 7%.

As a result, the required minimum number of participants for this study was calculated to be 71. The option in Google Forms that prevents the submission of partially-answered or partially-filled in items made it impossible to submit an incomplete survey form. As a result, when the number of responses reached 71, the web-based open E-survey link was closed and responses were analyzed.

Before the web-based open E-survey questionnaire was given to the real study population, a pilot study was conducted on 30 healthcare professionals who were later eliminated from the research. The objective of the pilot study was two-fold: first, to test and develop research methods, and second, to impose the type of analysis and processes that would be required when the questionnaire was developed. The Cronbach's alpha score is 0.821. As a result, the material validity and reliability of the instrument were established.

The questionnaire contained 2 parts: part 1 included details regarding socio-demographic factors like gender, education, occupation, total family members, monthly family income, area of residence, etc. and part 2 included changes in the behavior of the child during lockdown and after lockdown, like food intake, self-feeding, hygiene practices, physical activities, screen time, time spent with parents, sleep duration, etc. Thus, a draft of the web-based open E-survey questionnaire was created.

Statistical analysis: the data collected were entered in a Microsoft Excel 2019 spreadsheet followed by analysis using SPSS version 26 (Statistical Package for the Social Sciences) Windows, Version 26.0. (IBM Corp. Released 2019. IBM SPSS Statistics for Armonk, NY, USA). The demographic factors such as gender, education, occupation, income, etc. were represented using percentages. The associations between the selected variables and lockdown-related changes were found using the paired t-test, McNemar's test and Wilcoxon signed-rank test. The data distribution was represented using appropriate tables. A p-value of less than 0.05 was considered statistically significant.

Results

Using an online questionnaire, 71 responses were collected from participants. Descriptive analysis of the demographic details of the participants showed the following findings (Table 1).

From the above table, we see that the majority of the participants i.e., 41 (57.3%) were females. The majority of the fathers were graduates (36 [50.7%]) followed by 31 (43.7%) of whom were postgraduates. Among the mothers, 41 (58.6%) were graduates followed by 24 (34.3%) and 6 (7.1%) who had postgraduate and high school qualifications respectively.

A higher proportion of the fathers (40 [55.7%]) and 21 (29.5%) of the mothers were in professional positions.

The majority belonged to a nuclear family type (47 [66.2%]) and 64 (90.2%) of the participants were from the urban area. The median number of family members was found to be four and the median number of siblings was one.

From table 2, it is seen that there was a great increase in the consumption of homemade food (64 [90.1%]) during the lockdown period. Though there was no increase in food intake (38 [53.6%]), there was an increase in self-feeding (32 [45.1 %]) during the

Table 1. Demographic characteristics of the participants (n = 71)

Variable	Characteristics	Frequency (n)	Percentage (%)
Gender of the child	Male	30	42.3
	Female	41	57.3
Education qualification of the father	Postgraduate	31	43.7
	Graduate	36	50.7
	Intermediate/diploma	2	2.8
	High school	2	2.8
Education qualification of the mother	Postgraduate	24	34.3
	Graduate	41	58.6
	High school	6	7.1
Occupation of the father	Legislators, senior officials, managers	1	1.4
	Professional	40	55.7
	Technicians and associate professionals	13	18.6
	Clerks	2	2.9
	Skilled worker and shop and market sales	13	18.6
	Skilled agriculture and fishery worker	2	2.9
Occupation of the mother	Professional	21	29.5
	Technicians and associate professionals	17	23.9
	Clerks	3	4.2
	Skilled worker and shop and market sales	3	4.2
	Unemployed/homemaker	27	38.2
Type of family	Nuclear	47	66.2
	Joint	22	30.9
	3rd generation	2	2.8
Area of residence	Rural	7	9.8
	Urban	64	90.2

lockdown. The participants also felt that there was an improvement in the household practices of cooking, storing, and feeding (68 [95.8%]) during the lockdown.

55 (78.6%) participants agreed that they had tried new dishes of nutritional value during the lockdown period which was probably also reflected in the reduction of junk food consumption (58 [82.9%]) during the lockdown.

40 (56.3%) of the parents felt that they were able to get their children more involved in physical activities and 60 (84.5%) of them became more frequently involved in their children's activities, such as storytelling/singing songs during bathing, feeding, etc. during the lockdown period (Fig. 1).

From table 3, we find that in the majority, the amount of time spent (in hours) with the children after the lockdown was less than five hours in 29 (41.4%) while the time spent had increased to 5-10 hours for 34 (48.6%) of the parents during lockdown. Using Mc Nemar's test, the amount of time spent by the parents with their children during and after lockdown showed a statistically significant increase ($p < 0.0001$). This difference was also significant using the Wilcoxon signed-rank test for comparing the average time spent during and after lockdown.

When the parents were asked if screen time had increased during the lockdown, 56 (78.8%) of the parents replied 'yes' while 15 (21.2 %) of the parents replied 'no'. The Wilcoxon signed-rank test for comparing the average time spent during and after lockdown shows a statistically significant difference ($p = 0.001$) (Table 4).

31 (43.6%) parents felt that their children's sleep duration increased during the lockdown while 40 (56.4%) did not find any difference in sleep duration. When a paired t-test was applied for analyzing sleep duration during and after the lockdown, it showed statistical significance ($p < 0.001$) (Table 5).

From figure 2 we see that during and after the lockdown the mother was the chief caretaker of the child followed by the father and grandparents.

Discussion

This study was carried out to assess physical activity and sedentary behavior in children and their parents to assess the impact of the COVID-19 pandemic. According to this study, during the lockdown period, there was a substantial increase in the consumption of homemade meals, an improvement in cooking, storage, and feeding activities, as well as a decrease in junk food intake. The

Table 2. Descriptive analysis of the responses by the parents

Question	Yes	No
	n (%)	n (%)
Do you think your child's food intake was higher during the lockdown, compared to afterwards?	33 (46.4)	38 (53.6)
Was there an increase in the consumption of homemade food compared to readymade food (Maggi, Cerelac, etc.) during the lockdown period?	64 (90.1)	7 (9.9)
Was your child's self-feeding better during the lockdown period?	32 (45.1)	39 (54.9)
Were the household practices of cooking, storing, and feeding better during the lockdown period?	68 (95.8)	3 (4.2)
Were any new dishes with nutritious foods tried during the lockdown period?	56 (78.9)	15 (21.1)
Did junk food consumption go down during this period?	59 (83.1)	12 (16.9)
During the lockdown, were you able to get your children more involved in physical activities than usual?	40 (56.3)	31 (43.7)
Did you engage more frequently with your children in storytelling/singing songs etc., while bathing or feeding during this period?	60 (84.5)	11 (15.5)

Table 3. Frequency table showing the amount of time parents spent with their child

Question	Frequency (n)	Percentage (%)
The duration of time spent with the child in a day (in hours) after the lockdown		
< 5 hours	29	41.4
5-10 hours	26	37.2
10 hours	15	21.4
The duration of time spent with the child in a day (in hours) during the lockdown		
< 5 hours	8	11.4
5-10 hours	34	48.6
10 hours	28	40.0

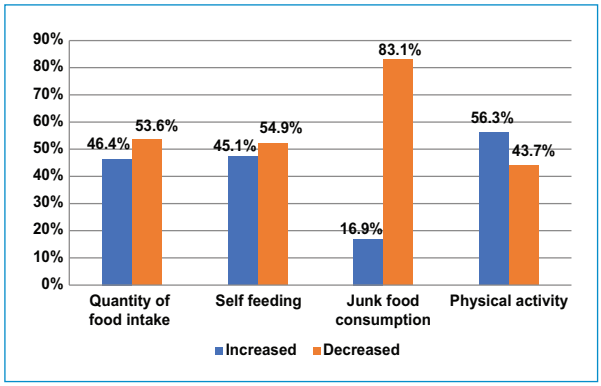

Figure 1. Changes during lockdown.

Table 4. Impact of lockdown on screen time and parenting

Variables	Category	Median	IQR	p-value
Screen time (hours)	After lockdown	1.5	1-2	< 0.001*
	During lockdown	4	2-6	
Time spent by parent with child (hours)	After lockdown	5.50	4-10	< 0.001*
	During lockdown	10	6-15	

*Wilcoxon signed rank test.

majority of the parents were able to get their children more involved in physical activities, and they became more regularly involved in their children's activities such as storytelling/singing songs while washing, feeding, and so on. Furthermore, the amount of time spent with the children increased during the lockdown period. The study also found that the children's screen time and sleep duration increased during lockdown compared to the post-lockdown period.

This study showed an increase in the consumption of homemade meals and a decrease in junk food intake. This was different when compared to a study carried out in Italy by Angelo Pietrobelli et al. where there were no changes in reported vegetable and fruit intake while the intake of potato chips, red meat, and sugary drinks increased significantly during the lockdown[12]. Another study conducted by Rubén López-Bueno et al. in Spain, showed a reduction in daily fruit and vegetable consumption during the COVID-19 confinement[13].

In our study, the majority of the parents were able to get their children more involved in physical activities,

Table 5. Impact of lockdown on sleep

Variables	Category	Mean	SD	t	p-value
Duration of sleep (hours)	After lockdown	8.74	2.357	–4.943	< 0.001*
	During lockdown	9.63	2.051		

*Paired t-test.

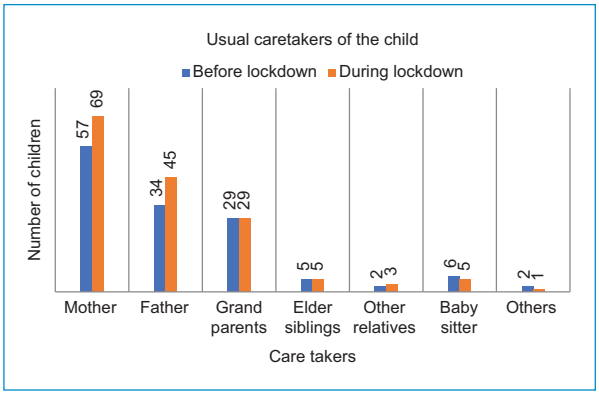

Figure 2. Multiple bar diagram showing the child's caretakers during and after the lockdown.

and they became more regularly involved with their children while different studies carried out around the world showed a negative effect of the COVID-19 pandemic on physical activities. 36 percent of parents in the US, 94 percent of parents in South Korea, and 42 percent of parents in the Netherlands said their child was less physically active during the COVID-19 epidemic than they were before the pandemic[14-16]. However, a study carried out in Germany by Steffen C. E. Schmidt et al. reported an increase in habitual physical activity among children and adolescents, similar to our study[17].

According to our data, screen time increased during the lockdown compared to the post-COVID period. This was in line with previous studies around the world[12,18,19].

Our study's findings also showed that there was a significant change in sleep duration during the pandemic period. This was in line with earlier studies that had been carried out globally during the pandemic[12,13,20,21].

Our study adopted an open, web-based E-survey methodology. The cost-effectiveness, minimal time commitment, participant accessibility, and environmental friendliness of the survey method were strengths to this study. Some of the limitations of our study include the small sample size, the parent-report design of the study, and the potential for recall bias. Furthermore, the findings might not apply to other countries. Future research should evaluate the COVID-19 virus outbreak's long-term effects as well as the changes in children's and adolescents' activity patterns.

Conclusion

The results demonstrate that, on average, the children's food habits improved and parents were able to enhance their children's participation in physical activity while the children's screen time and sleep duration increased during lockdown in comparison to the post-lockdown period. To avoid long-term health concerns during the present and potential future pandemics, initiatives to increase physical activities and limit sedentary behavior, particularly screen time, in children are needed, otherwise, beyond the immediate impact of viral infection, the devastating COVID-19 pandemic will have unintended consequences.

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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 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.

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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PORTUGUESE JOURNAL OF PEDIATRICS

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ORIGINAL ARTICLE

The impact of the pandemic on sports practice: a school-based study

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Abstract

Introduction and Objectives: Sports practice (SP) encourages physical, cognitive, and behavioral growth in children and adolescents. The COVID-19 pandemic significantly disrupted SP among children and adolescents, leading to increased screen time and sedentary behavior. We aimed to evaluate the variables that affected SP during lockdown and after its conclusion. **Methods:** In a cross-sectional survey conducted between April and June 2022 in multiple schools in the districts of Porto, Vila-Real, and Viseu, an SP evaluation questionnaire was given to parents and students enrolled in basic education. **Results:** 330 children and adolescents aged six to 15 took part, with similar numbers of males and females, of whom 28 had comorbid conditions. A third of their parents practiced sports. 186 (56%) of the participants were engaging in physical activity outside of school, with competition accounting for 43% of that. The SP of the participants was influenced by the parents' SP (father: $p = 0.01$; mother: $p = 0.01$) and the parents' educational level (father: $p = 0.01$; mother: $p = 0.01$). During the lockdown period, 91% of students suspended SP, of whom 23% did not resume said activity. Parental SP (parent $p = 0.03$; mother $p = 0.02$) and competitive SP ($p = 0.05$) accounted for a quicker return to sports activity. Competitive SP ($p < 0.01$) was the factor that had the most immediate impact on an early return to sport. **Discussion:** Sport is crucial for fostering children's and adolescents' relationships, which have been hampered by the COVID-19 pandemic. To encourage children and young people to participate in SP and move toward healthy living from a physical, mental, and social perspective, it is crucial to emphasize parents' role in forming new habits in children and adolescents.

Keywords: Sports. School health services. COVID-19.

O impacto da pandemia na prática desportiva: um estudo de base escolar

Resumo

Introdução e Objetivos: A prática desportiva (PD) promove o desenvolvimento físico e cognitivo-comportamental das crianças e adolescentes. A pandemia da COVID-19 levou a uma diminuição significativa da participação desportiva entre crianças e adolescentes, levando ao aumento do tempo de ecrã e ao comportamento sedentário. Pretendemos avaliar as variáveis que afetam a PD e a sua retoma após um período de inatividade. **Métodos:** Num inquérito transversal realizado entre abril e junho de 2022 em diversas escolas dos distritos do Porto, Vila-Real e Viseu, foi aplicado um questionário de avaliação de SP aos pais e alunos do ensino básico. **Resultados:** Participaram 330 crianças e adolescentes dos 6 aos 15 anos, com distribuição semelhante entre os sexos, dos quais 28 apresentavam comorbidades. Um terço dos pais praticava desporto.

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186 (56%) dos participantes praticavam atividade física fora da escola, sendo a competição responsável por 43% disso. A PD dos participantes foi influenciada pela PD dos pais (pai: p = 0,01; mãe: p = 0,01) e pela escolaridade dos pais (pai: p = 0,01; mãe: p = 0,01). Durante o período de confinamento, 91% dos estudantes suspenderam a PD, 23% dos quais não retomaram. Um retorno mais rápido à PD foi explicado pela PD parental (pai: p = 0,03; mãe: p = 0,02) e PD competitiva (p = 0,05). A PD competitiva (p < 0,01) foi o fator que teve impacto mais imediato no regresso precoce ao desporto. **Discussão:** A PD é fundamental para fomentar o relacionamento entre crianças e adolescentes e foi prejudicada pela pandemia da COVID-19. Para incentivar crianças e jovens à PD, e avançarem em direção a uma vida saudável do ponto de vista físico, mental e social, é fundamental compreender e incentivar os pais no seu papel de formação e promoção de novos hábitos nas crianças e adolescentes.

Palavras-chave: Desporto. Saúde escolar. COVID 19.

Keypoints

What is known
- Sports practice is important for child development.
- There has been a drastic drop-in sports practice in recent years, in pediatric age.

What is added
- Parents' sports practice is a predictor of their children's sports practice.
- Children who play competitive sports are more likely to resume some kind of sports practice after a period of lockdown.

Introduction

In today's society, marked by technology and industrialization, daily activities require less and less physical effort[1]. Children, often following the example of adults, are also increasingly sedentary. To combat a sedentary lifestyle and promote healthier lifestyle habits, in Portugal, Physical Education is part of the Basic Education curriculum, a discipline that promotes sports practice (SP) to encourage the development of fundamental psychomotor skills, required by the different stages of motor, cognitive, social and affective development[2].

It is in basic education that these abilities are put to the test, and it is also at this age that children begin to develop the habits that will shape their future lifestyle. For a healthy lifestyle, several factors of everyday life need to be in balance. SP, healthy eating and living together in groups are important, but the attraction to screens and fast food often distances children from this goal. There is a vast amount of literature showing that the progressive increase in screen time and the sedentary lifestyle, associated with the current pandemic situation and the consequent lockdowns, led to a drastic drop in SP in children in 2020-2021[3,4].

Thus, in this phase of the aftermath of the pandemic, it is important to recover pre-pandemic levels of SP in order to then focus on the objective of achieving, and eventually surpassing, the targets proposed by the WHO for the practice of physical exercise by 2030[5].

Taking this information into account, the main objectives of this study were to evaluate the factors that influenced SP in children and adolescents of basic education and the factors that lead to the return to sports after a period of inactivity (lockdowns implemented by the government as an almost mandatory period of inactivity) among children and adolescents with regular SP out of school. The factors that contributed to an earlier return to SP were then also evaluated.

Methods

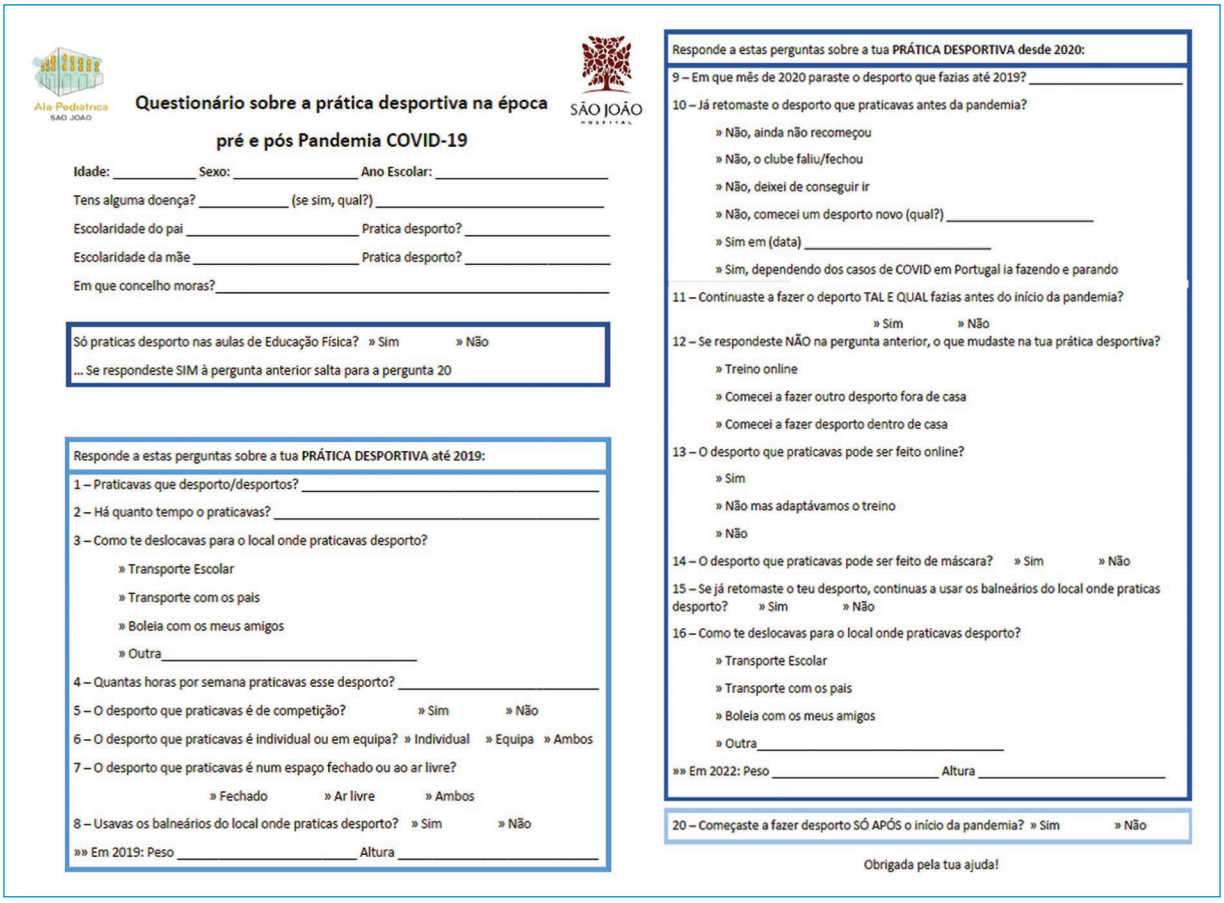
Type of study and participants

School-based cross-sectional study in which guardians and students from primary schools in the districts of Viseu and Porto were interviewed, after approval by their educational council. Information was collected between April and June 2022.

Assessment of physical activity

A questionnaire was developed based on pre-existing questionnaires for the qualitative assessment of physical activity[6], which could be answered in person and online (via Google Form©).

The questionnaire (Fig. 1) was divided into 2 parts: SP assessment until 2019 (the year prior to the start of the COVID-19 pandemic) and SP assessment after the start of the pandemic. To begin with, clinical data (comorbidities, weight and height), demographic information (age, education, location) and SP details of the parents and children were evaluated. It was assessed



Questionário sobre a prática desportiva na época pré e pós Pandemia COVID-19

Idade: _____ Sexo: _____ Ano Escolar: _____

Tens alguma doença? _____ (se sim, qual?) _____

Escolaridade do pai _____ Pratica desporto? _____

Escolaridade da mãe _____ Pratica desporto? _____

Em que concelho moras? _____

Só praticas desporto nas aulas de Educação Física? » Sim » Não

... Se respondeste SIM à pergunta anterior salta para a pergunta 20

Responde a estas perguntas sobre a tua **PRÁTICA DESPORTIVA até 2019:**

1 – Praticavas que desporto/desportos? _____

2 – Há quanto tempo o praticavas? _____

3 – Como te deslocavas para o local onde praticavas desporto?

» Transporte Escolar

» Transporte com os pais

» Boleia com os meus amigos

» Outra _____

4 – Quantas horas por semana praticavas esse desporto? _____

5 – O desporto que praticavas é de competição? » Sim » Não

6 – O desporto que praticavas é individual ou em equipa? » Individual » Equipa » Ambos

7 – O desporto que praticavas é num espaço fechado ou ao ar livre?

» Fechado » Ar livre » Ambos

8 – Usavas os balneários do local onde praticas desporto? » Sim » Não

»» Em 2019: Peso _____ Altura _____

Responde a estas perguntas sobre a tua **PRÁTICA DESPORTIVA desde 2020:**

9 – Em que mês de 2020 paraste o desporto que fazias até 2019? _____

10 – Já retomaste o desporto que praticavas antes da pandemia?

» Não, ainda não recomeçou

» Não, o clube faliu/fechou

» Não, deixei de conseguir ir

» Não, comecei um desporto novo (qual?) _____

» Sim em (data) _____

» Sim, dependendo dos casos de COVID em Portugal ia fazendo e parando

11 – Continuaste a fazer o deporto TAL E QUAL fazias antes do início da pandemia?

» Sim » Não

12 – Se respondeste NÃO na pergunta anterior, o que mudaste na tua prática desportiva?

» Treino online

» Comecei a fazer outro desporto fora de casa

» Comecei a fazer desporto dentro de casa

13 – O desporto que praticavas pode ser feito online?

» Sim

» Não mas adaptávamos o treino

» Não

14 – O desporto que praticavas pode ser feito de máscara? » Sim » Não

15 – Se já retomaste o teu desporto, continuas a usar os balneários do local onde praticas desporto? » Sim » Não

16 – Como te deslocavas para o local onde praticavas desporto?

» Transporte Escolar

» Transporte com os pais

» Boleia com os meus amigos

» Outra _____

»» Em 2022: Peso _____ Altura _____

20 – Começaste a fazer desporto SÓ APÓS o início da pandemia? » Sim » Não

Obrigada pela tua ajuda!

Figure 1. Questionnaire applied in the study.

whether the children's SP was restricted to just physical education or whether they also practiced sports during extracurricular hours. Students who regularly practiced sports outside of school were asked about the sports practiced, the overall time of the SP as well as its weekly schedule, the mode of travel, the level of competition, whether the SP was in a team or individual, whether it was in an indoor or outdoor space, and about the use of changing rooms. In the second part of the questionnaire, the re-uptake of the sport was evaluated (and how that happened) and the adaptation measures necessary to maintain regular SP in a period of lockdown, namely the change of the place and/or the sport practiced. Students who only practiced school sports were asked if they started SP after the start of the pandemic.

The questionnaire was subsequently sent to the academic councils of various school groups in the districts of Porto, Viseu and Vila-Real. After approval by the academic council, the questionnaires were distributed by the educational community to be answered by guardians and children.

Statistical analysis

Means and standard deviations were used to describe continuous variables with normal distribution.

The clinical and demographic parameters already mentioned and their relationship with SP and subsequently the children's return to sports were evaluated. For this purpose, crosstab analysis was performed using Chi-Square and Fisher's Exact Test as statistical measures. A logistic regression was then performed to assess which variables determined the SP and sports recovery. A survival analysis was also carried out to ascertain the characteristics of SP that motivated an earlier return to sports. The SPSS Software version 27.0 statistical analysis was used, with a p-value of less than 0.05 considered to be statistically significant.

This study was evaluated by the Hospital's Ethics Committee and a consent form was not required.

Results

There were 330 responses to the questionnaire from students aged between six and 15 (mean age) 10.56 years (standard deviation 2.8 years) with similar numbers from each gender (164 females and 166 males). The average Body Mass Index (BMI) of children who practiced sports as an extracurricular activity was 18.45 (standard deviation 4.02), whereas the average BMI of children who only practiced sports in physical education was 18.90 (standard deviation 3.65). This difference was not found to be statistically significant ($p = 0.53$). Table 1 presents the basic characteristics of the sample of students. 28 children had at least one medical comorbidity (Table 2), with allergic pathology being the most frequently mentioned.

Table 1. Baseline characteristics of the sample

	n	%
Male	166	50.3
Comorbidities	28	8.5
Regular sports practice outside of school	187	56.7
Competitive sports	81	43.5
Sports practice time during the week		
< 2 hours	58	31.2
2-6 hours	103	55.4
> 6 hours	25	13.4
Time practicing sports		
< 1 year	29	15. 5
1-3 years	76	40.9
> 3 years	81	43.5
Indoor sports	107	57.5
Group sports		
Individual	39	21.0
Team	83	44.6
Both	40	21.5
Changing rooms	129	69.4
Parents' sports practice		
Father	113	34.5
Mother	110	33.1
Parents' educational status		
Father		
Elementary	114	35.4
High	100	31.1
University	108	33.5
Mother		
Elementary	56	17.2
High	99	30.5
University	170	52.3

Sports activity in the pre-pandemic season

187 children (56.7%) played sports regularly (the sports practiced are shown in Table 3) outside of school and the most-commonly mentioned sports were football and swimming. 43% practiced competitive sports and the majority practiced team sports, between two and six hours a week, for more than three years. 107 (57.5%) of the children practiced sports indoors. The factors that influenced the SP of these children were parental sports activity (father $p < 0.01$; mother $p < 0.01$), that is, if the parents practiced sports, the child was more likely to do so, and parental education (father $p < 0.01$; mother $p < 0.01$). In this case, the higher the parental academic degree, the more likely it is that their children practice sports.

Table 2. Children's comorbidities reported by parents

Diabetes	Pulmonary pathology	Spina bifida
Allergic pathology	Epilepsy	Cardiac arrhythmia
Celiac disease	Attention deficit hyperactivity disorder	Immunoglobulin deficiency
Lactose intolerance	Autism spectrum disorder	Migraine

Sports activity during the pandemic

160 (91.7%) children suspended SP during the lockdown period, 41 (22.5%) of whom did not resume it. The rest found themselves unable to continue practicing their usual sport even through remote means, which led to changes in the SP.

Regarding SP per se, 62 guardians (33.7%) reported that the sport practiced by their children could be, and was at some point, practiced wearing a mask. There was a statistically significant reduction ($p < 0.01$) in the use of changing rooms since, after the beginning of the pandemic, only 86 (48.9%) children used the changing rooms after SP compared to 129 (69.4%) before the start of the pandemic.

Regarding the type of sport practiced, of the 160 children who suspended sports practice during the pandemic, 80 (50.0%) resumed their usual SP, 33 (20.6%) resumed and suspended it by extraordinary government measures in the context of the pandemic, 12 (7.5%) started to practice sports only online and 35 (21.9%) changed their sport. The factors that influenced these children's return to sports were parental sports activity (father $p = 0.03$; mother $p = 0.02$) and the practice of competitive sports ($p = 0.05$). Thus, as with SP, for

Table 3. Sports practiced by children

Football*	Swimming†	Dancing
Roller skating	Martial arts	Gym
Handball	Horse riding	Basketball
Table tennis	Tennis	Gymnastics
Athletics	Volleyball	Cycling

Football and swimming were the most-commonly reported sports.
*22 children (15.5%).
†27 children (19.0%).

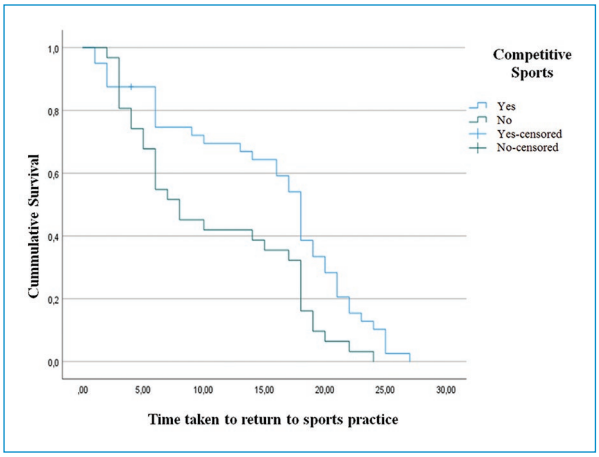


Figure 2. Kaplan Meier survival curve assessing return to sports practice among children who practice competitive and non-competitive sports.

sports resumption, if the parents practice sports, it is more likely that the child will resume sports after a period of inactivity. The return to sports was more significant for the group of children who practiced sports competitively.

Of the variables studied, the only one that influenced the earlier resumption of sports activity was the practice of competitive sports (Fig. 2) log-rank: 7.092 (p = 0.008).

Of the children who did not practice sports regularly outside of school, 13 (9.7%) started sporting activities after the start of the pandemic.

Discussion

Sport is important for creating bonds between children, something that was somewhat interrupted by the COVID-19 pandemic[7].

The change in SP and the decrease in the use of changing rooms after the start of the pandemic was expected and verified in this study. Do not forget that in our population the most-practiced sports were team sports or water-based sports, so parental involvement is one of the factors to be taken into account[8] and, in the case of swimming, many pools had not yet opened to the public when this survey was carried out.

This paper focuses on the factors that lead to SP in children in order to then identify key points and strategies to encourage SP in this age group. From our findings, and this is consistent with literature more generally[7,9-12], the parental role is crucial in providing a trigger for the uptake of SP, which must then be perpetuated with the child. Therefore, SP promotion strategies should, in an initial phase, start at the parental level: to raise awareness of its importance and provide mechanisms to encourage SP in their children, as well as positive feedback for its continuation[11].

Furthermore, children engaged in competitive sports showed a considerably higher likelihood of returning to sports earlier than their peers (p = 0.05). The graph illustrating the influence of competitive sports on the timing of sports resumption, with a log-rank of 7.092 (p = 0.008), emphasizes the significance of structured, competitive sports programs in motivating children to re-engage in SP swiftly.

Despite there being three different districts from a demographic point of view between Porto (more urban) and Viseu/Vila-Real (more rural), there were no significant differences in terms of SP in the sample. This is because, even though there is a greater selection of sports and clubs for SP in Porto, the districts of Viseu and Vila-Real have a long tradition in terms of sport, something that seems to have passed from generation to generation and that remains in children today.

One limitation of our study relates to the questionnaire applied. Despite being based on tools already validated in other countries, they have not been validated for our population and only provide a qualitative assessment of the participant's SP. In future, it would be important to create and use a validated tool for this age group, to make a formal and quantitative assessment of SP and the factors that influence this, considering the results shown in this article and literature more generally.

Also, the 10% of children in the sample who began SP after the start of the pandemic should not be underestimated. In Portugal, and across Europe, we live in an era of globalization and technological expansion, which is leading to a progressive increase in screen time. Despite the well-documented harm that these tools can bring, they can also be used to promote SP, and the influence of certain figures in media, such as social networks and television, should not be overlooked. It is important that digital influencers and public

figures also play an active role in promoting SP. It would also be interesting to evaluate and quantify the role of these new ways of promoting SP in children in a future study.

This study not only emphasizes the positive influence of parental involvement but also underscores the importance of structured competitive sports in encouraging children to quickly resume physical activities. Understanding these factors can inform strategies that promote sports participation among children, ultimately contributing to their overall health and well-being. Thus, it is essential to raise parents' awareness of their active role in their children's lives in promoting physical activity, to bring children closer to a healthier lifestyle from a physical and mental point of view[7,12].

Awards and prior presentations

Some of the results from this paper were submitted and presented at the 9th Congress of the European Academy of Paediatric Societies, in Barcelona, and at the 22nd Congresso Nacional de Pediatria, in Porto, both in 2022.

Funding

None.

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 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.

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

Association of genetic variants of the Fat Mass and Obesity (FTO) gene and obesity in children

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Abstract

Introduction and Objectives: Single nucleotide variants (SNVs) of the gene associated with fat mass and obesity (FTO) make a significant contribution to the violation of energy metabolism and the development of obesity. Study the associations between SNVs of the FTO gene and the development of metabolic disorders in children with obesity. **Methods:** 252 obese children aged between six and 18 were examined. The main group (n = 152) represented children with metabolically unhealthy obesity (MUO). The control group (n = 100) consisted of children with metabolically healthy obesity (MHO). Whole genome sequencing (CeGat, Germany) was performed in 31 children from the main group and 21 children from the control group. **Results:** The association with the development of obesity is higher for the A allele rs2287142 (t = 2.29) and the T allele SNV rs17823223 (t = 6.34) compared to healthy individuals. Serum IL-6 levels in individuals with MHO depend on SNV rs2287142 (r = 0.73). The A allele of SNV rs1080312 is associated with basal hyperglycemia (r = 0.43) and impaired carbohydrate tolerance (r = 0.33), but negatively correlates with low serum cholesterol and low-density lipoprotein cholesterol (LDL-C) (r = –0.42 and r = –0.39, respectively). The T allele of SNV rs778691805 is associated with high levels of LDL-C in blood serum (r = 0.33). The T allele of SNV rs17823223 is negatively associated with basal hyperglycemia (r = –0.51) and directly correlates with high-density lipoprotein cholesterol (r = 0.33) ($p < 0.05$). **Discussion:** In obese children, SNV rs2287142 is associated with pro-inflammatory status and SNVs rs1080312, rs17823223, and rs778691805 of the FTO gene are associated with metabolic markers.

Keywords: Gene associated with fat mass and obesity. Analysis of single nucleotide gene variants. Children. Metabolically unhealthy obesity. Metabolically healthy obesity.

Associação de variantes genéticas do gene Fat Mass and Obesity (FTO) e obesidade em crianças

Resumo

Introdução e Objetivo: Variantes de nucleotídeo único (single nucleotide variants - SNV) do gene associado à massa gorda e obesidade (fat mass and obesity - FTO) contribuem significativamente para a violação do metabolismo energético e o desenvolvimento da obesidade. O objetivo é estudar as associações do SNV do gene FTO com o desenvolvimento de distúrbios metabólicos em crianças com obesidade. **Métodos:** Foram examinadas 252 crianças com obesidade de 6 a 18 anos. O grupo principal (n = 152) foi representado por crianças com obesidade metabolicamente não saudável (metabolically unhealthy obesity - MUO). O grupo controle (n = 100) consolidou-se de crianças com obesidade metabolicamente saudável

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(metabolically healthy obesity - MHO). O sequenciamento completo do genoma (CeGat, Alemanha) foi realizado em 31 crianças do grupo principal e 21 crianças do grupo controle. **Resultados:** A associação com o desenvolvimento de obesidade é maior para o alelo A rs2287142 (t = 2,29) e o alelo T SNV rs17823223 (t = 6,34) do que em indivíduos saudáveis. O nível sérico de IL-6 em MHO depende de SNV rs2287142 (r = 0,73). O alelo A do SNV rs1080312 está associado à hiperglicemia basal (r = 0,43) e tolerância prejudicada a carboidratos (r = 0,33), mas se correlaciona negativamente com baixo colesterol sérico, colesterol de lipoproteína de baixa densidade (LDL-C): r = –0,42, r = –0,39, respectivamente. O alelo T do SNV rs778691805 está associado a um alto nível de LDL-C no soro sanguíneo (r = 0,33). O alelo T do SNV rs17823223 está negativamente associado à hiperglicemia basal (r = –0,51) e se correlaciona diretamente com o colesterol de lipoproteína de alta densidade (r = 0,33), p < 0,05. **Discussão:** Em crianças obesas, o SNV rs2287142 está associado ao estado pró-inflamatório, e o SNV rs1080312, rs17823223, rs778691805 do gene FTO está associado a marcadores metabólicos.

Palavras-chave: Gene associado à massa gorda e obesidade. Análise de variantes de genes de nucleotídeo único. Crianças. Obesidade metabolicamente não saudável. Obesidade metabolicamente saudável.

Keypoints

What is known
– The role of the FTO gene in the accumulation of body fat mass.

What is added
– SNVs rs1080312, rs17823223, and rs542356043 of the FTO gene in children with obesity were identified by us for the first time.

Introduction

According to World Health Organization (WHO) experts worldwide, by 2030 more than one billion people will be obese. Obesity induces the development of metabolic disorders, which significantly worsen a person's state of health and can cause premature death. Overweight and obesity are thought to cause 2.8 million deaths each year[1,2]. A significant contribution to the development of obesity, especially in children, is brought by genetic factors. One of the genes associated with the development of obesity has been identified as a gene associated with fat mass and obesity (FTO)[3-5].

The human FTO gene is located on the long arm of chromosome 16 (16q12.2), consists of nine exons and eight introns, and encodes RNA demethylase, 2-oxoglutarate (2-OG) Fe(II)-dependent dioxygenase of the AlkB family[6,7].

The FTO gene is mainly expressed in neurons of the arcuate nucleus of the hypothalamus, adipocytes, and skeletal muscle myocytes[8].

The RNA demethylase protein, FTO protein, contains the canonical binding motif of the substrate and cofactor α-ketoglutarate (RxxxxxR) and the binding motif of Fe^{2+} (HxDxnH). RNA demethylase FTO demethylates the methylated sixth nitrogen atom of adenine (N6-methyladenosine [m6A]) and N6,2'-O-dimethyladenosine (N6,2'-O-dimethyladenosine [m6Am]) of messenger RNA (mRNA); m6A into U6RNA; m6Am small nuclear RNA and N1-methyladenosine (N1-methyladenosine [m1A]) transfer RNA. The main nitrogenous substrate of FTO is m6A, which is the most common methylation modification of the region between the stop codon and the start codon of the 3' untranslated region of messenger RNA[7,9,10].

Methylation of 6A modulates the activity of alternative splicing, translation, transport, and mRNA degradation. FTO-mediated mRNA demethylation of factors involved in appetite regulation (ghrelin), adipogenesis (RUNX1T1), and autophagy (ATG5 and ATG7) promotes obesity[11]. It has been demonstrated that overexpression of the FTO gene in experimental animals is accompanied by fat accumulation and an increase in body weight, while FTO gene knockout is characterized by a deficiency in body weight and adipose tissue[12-14].

Genome-wide association studies (GWAS) have demonstrated a high frequency of single nucleotide variants (SNVs), such as rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002, rs11075995, and rs1121980, in the FTO gene in patients with obesity[15-17].

It has been demonstrated that SNVs rs9930506, rs1421085, rs8050136, rs1121980, rs17817449, rs3751812 and rs7202116, located in the region of intron 1 of the FTO gene, are highly associated with overweight and obesity[18-24].

The classic SNV of the FTO gene is rs9939609, the presence of which increases the risk of developing obesity by 1.67 times[25-28].

At the same time, associations of SNVs of the FTO gene with metabolic disorders in obese children remain virtually unexplored.

The aim of the study was to explore the associations of SNVs of the FTO gene with the development of metabolic disorders in children with obesity.

Materials and methods

Ethical approval

Participants provided written informed consent, and research protocols and procedures were approved according to the ethical standards of the Helsinki Declaration 2013 and by the Human Research Ethics Committee (ethical approval DSMU/EC/19/1107). Time of data collection: January 2020 – February 2023.

Study design

Observational, analytical, longitudinal, cohort study[29].

Inclusion criteria

Children with polygenic obesity (BMI ≥ 97th percentiles) aged between six and 18.

Exclusion criteria

Monogenic and secondary forms of obesity; hereditary syndromes accompanied by obesity; diseases, the treatment of which requires the use of medications that affect the metabolism of carbohydrates and lipids; pregnancy.

Setting

The Children's Endocrinology Department. 252 children of the Caucasian group, aged between six and 18, with a diagnosis of obesity were examined. To verify the diagnosis, the obesity classification recommended in clinical practice was used: Order of the Ministry of Health of Ukraine No. 254 of 27.04.2006 "Protocol for the provision of medical care to obese children" and Order of the Ministry of Health of Ukraine No. 1732 of 24.09.2022 On the approval of standard medical assistance for "obesity in children".

The main group (n = 152) represented children with metabolically unhealthy obesity (MUO) and the control group (n = 100) consisted of patients with metabolically healthy obesity (MHO).

Criteria for inclusion in the main group

The presence of abdominal obesity[30] and two of the following criteria: hyperglycemia and/or hyperinsulinemia; dyslipidemia; systolic blood pressure (SBP) and diastolic blood pressure (DBP) above the 90th percentile for a given age, gender, and height[31]. Anthropometric data were collected by a nurse in the emergency department; children wore underwear, but no shoes. Height (m) was measured using a Heightronic Digital Stadiometer® to the nearest 0.01 m. Body mass (kg) was measured using a Tefal Bodysignal body composition analyzer (France). Waist circumference (WC) and hip circumference (HC) were measured using a standardized anthropometric tape, establishing the circumference at the midpoint between the top of the iliac crest and the lower part of the lateral rib cage to the nearest 0.01 m. Body Mass Index (BMI) was converted to standardized BMI (BMI SDS) by means of the current WHO growth references[32]. SBP and DBP were measured using the Dinamap ProCare (GE Healthcare) digital oscillometric device.

Immunochemical examination

The studies were carried out in a certified Synevo laboratory (Dnipro, Ukraine). The material for the study was venous blood.

To study carbohydrate metabolism disorders, the levels of basal glycemia and insulinemia were determined through immunochemical testing with electrochemiluminescence detection (ECLIA). Included in the main group were obese children with a glycemic level equal to or greater than 5.6 mmol/L and/or an increase in insulinemia > 90th percentile according to the percentile curves recommended by the Identification and prevention of Dietary - and lifestyle-induced health Effects In Children and infantS (IDEFICS) consortium for the European population according to the child's age and gender[33-34].

To study lipid metabolism disorders, levels of high-density lipoproteins (HDL-C), low density lipoproteins (LDL-C), and triglycerides (TG) were determined through the enzymatic-colorimetric method using kits from Roche Diagnostics (Switzerland) and a Cobas 6000 analyzer. The main group included obese children with HDL-C < 1.03 mmol/l or under the 10th percentile of the age norm or increased TG ≥ 1.7 mmol/l or above the 90th percentile of the age norm[35].

Molecular and immunological examination

To study the role of pro-inflammatory markers in the development of meta-inflammation in obesity in children, IL-1β and IL-6 levels in blood serum were determined in the certified Synevo laboratory (Dnipro, Ukraine). Interleukin-1β

was investigated through immunochemical methods with chemiluminescence detection (CLIA). Analyzer and test system: Immulite (Siemens AG), Germany. The reference value was considered to be IL-1β 0-5 pg/ml. Interleukin-6 was determined by an enzyme-linked immunosorbent assay (ELISA) using a Cobas 6000/Cobas 8000 kit provided by Roche Diagnostics (Switzerland). The reference value was considered to be IL-6 1.5-7.0 pg/ml.

Leptin was determined using ELISA. Analyzer and test system: Tecan Sunrise, LDN (Germany). The reference value of leptin levels for boys was 2-5.6 ng/ml and for girls it was 3.7-11.1 ng/ml. Adiponectin was tested using ELISA. Analyzer and test system: Mediagnost GmbH (Germany). The results were interpreted as follows: over 10 μg/ml represented a low cardiovascular risk; 7-10 μg/ml represented a moderate cardiovascular risk; 4-7 μg/ml represented a high cardiovascular risk; under 4 μg/ml represented a very high cardiovascular risk.

Molecular genetic testing

To study the contribution of SNVs of the FTO gene in the formation of MUO, a molecular genetic study was carried out using next-generation whole-genome sequencing (NGS) according to the recommendations of the American College of Medical Genetics and Genomics (ACMG)[36] in 52 patients (31 children from the main group and 21 controls) with venous blood sampling in a certified CeGat laboratory (Tubingen, Germany) using the Illumina CSPro® Certified service provider platform.

The average amount of DNA (μg) in samples was 0.875. Library Preparation: Quantity used 50 ng. Library Preparation Kit: Twist Human Core Exome plus Kit (Twist Bioscience). Sequencing parameters: NovaSeq 6000; 2 x 100bp. QC values of sequencing, Q30 value: 96.07%.

Bioinformatics analysis

Bioinformatic analysis – demultiplexing of the sequencing reads was performed with Illumina bcl-2fastq (version 2.20). Adapters were trimmed using Skewer (version 0.2.2)[37]. DNA-Sequencing: trimmed raw reads were aligned to the human reference genome (hg19-cegat) using the Burrows-Wheeler Aligner (BWA – mem version 0.7.17-cegat)[38-41].

ABRA (version 2.18) and Genotype Harmonizer v.1.4.20 were used for local restructuring of readings in target regions to improve accuracy in the detection of indels in the genome during mutagenesis[42,43].

The reference sequence was obtained from the National Center for Biotechnology Information RefSeq database[44].

Statistical analysis

A statistical analysis of the results obtained was carried out using the Statistica 6.1 software package (No. AGAR909E415822FA) with the help of a personal computer with an Intel Pentium 4 processor. Depending on the test result, parametric and nonparametric statistical methods were used. Correlation analysis was used to analyze 100 indicators of clinical, laboratory-instrumental, and molecular genetic examinations in 252 children. The Pearson correlation method was used to assess the relationship between quantitative traits and Spearman's analysis (r), a non-parametric ranking method, was used to assess qualitative traits. Only essential connections were taken into account ($p < 0.05$).

Results

Molecular immunological studies showed obesity levels of pro-inflammatory and anti-inflammatory adipokines and cytokine IL-6 in the blood serum (Table 1).

As a result of whole-genome sequencing in 52 children with obesity, we identified five SNVs: rs1080312 (G > A), rs2287142 (G > A), rs17823223 (C > T), rs542356043 (G > A), and rs778691805 (G > T). We did not find significant associations of SNVs in the FTO data with body mass and BMI in children.

The distribution of genotype frequencies was in Hardy-Weinberg equilibrium in both groups of children with different obesity phenotypes.

Molecular genetic characteristics of the identified SNVs of the FTO gene are presented in table 2.

Among the identified SNVs of the FTO gene, the most highly pathogenic are three nonsynonymous variants: rs778691805, rs542356043, and rs1080312 (CADD = 17.32, 8.63, and 7.84, respectively).

Associations between SNVs of the FTO gene and obesity phenotypes in children

The frequency of occurrence of SNVs of the FTO gene in children with different obesity phenotypes is presented in table 3.

In children with the MHO phenotype, the allele frequency (AF) of the mutated A allele of SNV rs1080312 (t = 3.32) and rs2287142 (t = 2.29), and T allele SNV rs17823223 (t = 6.34) and rs778691805 (t = 2.29) of the FTO gene was significantly higher than the AF of these polymorphisms in healthy non-Finnish Europeans ($p < 0.05$). In children with MUO, the AF of the mutated A allele SNV rs2287142 (t = 2.74) and T allele SNV rs17823223 (t = 3.27) of the FTO gene was significantly

Table 1. Mean concentration (M ± m) and median (Me)* values of blood serum inflammation markers in children with different phenotypes of obesity

Indicator	Reference values	MUO (n = 152)		MHO (n = 100)		p
		M ± m	Me	M ± m	Me	
IL-1β (pg/ml)	0-5	2.5 ± 0.3	1.9	1.8 ± 0.7	1.7	> 0.05
IL-6 (pg/ml)	1.5-7	7.4 ± 0.5	6.8	4.3 ± 0.3	3.4	< 0.05
Leptin (ng/ml) Boys Girls	 2-5.6 3.7-11.1	 29.3 ± 8.9 47.8 ± 4.4	 25 45.2	 26.0 ± 6.4 32.5 ± 4.3	 24.4 28.5	 > 0.05 < 0.05
Adiponectin (μg/ml)	≥ 10	3.9 ± 0.8	3.1	7.7 ± 2.4	6.5	< 0.05

*Me with 95% CI median.

Table 2. Characteristics of SNV types of the FTO gene

SNV	Position	GnomAD _maxPOP	Ref	Alt	Consequence	Base change	CADD	RawScore	Clinical significance (ClinVar)
rs1080312*	53745367	AFR	G	A	Intronic	c. 45+7226G>A	7.84	0.35	not reported
rs2287142	53945351	EAS	G	A	Synonymous	c. 60G>A	0.14	–0.44	not reported
rs17823223	53999638	NFE	C	T	Intronic	c. 230+31617C>T	1.88	–0.05	not reported
rs542356043*	54013348	NFE	G	A	Intronic	c. 1364+45327G>A	8.63	0.42	not reported
rs778691805*	53859781	NFE	G	T	Missense	c. 129G>T	17.32	1.68	not reported

*SNV of the FTO associated with high levels of CADD.
GnomAD_maxPOP: frequency distribution of FTO mutations; AFR: African; EAS: East Asian; NFE: Non-Finnish European; Ref: reference allele; Alt: alternative allele; Consequence: functional consequence of the variation in relation to the transcript; c: the nucleotide change and position relative to the coding sequence of the affected transcript in HGVS nomenclature; CADD: combined annotation dependent depletion.
CDS Position Reference Base > Alternative Base. Example: c. 223A>T (c.[1] - interpretation for DNA coding sequence)[44]. This column is empty if the variant is intergenic.

Table 3. The frequency of occurrence of the SNV of the FTO gene in children with different obesity phenotypes

SNV	gnomAD browser		The frequency of occurrence of major and minor options (%)				The value of Student's t-test in Welch's modification		
	Popmax AF (HOM^P), %	AF NFE, (HOM^P), %	MHO		MUO		t_1	t_2	t_3
			(HOM^N), %	(HET/ HOM^P), %	(HOM^N), %	(HET/ HOM^P), %			
rs1080312	0.17	0.02	90	10	97	3	3.32*	1.74	2.03*
rs2287142	0.06	0.002	95	5	93	7	2.29*	2.74*	0.6
rs17823223	0.12	0.13	71	29	90	10	6.34*	3.27*	3.49*
rs542356043	0.00005	0.0002	100	0	97	3	0.01	1.76	1.76
rs778691805	0.000003	0.00002	95	5	100	0	2.29*	0	2.29*

*Critical value of Student's t-test modified by Welch >1.97, at which the differences in the compared groups are significant ($p < 0.05$).
HOM^P: homozygous variant (biallelic single nucleotide substitution); HET: heterozygous variant (single allelic single nucleotide substitution); HOM^N: homozygous variant (absence of nucleotide substitutions); Popmax AF: maximum population allele frequency in the genome (gnomAD browser); AF NFE: allele frequency for non-Finnish Europeans in the genome (gnomAD browser); t_1: student's test of significance modified by Welch in the comparison groups MHO and healthy Non-Finnish Europeans; t_2: Student's test of significance modified by Welch in the comparison groups MUO and healthy Non-Finnish Europeans; t_3: Student's test of significance modified by Welch in the MUO and MHO comparison groups.

higher than the AF of these polymorphisms in healthy non-Finnish Europeans ($p < 0.05$). The allele frequency of the mutated A allele SNV rs1080312 ($t = 2.03$) and T allele SNV rs17823223 ($t = 3.49$) and rs778691805 ($t = 2.29$) of the FTO gene in MUO was also significantly lower than in children with MHO ($p < 0.05$). We found no significant differences in the allelic frequency of the mutated A allele SNV rs542356043 of the FTO gene among obese children and healthy non-Finnish Europeans ($p < 0.05$).

We found that in children with obesity, certain SNVs of the FTO gene that we identified are associated with both the level of inflammatory activity and laboratory markers of metabolic disorders.

Associations between SNVs of the FTO gene and markers of inflammatory activity

Based on the correlation analysis data, we found that the level of IL-6 in the blood serum of children with the MHO phenotype depended exclusively on SNV rs2287142 of the FTO gene ($r = 0.73$), whereas the content of pro-inflammatory interleukins (IL-1β and IL-6) in children with the MUO phenotype did not depend on the SNV of the FTO gene. We did not establish a significant correlation between the levels of leptin, adiponectin, and SNV of the FTO gene in obese children.

Associations between SNVs of the FTO gene and carbohydrate metabolism disorders

According to the correlation analysis data, indicators of carbohydrate metabolism are only associated with SNVs of the FTO gene in children with the MHO phenotype. Thus, SNVs rs17823223 and rs1080312 of the FTO gene are associated with glucose metabolism. The presence of the T allele of SNV rs17823223 is associated with a lower concentration of fasting serum glucose ($r = -0.51$), while carriage of the A allele of SNV rs1080312 is associated with a higher level of fasting glycemia ($r = 0.43$) and impaired carbohydrate tolerance ($r = 0.33$).

Associations between SNVs of the FTO gene and lipid metabolism disorders

It was found that in children with the MHO phenotype, SNVs rs778691805 and rs1080312 of the FTO gene are associated with lipid metabolism markers. And, if the T allele of SNV rs778691805 was associated with a high level of LDL-C in the blood serum ($r = 0.33$), then the A allele of SNV rs1080312 was associated with a low level of cholesterol and LDL-C in the blood serum

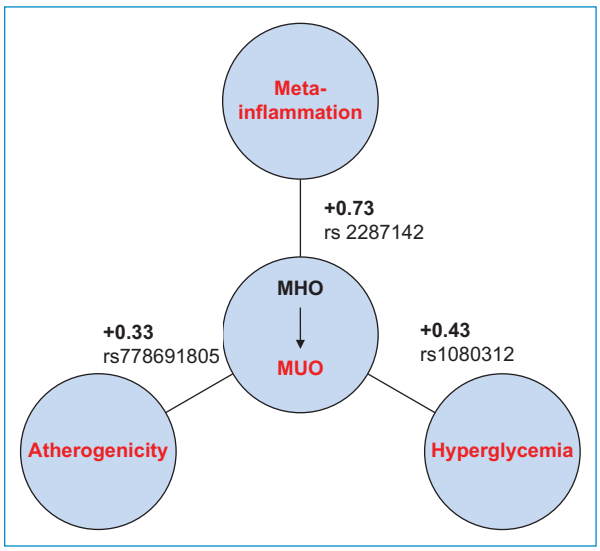

Figure 1. Correlation pleiad of associations between SNVs of the FTO gene and the development of metabolic disorders in children with obesity.

($r = -0.42$ and $r = -0.39$, respectively). In children with the MUO phenotype, only SNV rs17823223 was associated with lipid profile parameters; in individuals with the T allele of SNV rs17823223, a higher level of HDL-C in blood serum was noted ($r = 0.33$) (Fig. 1).

Discussion

We have identified SNVs of the FTO gene based on whole-genome sequencing in children with obesity, such as rs1080312, rs2287142, rs17823223, rs542356043, and rs778691805. It should be noted that SNVs rs1080312, rs17823223, and rs542356043 of the FTO gene in children with obesity were identified by us for the first time.

We found that in obese children, SNV rs2287142 is associated with pro-inflammatory status, and SNVs rs1080312, rs17823223, and rs778691805 are associated with metabolic markers. The rs542356043 variant of the FTO gene was not associated with any of the pro-inflammatory or metabolic markers. It was shown that in children with the MHO phenotype, SNV rs2287142 of the FTO gene is highly associated with IL-6 fluctuations. Individuals with the A allele have a higher level of IL-6 in their blood serum. The rs2287142 variant is located in the enhancer/silencer region of the cis-regulatory element of the FTO gene, changes in which can lead to alternative RNA splicing and the generation of functionally different isoforms[45]. FTO gene knockout has been shown to increase the level of IL-6 in adipose tissue[46]. It is possible that the A allele of SNV rs2287142

is associated with the production of FTO isoforms with low functional activity.

It is of interest that two SNVs (rs17823223 and rs1080312) of the FTO gene are multi-directionally associated with lumen glucose in children with the MHO phenotype. Carriage of the T allele of the missense variant of SNV rs17823223 prevents the development of glycemia, while the A allele of the intron variant of SNV rs1080312 promotes the development of fasting glycemia. Given that FTO, by enhancing the activity of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase 1, induces gluconeogenesis[47], it is possible to suggest that SNV rs17823223 leads to a decrease in FTO activity, while SNV rs1080312 is accompanied by an increase in FTO expression. Missense variant rs17823223 is accompanied by the replacement of a threonine residue with a methionine residue at position 457 (Thr457Met), which can lead to a decrease in the functional activity of the FTO protein. However, the dependence of glucose metabolism and insulin secretion in these variants of the FTO gene remains unexplored. It should be noted that in experimental animals with a FTO gene knockout, hyperglycemia does not develop and high glucose tolerance was observed. At that time, SNV rs9939609, which is characterized by overexpression of the FTO gene, is accompanied by severe hyperglycemia[48,49].

Of interest is the fact that elevated levels of both mRNA and FTO protein in muscle are characteristic of type 2 diabetes mellitus, regardless of the presence of obesity and insulin resistance[50].

We found that SNVs rs1080312, rs17823223, and rs778691805 in children with obesity are associated with the concentration levels of some lipid fractions in blood serum. In all likelihood, SNVs rs1080312 and rs17823223 have a protective antiatherogenic effect, and rs778691805, on the contrary, has a weak but atherogenic effect. It is known that, on the one hand, FTO, by reducing the expression of mRNA of carnitine palmitoyltransferase 1, hormone-sensitive lipase, and triglyceride lipase, inhibits the activity of fatty acid oxidation and lipolysis; and on the other hand, by inducing the expression of activating transcription factor 4, it stimulates the expression of lipogenic genes, which leads to increased *de novo* lipogenesis in the liver[47,51].

Also, FTO stabilizes the mRNA of sterol regulatory element-binding transcription factor 1 (SREBF1) and carbohydrate-response element-binding protein (ChREBP), two major lipogenic transcription factors[52]. Thus, FTO promotes triglyceridemia. Based on these data, it is likely that SNVs rs1080312 and rs17823223 cause a decrease in FTO expression or activity, respectively. At the same time, rs778691805 leads to an increase in FTO expression. However, further experimental and clinical studies are needed to confirm this assumption.

Conclusions

- In obese children, SNV rs2287142 is associated with pro-inflammatory status, and SNVs rs1080312, rs17823223, and rs778691805 of the FTO gene are associated with metabolic markers.
- In children with the MHO phenotype, SNVs rs17823223 and rs1080312 of the FTO gene have different associations with serum glucose values. Carriage of the T allele of the missense variant of SNV rs17823223 prevents the development of glycemia, while the A allele of the intron variant of SNV rs1080312 contributes to the development of basal hyperglycemia.
- SNVs rs1080312, rs17823223, and rs778691805 in children with obesity are associated with the concentration levels of some lipid fractions in blood serum. SNVs rs1080312 and rs17823223 have a protective antiatherogenic effect due to a corresponding decrease in the expression or activity of the FTO gene, and rs778691805, on the contrary, has a weak but atherogenic effect due to an increase in FTO expression.
- In obese children, the missense mutation SNV rs17823223 of the FTO gene is associated with the accumulation of fat mass but is not associated with metabolic disorders.

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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 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 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.

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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NARRATIVE REVIEW

Bronchopulmonary dysplasia: preventive measures and therapeutic approach until discharge from the neonatal unit

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common long-term respiratory morbidity affecting very preterm infants and has a negative impact on future lung function and quality of life. BPD management during a neonatal intensive care unit (NICU) stay is mainly based on a set of preventive measures. Despite improvements in pharmacological and non-pharmacological research, only a few therapeutic measures available are supported by high-quality evidence. This review essentially focuses on preventive and therapeutic options for preterm neonates at risk of, or with established, BPD, during their NICU stay.

Keywords: Bronchopulmonary dysplasia. Preterm infant. Prevention. Treatment.

Displasia broncopulmonar: medidas preventivas e abordagem terapêutica antes da alta da unidade de neonatologia

Resumo

A displasia broncopulmonar (DBP) é a morbidade respiratória a longo prazo mais comum em recém-nascidos de grande prematuridade e tem um impacto negativo na função pulmonar e na qualidade de vida futura. A abordagem terapêutica da DBP durante a permanência na unidade de cuidados intensivos neonatais (UCIN) baseia-se essencialmente na adoção de um conjunto de medidas preventivas. Apesar dos avanços na investigação de novos agentes farmacológicos e medidas não farmacológicas, apenas algumas das medidas terapêuticas disponíveis são apoiadas por evidências de alta qualidade. Esta revisão aborda as medidas preventivas e terapêuticas a utilizar em recém-nascidos pré-termo em risco de desenvolver ou com DBP estabelecida, durante sua permanência na UCIN.

Palavras-chave: Displasia broncopulmonar. Prevenção. Tratamento. Recém-nascido pré-termo.

Keypoints

What is known
- Management of bronchopulmonary dysplasia is based on a set of preventive and therapeutic measures.

What is added
- This review brings together preventive and therapeutic measures to be used in BPD.

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common long-term respiratory morbidity affecting preterm infants, and the risk of its occurrence is inversely proportional to the gestational age at birth[1,2].

The technical and scientific advances that have taken place in the area of neonatology in recent decades have paved the way for the survival of more and more infants with very low gestational ages, even though the prevalence of BPD has not decreased, affecting up to 45% of infants born below 29 gestational weeks[2,3]. However, these scientific advances have modified the phenotype of the disease, leading to the emergence of a "new" BPD, as opposed to the "old" BPD, previously called chronic lung disease of prematurity[4].

BPD is the result of abnormal pulmonary alveolarization, vascularization, and airway development, in which several prenatal, perinatal and postnatal factors act simultaneously and in sequence, which translates into chronic dependence on supplemental oxygen[5]. Today, we know that BPD is not merely a lung disease, but a systemic condition with lifelong implications for adult health and quality of life[6,7]. The pathophysiology of BPD is complex and is beyond the scope of this article[8-22]. The strongest risk factors for BPD are prematurity and low birth weight[1]. BPD risk factors, beyond variation in practices at the neonatal intensive care unit (NICU), are listed in table 1[9-11].

This article focuses, essentially, on preventive and therapeutic measures that are currently recommended for preterm neonates at risk of, or with established, BPD, during their NICU stay. This article does not address aspects related to the treatment and follow-up of patients with BPD after discharge from the NICU.

Table 1. Risk factors for bronchopulmonary dysplasia[9-11]

Antenatal	Lower socioeconomic status Lower maternal education Lower gestational age Male gender White race Fetal growth restriction Maternal smoking Multiple gestations Oligohydramnios Family history of atopic disease Chorioamnionitis Preeclampsia Pre-existing hypertensive disorders Gestational diabetes Maternal obesity Absence of antenatal steroids
Perinatal	C-section Hyperoxia High inflation pressures Intubation in the delivery room Respiratory tract colonization with *Ureaplasma parvum* and *Ureaplasma urealyticum*
Postnatal	Severity of acute respiratory distress syndrome Surfactant administration Apnea Hyperoxia Mechanical ventilation Prolonged patency of the ductus arteriosus Excessive fluids administration Ventricular dysfunction Intracardiac shunts Sepsis Inflammation Air leaks or pulmonary interstitial emphysema Pulmonary hypertension Systemic and pulmonary infections Prematurity-related comorbidities Nutritional deficits Extrauterine growth restriction Vitamin A deficiency

BPD definition and diagnostic criteria

BPD was first described in 1967 by Northway, in moderately preterm infants in the pre-surfactant era, when supplemental oxygen was the primary therapy for severe respiratory distress syndrome (RDS) and mortality was over 50%[23]. In 1988, Shennan defined BPD as the requirement for supplemental oxygen at 36 weeks post-menstrual age, based on a positive predictive value of 63% for abnormal pulmonary outcomes at two years of age[24]. In 2001, the *Eunice Kennedy Shriver-National Institute of Child Health and Human Development* (NICHHD) workshop developed a more comprehensive definition for BPD, made after 28 cumulative days of supplemental oxygen; with severity based on oxygen use at 36 weeks post-menstrual age, with a scale of mild (room air), moderate (< 30% supplemental oxygen), and severe (> 30% supplemental oxygen or positive pressure) (Table 2)[25]. In 2004, Walsh et al.[26] added a 'physiological' test to the NICHHD workshop definition to assess the need for supplemental oxygen at 36 weeks post-menstrual age; infants were classified as having BPD if oxygen saturation fell to values of < 90% within 60 minutes of a room air challenge test. In 2018, the NICHHD workshop provided a review of the BPD definition, that removed the requirement for 28 days of oxygen therapy prior to 36 weeks post-menstrual age, but added a requirement for radiographic confirmation of parenchymal lung disease and used a severity grading of

Table 2. The 2001 and 2018 definitions of bronchopulmonary dysplasia from the National Institute of Child Health and Human Development[25,27]

Gestational age	< 32 weeks	≥ 32 weeks			
Time points of assessment	36 weeks PMA or discharge to home, whichever comes first	> 28 d but < 56 d postnatal age or discharge to home, whichever comes first			
Treatment with oxygen > 21% for at least 28 days PLUS					
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first			
Moderate BPD	Need* for < 30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need* for < 30% oxygen at 56 days postnatal age or discharge, whichever comes first			
Severe BPD	Need* for ≥ 30% oxygen and/or positive pressure (PPV or N-CPAP), at 36 weeks PMA or discharge, whichever comes first	Need* for ≥ 30% oxygen and/or positive pressure (PPV or N-CPAP), at 56 days postnatal age or discharge, whichever comes first			
2018 - Eunice Kennedy National Institute of Child Health and Human Development suggested refinements to the definition of BPD					
A premature infant (< 32 weeks' gestational age) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks PMA requires 1 of the following FiO_2 ranges/oxygen levels/O_2 concentrations for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90%-95% range.					
Grades	**Invasive IPPV***	**N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min**	**Nasal cannula flow of 1- < 3 L/min**	**Hood O_2**	**Nasal cannula flow of < 1 L/min**
I	-	21	22-29	22-29	22-70
II	21	22-29	≥ 30	≥ 30	70
III	> 21	≥ 30			
III (A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g., necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc.). *Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents.				

*A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range. BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen > 21% and/or positive pressure for non-respiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen > 21% means that the infant received oxygen > 21% for more than 12 h on that day. Treatment with oxygen > 21% and/or positive pressure at 36 weeks PMA, or at 56 d postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 weeks PMA, 56 d postnatal age, or discharge.
BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; IPPV: intermittent positive-pressure ventilation; NCPAP: nasal continuous positive airway pressure; NIPPV: non-invasive positive pressure ventilation; PMA: post-menstrual age; PPV: positive-pressure ventilation.

I-III that incorporated newer modes of non-invasive ventilation[27]. This NICHHD 2018 definition needs to be validated in a large neonatal population. Since then, other definitions have been proposed: in 2017, Isayama et al.[28] proposed the use of oxygen and/or respiratory support as a better indicator of chronic respiratory insufficiency compared to just oxygen, and that assessment at term-equivalent age (40 weeks post-menstrual age) increases the predictive value; in 2019, Svedenkrans et al.[29] proposed the modification of a 'physiological test' that uses the simultaneous measurement of FiO_2 and peripheral saturation to calculate the rightward shift of the oxyhemoglobin dissociation curve at any given point in time; in 2019, Jensen et al.[30] proposed a modification of NICHHD workshop definition, which uses positive pressure instead of supplemental oxygen to classify BPD severity at 36 weeks post-menstrual age. The scale is: no

BPD (no support), grade 1 (nasal cannula ≤ 2 L/min), grade 2 (nasal cannula > 2 L/min or non-invasive positive airway pressure), and grade 3 (invasive mechanical ventilation).

If a BPD diagnosis, or definition, can predict pulmonary outcomes in childhood, how those long-term pulmonary outcomes should be defined remains a challenge for neonatologists and pediatric pulmonologists, and new definitions will, very likely, emerge in the future.

BPD prevention and treatment

BPD is not limited to the perinatal period. Affected infants will not only have respiratory morbidities in their childhood and adult life, (decreased lung function, increased incidence of emphysema, higher risk of wheezing) but also present decreased right ventricular function, increased cardiovascular risk, and a higher incidence of arterial hypertension in adolescence and adulthood[31-34]. BPD is also associated with retinopathy of prematurity and neurological morbidities like developmental delay and cerebral palsy[35,36]. Some studies have suggested that BPD is an independent risk factor for poor neurodevelopmental outcomes, even in the absence of definite brain injuries, such as intraventricular hemorrhage or hypoxic ischemic encephalopathy[37,38]. For example, motor functions, cognitive development, and academic progress are worse in preterm infants with BPD than in those without it[39], and strategies to protect the lungs might also be neuroprotective.

Every measure should be taken to minimize the abnormal development of the lung after birth, as well as its impact on the well-being, development, and growth of the very premature child. In this way, BPD "treatment" is, to start with, based on prevention.

Preventive measures include adequate pregnancy follow-up, prevention of preterm delivery and intrauterine infection, reducing exposure to ventilation using an endotracheal tube, and measures to avoid or minimize long-term lung and brain damage[39].

Antenatal care and delivery room stabilization

Measures that can be taken in the antenatal period that also aim to promote pulmonary development are similar to those recommended for the prevention of RDS in preterm infants (Table 3)[40].

Extremely low gestational age preterm infants should be delivered in tertiary centres[41]. Antibiotics can delay preterm delivery and reduce neonatal morbidity in cases of prenatal pre-labor rupture of membranes (PPROM); co-amoxiclav should be avoided in women due to the increased risk of neonatal necrotizing enterocolitis[42]. Tocolytic drugs are recommended for delaying birth, permitting safe *in utero* transfer to a tertiary center, and giving prenatal corticosteroids time to take effect[43]. Given the neuroprotective beneficial effects of magnesium sulphate on reducing cerebral palsy at two years of age, this should be given to women at risk of preterm birth[44].

Antenatal corticosteroids have been shown to promote lung maturation and prevent RDS in a preterm neonate[45]. Since 1995, antenatal corticosteroids have been recommended for impending preterm birth below 34 weeks of gestation[46]. Some observational studies suggest that antenatal corticosteroids, together with other active management practices, reduce mortality at gestations as low as 22 weeks[47]. When given before elective Caesarean section up to 39 weeks, they reduce the risk of admission to NICU, although there is currently insufficient data to draw any firm conclusions[48]. Optimal treatment up to the delivery interval is more than 24 hours and less than seven days after starting steroid treatment; after 14 days, the benefits are reduced. Advanced labor should not be a reason to refrain from therapy with corticosteroids since the beneficial effects of the first dose start within a few hours. The same applies to magnesium sulphate[49]. The WHO recommends that a single repeat course of steroids between 24 and 34 weeks of gestation may be considered if preterm birth does not occur within seven days after the initial course and there is a high risk of preterm birth in the next seven days[50]. According to Asztalos E.V. et al.[51], a repeat course given after 32 weeks' gestation does not seem to improve outcome. The most common regimens include betamethasone and dexamethasone in a total dose of 24 mg (four doses of dexamethasone 6 mg IM 12 hours apart or two doses of betamethasone 12 mg IM 24 hours apart)[50].

The attitudes in the delivery room should be to support the transition; however, the guidelines of the *European Resuscitation Council*[52] should be followed whenever a resuscitation is needed. Body temperature should be maintained with a polyethylene bag and radiant warmer, and it is feasible to provide advanced resuscitation with the umbilical cord intact since fully-equipped mobile trolleys have been developed in order to allow bedside resuscitation with an intact cord[53]. Delayed (60 seconds) cord clamping is advised[54]. Umbilical cord milking may be an alternative to delayed cord clamping in emergency situations, but

Table 3. Summary of recommendations, from the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2022 Update*[40]

Prenatal care	– Mothers at high risk of preterm birth < 28-30 weeks' gestation should be transferred to perinatal centers with experience in RDS management – In women with a singleton pregnancy and a short cervix in mid-pregnancy or previous preterm birth, vaginal progesterone treatment should be used to increase gestational age at delivery and reduce perinatal mortality and morbidity – In women with symptoms of preterm labor, cervical length and accurate biomarker measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids – Clinicians should offer a single course of prenatal corticosteroids to all women at risk of preterm delivery from when pregnancy is considered potentially viable up to 34 weeks' gestation, ideally at least 24 h before birth – A single repeat course of steroids may be given in threatened preterm birth before 32 weeks' gestation if the first course was administered at least 1-2 weeks earlier – Neuroprotector magnesium sulphate (MgSO4) should be administered to women in imminent labor before 32 weeks' gestation – In women with symptoms of preterm labor, cervical length and fibronectin measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids – Clinicians should consider short-term use of tocolytic drugs in very preterm pregnancies to allow completion of a course of corticosteroids and/or in utero transfer to a perinatal center
Delivery room stabilisation	– If clinical condition allows, delay clamping the umbilical cord for at least 60s, to promote placento-fetal transfusion. When not feasible, consider umbilical cord milking in infants with gestational age > 28 weeks – Use a T-piece device, rather than bag and mask – In spontaneously breathing babies, stabilize with CPAP. If apneic or bradycardic, start mask ventilation/ inflations, at initial CPAP pressures of 6-8 cm H2O and PIP 20-25 cm H_2O; do not use sustained inflations as there is no long-term benefit – Oxygen for resuscitation should be controlled using a blender; use an initial FiO_2 of 0.30 for babies < 28 weeks' gestation, 0.21-0.30 for those 28-31 weeks, and 0.21 for 32 weeks' gestation and above; FiO_2 adjustments up or down should be guided by pulse oximetry; aim for SpO_2 of 80% or more (and heart rate over 100/min) by 5 minutes of age – Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs; babies who require intubation for stabilization should be given surfactant – Plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilization in the delivery suite for babies < 32 weeks' gestation to reduce the risk of hypothermia; hyperthermia should also be avoided
Surfactant	– If babies < 30 weeks of gestation require intubation for stabilization, they should be given an animal-derived surfactant preparation; babies with RDS needing treatment should be given an animal-derived surfactant preparation – A policy of early rescue surfactant should be standard, but there are occasions when surfactant should be given in the delivery suite, such as when intubation is needed for stabilization – Babies with RDS should be given rescue surfactant early in the course of the disease; a suggested protocol would be to treat babies who are worsening when FiO_2 > 0.30 on CPAP pressure of at least 6 cm H_2O, or if lung ultrasound suggests surfactant need – Poractant alfa at an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or 100 mg/kg of beractant for rescue therapy – LISA is the preferred mode of surfactant administration for spontaneously breathing babies on CPAP, provided that clinicians are experienced with this technique – Laryngeal mask surfactant may be used for more mature infants > 1.0 kg – A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS, such as persistent high oxygen requirement and other problems have been excluded
Oxygen beyond stabilization	– In preterm babies receiving oxygen, the saturation (SpO_2) target should be between 90 and 94% – Alarm limits should be set to 89 and 95% – Protocols for screening and treating preterm babies for ROP should be in place
Non-invasive respiratory support	– CPAP or (s) NIPPV should be started from birth in all babies at risk of RDS, such as those < 30 weeks' gestation who do not need intubation for stabilization – The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask with a starting pressure of about 6-8 cm H_2O; positive end-expiratory pressure (PEEP) can then be individualized depending on clinical condition, oxygenation, and perfusion; ability to escalate to NIPPV will reduce the need for invasive mechanical ventilation in some infants – CPAP with early rescue surfactant is considered optimal management for babies with RDS – BIPAP devices confer no advantages over CPAP alone. Synchronized NIPPV, if delivered through a ventilator, can reduce the need for ventilation or reduce the need for re-ventilation following extubation and may reduce BPD – HFNC can be used as an alternative to CPAP for some babies with the advantage of less nasal trauma, provided the center has access to CPAP or NIPPV for those failing this mode

(*Continues*)

Table 3. Summary of recommendations, from the *European Consensus Guidelines on the Management of Respiratory Distress Syndrome - 2022 Update*[40] (*continued*)

Invasive MV strategies	– After stabilization, MV should be used in babies with RDS when other methods of respiratory support have failed; duration of MV should be minimized – Lung protective modes such as volume target ventilation or high-frequency oscillation ventilation should be the first choice for babies with RDS who require MV – When weaning from MV, it is reasonable to tolerate a modest degree of hypercarbia provided the pH remains above 7.22; avoid pCO_2 < 4.7 kPa (35 mmHg) when on MV to reduce brain injury – INO in preterm babies should be limited to a therapeutic trial for those in whom there is documented pulmonary hypertension with severe respiratory distress and stopped if there is no response – Caffeine (20 mg/kg loading, 5-10 mg/kg maintenance) should be used to facilitate weaning from MV; early caffeine should be considered for babies at high risk of needing MV, such as those on non-invasive respiratory support – A short tapering course of low dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1-2 weeks – Inhaled budesonide can be considered for infants at very high risk of BPD – Opioids should be used selectively when indicated by clinical judgment and evaluation of pain indicators; the routine use of morphine or midazolam infusions in ventilated preterm infants is not recommended
Monitoring and supportive care	– Core temperature should be maintained between 36.5 and 37.5°C at all times – Most babies should be started on intravenous fluids of 70-80 mL/kg/day in a humidified incubator, although some very immature babies may need more; fluids must be tailored individually according to serum sodium levels, urine output, and weight loss – Parenteral nutrition should be started from birth; amino acids 1.5-2 g/kg/day should be started from day one and quickly built up to 2.5-3.5 g/kg/day; lipids 1-2 g/kg/day should be started from day one and built up to a maximum of 4.0 g/kg/day as tolerated – Enteral feeding with mother's milk should be started from the first day if the baby is hemodynamically stable – In infants with RDS, antibiotics should be used judiciously and stopped early when sepsis is ruled out
Managing blood pressure and perfusion	– Treatment of hypotension is recommended when it is confirmed by evidence of poor tissue perfusion such as oliguria, acidosis, and poor capillary refill rather than purely on numerical values; treatment will depend on the cause – If a decision is made to attempt therapeutic closure of the PDA, then indomethacin, ibuprofen, or paracetamol can be used with a similar efficacy; paracetamol is preferred when there is thrombocytopenia or concerns about renal function – Hemoglobin (Hb) concentration should be maintained within acceptable limits; Hb thresholds for infants with severe cardiopulmonary disease are 12 g/dL (HCT 36%), 11 g/dL (HCT 30%) for those who are oxygen dependent, and 7 g/dL (HCT 25%) for stable infants beyond 2 weeks of age
Miscellaneous	– Surfactant can be used for RDS complicated by congenital pneumonia – Surfactant therapy can be used to improve oxygenation following pulmonary hemorrhage – Surfactant therapy can be used to improve oxygenation following meconium aspiration syndrome

BIPAP: bi-level positive airway pressure; CPAP: continuous positive airway pressure; FiO_2: fraction of inspired oxygen; GA: gestational age; HFNC: high flow nasal cannula; HTC: hematocrit; INO: inhaled nitric oxide; LISA: less invasive surfactant administration; MV: mechanical ventilation; NIPPV: nasal intermittent positive pressure ventilation; PDA: patent ductus arteriosus; PIP: peak inspiratory pressure; RDS: respiratory distress syndrome; SpO_2: peripheral saturation of oxygen.

should not be used in preterm infants below 28 weeks of gestational age because of an increased risk of intraventricular hemorrhage[55]. Oxygen for resuscitation should be controlled using a blender, using an initial FiO_2 of 0.30 for babies of < 28 weeks' gestation, 0.21-0.30 for those at 28-31 weeks, and 0.21 for 32 weeks› gestation and above[40]. Babies breathing spontaneously should be started on nasal continuous positive airway pressure (NCPAP) rather than intubated in the delivery room to reduce the risk of BPD[56]. Recent data does not support the routine use of sustained inflations at birth and it does not reduce the risk of BPD[57,58]. Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs[40].

Early respiratory support

Data from randomized controlled trials and meta-analyses support the early initiation of NCPAP for preterm neonates at risk of BPD[56,59-61]. Nasal bi-level CPAP (or biphasic CPAP or SiPAP) and nasal intermittent positive pressure (NIPPV) have been shown to reduce the need for intubation when compared to NCPAP, although they are not associated with a reduced risk for BPD[62]. Nasal bi-level CPAP uses delta pressures of 3-6 cmH_2O above positive end expiratory pressure (PEEP) and is not as effective as NIPPV given by a ventilator device in reducing hypercarbia[63]. A subgroup analysis of a large multicenter randomized controlled trial comparing outcomes of infants on NIPPV versus bi-level NCPAP

did not show a significant difference in the composite outcome of BPD or BPD/death, but morbidity was higher in the bi-level NCPAP group[63].

A recent meta-analysis of eight trials involving 463 patients, showed that nasal high-frequency oscillatory ventilation (NHFOV) significantly improved CO_2 clearance and reduced the need for intubation compared to NCPAP/bi-level CPAP[64].

NIV-NAVA (non-invasive neurally-adjusted ventilatory assist) detects the electrical activity of the diaphragm and is able to synchronize non-invasive ventilation with the patients' inspiratory efforts, allowing for a decrease in the work of breathing. According to a study by Yagui A.C. et al., in infants with respiratory distress after birth, no differences in treatment failures were observed between NIV-NAVA and NCPAP[65]. Other small, randomized controlled trials have shown that NIV-NAVA is as effective as NCPAP in preventing extubation failure, but large trials studying the outcome of BPD in extremely preterm infants are needed before NIV-NAVA can be routinely recommended[66].

High-flow nasal cannula has become popular but showed similar results when compared to NCPAP in relation to the risk of BPD, air leak syndrome, and nasal injury[67].

Invasive mechanical ventilation

If intubation cannot be avoided and invasive mechanical ventilation has to be started, strategies using volume-targeted ventilation are advised[68]. One meta-analysis by Klingenberger C. et al. demonstrated that infants ventilated using volume-targeted ventilation compared to traditional pressure-limited ventilation (PLV) modes had lower rates of death or BPD, pneumothoraces, hypocarbia, severe cranial ultrasound pathologies, and shorter durations of ventilation compared to infants ventilated using PLV modes[69].

Today, there are no strong recommendations for the primary use of high-frequency oscillatory ventilation (HFOV) in preterm infants, to prevent BPD. A systematic review and meta-analysis of ten randomized controlled trials, with the primary outcomes being death or BPD at 36 weeks' postmenstrual age, death or severe adverse neurological event, or any of these outcomes, did not support the use of HFOV on the basis of gestational age, birthweight for gestation, initial lung disease severity, or exposure to antenatal corticosteroids[70].

The requirement of invasive mechanical ventilation at day seven of life is associated with an increased risk for BPD. The general advice is to wean during the first week of life and attempt extubation if settings are low[67]. In invasively ventilated preterm infants, the total number of ventilation days is more predictive of BPD than the number of courses of invasive ventilation[71].

Permissive hypercarbia is a reasonable strategy to allow a moderate increase in $PaCO_2$ during weaning, provided the pH is acceptable[40].

Surfactant

Surfactant administration in the course of neonatal RDS is an important measure that improves lung compliance and helps to reduce ventilator settings, ventilator days, and supplemental oxygen requirements, while also facilitating extubation, thus reducing the risk of BPD[72].

Less-invasive surfactant therapies (LIST) use surfactant instillation through a thin tracheal catheter in spontaneously breathing infants, rather than administering surfactant through an endotracheal tube (InSurE technique). A systematic review and meta-analysis by Rigo V. et al. revealed that LIST strategies decrease the risks of BPD, of death or BPD, and of NCPAP failure compared to strategies where surfactant is administered through an endotracheal tube[73]. Specialized catheters designed for this method, known as less-invasive surfactant administration (LISA), are now commercially available. There is a better chance of achieving success when LISA is used without sedation. With the increased use of antenatal steroids and early initiation of NCPAP, outcomes are best if surfactant is reserved for infants showing clinical signs of RDS (early rescue administration)[40]. Poractant alfa, at an initial dose of 200 mg/kg, is associated with increased survival when compared with 100 mg/kg of beractant or 100 mg/kg of poractant alfa[74]. Third-generation synthetic surfactants containing proteins B and C have been shown to be promising[72]. Surfactant combined with budesonide significantly reduces BPD, but studies with long-term follow-up are needed before this can be routinely used[75].

Use of supplemental oxygen

The supplemental fraction of inspired oxygen (FiO_2) to be used in the delivery room and during the neonatal period has been the subject of several studies. At present, there is no doubt that continuous peripheral saturation of oxygen (SpO_2) monitoring should be started promptly after birth. Supplemental oxygen should be titrated in order to achieve a SpO_2 of over 80% by five minutes of life, because there is evidence of poorer outcomes where

this is not achieved[76]. Recommendations from the *European Resuscitation Council – guidelines 2021*[52] are for starting in room air at 32 weeks' gestation or more, 21-30% inspired oxygen at 28-31 weeks' gestation, and 30% inspired oxygen at < 28 weeks' gestation[77].

Although oxygen use is an unresolved issue, today for infants requiring supplemental oxygen after transition, most authors recommend the use of saturation targets within the 90-95% range[9,68].

Caffeine

The Caffeine for Apnea of Prematurity (CAP) trial showed that caffeine administration significantly reduced BPD in infants with a very low birth weight, as well as neurodisability at 18 months of age, and improved lung function at 11 years old[78-80]. The standard regimen includes a loading dose of 20 mg/kg of caffeine citrate, followed by 5-10 mg/kg/day; when started within the first two days of life, it appears to lead to a lower risk of BPD. Caffeine is used until drug therapy for apnea of prematurity is no longer needed. The optimal dosage and timing of initiation remain unknown[68]. The most positive effect on the lungs of preterm infants may derive from a reduced need for invasive mechanical ventilation[68].

Postnatal steroids

Dexamethasone reduces both the duration of mechanical ventilation and BPD. When used during the first week of life, dexamethasone increases the risk of neurodevelopment impairment and cerebral palsy; after the first week of life, the neurological effects are secondary to the risks of poor pulmonary outcomes[68]. A low-dose course of dexamethasone (0.89 mg/kg over 10 days) to invasively-ventilated preterm infants, after the first week of life, increases the likelihood of extubation, although it does not reduce BPD[81], and has a weak association with long-term morbidity[82].

Hydrocortisone treatment (4 mg per kilogram of body weight per day tapered over a period of 10 days) starting on postnatal day 14 to 28 did not result in substantially higher survival without moderate or severe BPD. Survival without moderate or severe neurodevelopmental impairment did not differ substantially between the BPD and the placebo groups[83].

In the PREMILOC trial, in extremely preterm infants, the rate of survival without BPD at 36 weeks of postmenstrual age was significantly increased by prophylactic low-dose hydrocortisone administered during the first ten postnatal days (1 mg/kg of hydrocortisone hemisuccinate per day, divided into two doses, for seven days, followed by one dose of 0.5 mg/kg per day for three days)[84]. In this study, hydrocortisone was not associated with a statistically significant difference in neurodevelopment at two years of age[85].

The STOP-BPD study group assessed the effect of hydrocortisone initiated between seven and 14 days after birth on death or BPD in mechanically-ventilated very preterm infants and found that hydrocortisone did not improve the composite outcome of death or BPD at 36 weeks' postmenstrual age. The authors concluded that these findings do not support the use of hydrocortisone for this indication[86].

Early use of inhaled budesonide is not recommended to prevent BPD, since its use was associated with an increase in mortality[87]. A meta-analysis of 17 trials of early- or late-inhaled corticosteroids showed a significant reduction in BPD without any increase in mortality, offering reassurance that inhaled corticosteroids can be added to current management of developing BPD in preterm infants[88,89]. Although promising, uncertainty about the optimal dose persists and this intervention needs to be tested further in larger, multicenter trials.

A systematic review and network meta-analysis assessed 14 corticosteroid regimens used to prevent BPD in preterm neonates with a gestational age of 32 weeks or younger and for whom a corticosteroid regimen was initiated within four weeks of postnatal age: moderately early-initiated, low cumulative dose of systemic dexamethasone (MoLdDX); moderately early-initiated, medium cumulative dose of systemic dexamethasone (MoMdDX); moderately early-initiated, high cumulative dose of systemic dexamethasone (MoHdDX); late-initiated, low cumulative dose of systemic dexamethasone (LaLdDX); late-initiated, medium cumulative dose of systemic dexamethasone (LaMdDX); late-initiated, high cumulative dose of systemic dexamethasone (LaHdDX); early-initiated systemic hydrocortisone (EHC); late-initiated systemic hydrocortisone (LHC); early-initiated inhaled budesonide (EIBUD); early-initiated inhaled beclomethasone (EIBEC); early-initiated inhaled fluticasone (EIFLUT); late-initiated inhaled budesonide (LIBUD); late-initiated inhaled beclomethasone (LIBEC); and intratracheal budesonide (ITBUD). A total of 62 studies involving 5,559 neonates (mean gestational age of 26 weeks) were included. The results of this study suggested that MoMdDX, a moderately early-initiated (8-14 days), medium cumulative dose (2-4 mg/kg), short course (< 8 days) of systemic dexamethasone might be the most appropriate regimen for preventing the risk of BPD or mortality at 36 weeks, with low-quality evidence. In view of the observed low

confidence in the evidence, the successful outcome and safety of this regimen need to be confirmed by an adequately-powered multicentric randomized controlled trial[90].

Late systemic corticosteroids have been reserved for infants who cannot be weaned from mechanical ventilation. The role of late systemic corticosteroids for infants who are not intubated is unclear and needs further investigation. Longer-term follow-up into late childhood is vital for assessing important outcomes that cannot be assessed in early childhood, such as the effects of late systemic corticosteroid treatment on higher-order neurological functions, including cognitive function, executive function, academic performance, behavior, mental health, motor function, and lung function. Further, randomized controlled trials of late systemic corticosteroids should include longer-term survival free from neurodevelopmental disability as the primary outcome[91].

Diuretic therapy

Preterm infants with evolving or established BPD may develop chronic, mild pulmonary edema. Diuretics have been used "off label" to prevent or treat BPD. Diuretic therapy with furosemide is associated with several adverse consequences, such as reduced weight gain, electrolyte losses, metabolic bone disease, and nephrocalcinosis[68]. Loop diuretics and thiazides are still used in preterm infants on high-level respiratory support and should be used judiciously and limited to those that show clinical improvement[9,68,92].

The association of the potassium-sparing diuretic spironolactone with hydrochlorothiazide was associated with modest improvements in respiratory support requirements, but significant electrolyte abnormalities and a slowing down in weight gain[93].

Due to the side effects and the absence of benefits, diuretics became not recommended for routine chronic use. Sporadic use may be considered in preterm infants with pulmonary edema and worsening respiratory status[94].

Inhaled bronchodilators

Muscular bronchial hyper-responsiveness is increased in infants with BPD but there is no evidence that the use of bronchodilators reduces BPD or mortality. Bronchodilators include beta-agonists (isoproterenol, salbutamol, levalbuterol, and terbutaline), anticholinergics (atropine and ipratropium), and methylxanthines (theophylline, aminophylline, and caffeine). Bronchodilators are now reserved for symptomatic severe BPD with asthma-like symptoms[68,94].

Fluid restriction and patent ductus arteriosus treatment

A high fluid intake during the first week of life may cause pulmonary edema and increase the risk of BPD[72].

Persistent patent ductus arteriosus (PDA) has been historically associated with the development of BPD. Mandatory closure versus a non-intervention approach for PDA gave rise to conflicting results. More studies are needed to assess the benefits and risks of non-intervention for hemodynamically significant PDA[9].

Nutritional strategies

Adequate nutrition will promote lung repair and growth. A low caloric intake during the first weeks of life is associated with BPD development[95].

Infants with early or developing BPD should be fed with human milk, preferably with fortified fresh maternal milk[68]. Ideally, infants with BPD should receive a fluid intake of no more than 135-150 ml/kg/day and an energy intake of 120-150 kcal/kg/day[96,97]. Providing high energy in a low volume remains a challenge and is the main cause of growth restriction in these infants. They need a nutritional strategy that encompasses early aggressive parenteral nutrition and the initiation of concentrated feedings of energy and nutrients. The order of priority is fortified mother's own milk, followed by fortified donor milk, and preterm enriched formulas[68]. Specialized nutritional strategies may be needed to overcome difficulties that are common in BPD infants, such as gastroesophageal reflux and poorly coordinated feeding[96]. Table 4 summarizes a practical nutritional approach to use in infants at risk of, or with, BPD[96,97].

Vitamin A

Preterm infants treated with intramuscular vitamin A were shown to have a lower risk of BPD at 36 weeks of gestational age; nevertheless, vitamin A did not reduce mortality, duration of mechanical ventilation, or length of hospital stay, and it did not improve neurodevelopmental outcomes at 18-22 months of age. Also, intramuscular administration is painful and must be repeated several times (i.e., 5000 U i.m. three times/week for a total of 12 doses) and has been associated with an increased risk of sepsis[98-100].

Enteral water-soluble vitamin A (5000 IU/day) started within 24 hours of introducing feeds and continued until 34 weeks' postmenstrual age improved plasma retinol

Table 4. Nutritional approach in infants at risk of, or with, established BPD[96,97]

Preventive nutritional approach in infants at high risk of BPD	
Avoid excessive fluid intake	In the first postnatal day: 80-100 mL/kg/day After the first postnatal week: 135-150 mL/kg/day
Provide adequate incubator humidity	In the first postnatal week: 60-70%
Maintain adequate temperature	Abdominal skin: 36.0-36.5°C Inspired air temperature (hood, CPAP, or ventilator): 34.0-41.0°C, relative humidity of 100%
Optimize early parenteral energy intake	In the first postnatal week: 80-100 kcal/kg/day After the first postnatal week: 120-150 kcal/kg/day
Optimize early parenteral amino acid intake	Start with 1.5-2 g/kg/day after birth Increase to 3.5 g/kg/day from the first 48-72 postnatal hours
Optimize early parenteral fat intake	Start with 1.0-2.0 g/kg/day within the first postnatal day Increase by 0.5-1.0 g/kg/day up to a maximum of 4.0 g/kg/day at 72-96 postnatal hours
Provide adequate intravenous glucose	Limit the rate to 12 mg/kg/min (ideal limit: 8.3 mg/kg/min)
Optimize early parenteral calcium (Ca) and phosphorus (P) intake	In the first postnatal week: parenteral Ca 32-80 mg/kg/day and P 31-62 mg/kg/day After the first postnatal week: parenteral Ca 100-140 mg/kg/day and P 77-108 mg/kg/day Parenteral Ca/P ratio: 1.3 (mass) or 1 (molar)
Provide adequate intravenous lipid soluble vitamins	Vitamin A (retinol) 227-455 µg/kg/day or 700-1500 IU/kg/day Vitamin E (α-tocopherol) 2.8-3.5 IU/kg/day
Provide adequate intravenous trace elements	Particularly zinc 400-500 µg/kg/day
Initiate early enteral feeding	Initiate minimal enteral feeding (12-24 mL/kg/day) prior to 3rd postnatal day Use preferably mother's own milk or donor human milk as second choice
Nutritional management in infants with established BPD	
Fluid restriction	Less than 150 mL/kg/day Ideally, up to 135 mL/kg/day
Optimize enteral energy intake	Ideally, 120-150 kcal/kg/day
Optimize enteral amino acid intake	< 1000g body weight: 4.0-4.5 g/kg/day 1000-1800g body weight: 3.5-4.0 g/kg/day
Optimize enteral lipid intake	Total lipid intake 4.8-6.6 g/kg/day Arachidonic acid 12-30 mg/kg/day Docosahexaenoic acid 18-42 mg/kg/day
Optimize enteral calcium and phosphate intake	Ca 120-140 mg/kg/day; 150-220 mg/kg/day P 60-90 mg/kg/day; 75-140 mg/kg/day Ca/P ratio: 2 (mass)
Optimize sodium intake if diuretics are used	Provide sodium supplement to maintain serum Na>135 mEq/L
Optimize enteral vitamin A intake	400-1000 µg/kg/day or 1320-3300 IU/kg/day
Optimize enteral vitamin E (α-tocopherol) intake	2.2-11 mg/kg/day
Supplemental iron	4 mg/kg/day, from 4-8 postnatal weeks up to 12 months of life

levels in extremely preterm infants but did not reduce the severity of BPD[101].

Pulmonary vasodilators

Pulmonary hypertension often complicates severe forms of BPD and increases mortality. Pulmonary hypertension should be looked for in moderate/severe forms at 36 weeks of post-menstrual age, or during aggravating BPD. The pulmonary hypertension results from a structural component (fixed component) caused by abnormal development of pulmonary vessels, and an increased vascular resistance (reactive component)[94]. This reactive component can be treated with

Table 5. Summary of BPD management *(adapted from ref[68,96,97,104])*

Evolving BPD (> 1 postnatal week until 36 weeks post-menstrual age)	
Dexamethasone	A low-dose course of dexamethasone (0.89 mg/Kg over 10 days) to invasively ventilated preterm infants, after the first week of life, increases the likelihood of extubation
Methylxantines	Maintain caffeine (started within the first 3 days of life) until apneas are no longer present
Ventilation	Avoid endotracheal tube ventilation, encourage non-invasive support Blood gas targets: pH 7.25-7.35; PaO_2 50-70 mmHg; $PaCO_2$ 50-60 mmHg
Nutrition (see table 5)	Fluid intake: 135-150 mL/kg/day Energy intake: 120-150 kcal/kg/day Enteral feeding: the order of priority is fortified mother's own milk, followed by fortified donor milk, and preterm enriched formulas
Diuretics	May improve respiratory mechanics and facilitate weaning of ventilatory support; continue only if there is a clear response
Inhaled corticosteroids	Can be used to improve symptoms
Established BPD (> 36 weeks post-menstrual age)	
Ventilatory strategy	Hood oxygen, low-flow nasal cannula, high-flow nasal cannula, NIPPV, NCPAP, invasive IPPV Ventilatory settings in severe BPD: tidal volume 8-12ml/kg; PIP needed to deliver tidal volume may vary between 30-40 mmHg; inspiratory time: 0.4-0.8 s; frequency: 20-30/sec; PEEP: 6-10 cmH2O Target SpO_2: 90-95%; if PH $\geq$ 95% Target blood gases: pH > 7.22; PaO_2 50-70 mmHg; $PaCO_2$ 45-60 mmHg Tracheostomy: no consensus when to perform; for infants still requiring mechanical ventilation at 90-100 days of life who failed several (> 5-7) attempts at extubation, a tracheostomy should be considered
Oxygen targets	After 40 weeks of postmenstrual age and the maturation of retinal vascularity (documented by ophthalmology), oxygen output should be sufficient to maintain a peripheral oxygen saturation (SpO_2) - $\geq$ 93%. In patients with documented pulmonary hypertension or poor weight gain a SpO_2 recommended is $\geq$ 95%
Echocardiographic screening for pulmonary hypertension	About 25% of infants with moderate or severe BPD have echocardiographic evidence of pulmonary hypertension Supplemental oxygen should be supplied when target oxygen saturations are > 95% for infants with proven pulmonary hypertension INO may be considered in individual cases of BPD during acute pulmonary hypertension crisis Analgesia and sedation should be used before procedures to avoid pulmonary hypertension crisis Sildenafil may be used to treat BPD-associated pulmonary hypertension in selected cases, after consultation with a pediatric cardiologist; bosentan is often used as a second-line therapy, after sildenafil
Diuretics	Diuretic therapy in preterm infants remains controversial, given its negative impact on growth and the risk for metabolic bone disease. Treatment with hydrochlorothiazide and spironolactone may be considered in infants with severe BPD. However, indications and duration of diuretic treatment should be discussed in a multidisciplinary team, involving cardiologists, neonatologists, pulmonologists, and nutritionists. Consider allowing infant to outgrow dose
Bronchodilators	May improve symptoms in subpopulations of affected infants
Inhaled corticosteroids	May improve symptoms in subpopulations of affected infants
Nutrition	Fluid restriction: less than 150 mL/kg/day, ideally, up to 135 mL/kg/day Optimize enteral energy intake: ideally, 120-150 kcal/kg/day
Immunization	Before discharge, start prophylaxis against respiratory syncitial virus infection during winter season

BPD: bronchopulmonary dysplasia; INO: inhaled nitric oxide; IPPV: intermittent positive pressure ventilation; NCPAP: nasal continuous positive airway pressure; NIPPV: nasal intermittent positive pressure ventilation; PEEP: positive end expiratory pressure; PH: pulmonary hypertension; PIP: peak inspiratory pressure; SpO_2: peripheral oxygen saturation.

pulmonary vasodilators including inhaled nitric oxide (iNO), sildenafil, and bosentan. Although iNO is not recommended for routine use for either BPD prophylaxis or BPD-associated pulmonary hypertension, its use may be considered in individual cases of BPD during acute pulmonary hypertension crisis[94].

Only two drugs have so far been approved by the regulatory European Medicines Agency (EMA) for

pediatric patients with pulmonary arterial hypertension, which is sildenafil (body weight ≥ 8 kg and > one year old) and bosentan (age > one year), and only bosentan has been approved by the Food and Drug Administration (FDA) for chronic use in children > three years of age. However, both sildenafil and bosentan are frequently used for acute and long-term treatment of infants with BPD-associated pulmonary hypertension. In the absence of randomized clinical trial data, use of pulmonary hypertension targeted medications in infants is based on expert opinion and experience, underlining the necessity of comprehensive evaluation in expert centers according to current international recommendations. Sildenafil, a selective phosphodiesterase-5 (PDE-5) inhibitor, prolongs smooth muscle relaxation, and its use has been increasing over time. Sildenafil may be used to treat BPD-associated pulmonary hypertension in selected cases, after consulting with a pediatric cardiologist[94]. Bosentan, a non-selective competitive antagonist of ET-1 receptor reverses entothelin-mediated smooth muscle constriction and is often used as a second-line therapy, after sildenafil, in severe BPD with pulmonary hypertension[94].

Macrolides

Respiratory tract colonization with the genital mycoplasma species Ureaplasma parvum and Ureaplasma urealyticum in preterm infants is a known risk factor for BPD. Specific virulence factors, pathogen-host interactions, and variability in genetic susceptibility contribute to chronic infection, inflammation, and altered lung development[102].

Macrolides inhibit neutrophil chemotaxis, tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 and consequently exert an anti-inflammatory action[94]. Studies with erythromycin did not show a decrease in either the incidence or severity of BPD in preterm infants[94]. Azithromycin showed inconsistent results and was associated with a reduction in BPD in some studies and, like erythromycin, is associated with development of hypertrophic pyloric stenosis. While azithromycin may decrease the incidence of BPD, there is insufficient evidence regarding dosage, duration, and timing of therapy, and its routine prophylactic use for BPD prevention in preterm infants is not recommended[94]. The AZTEC trial (ISRCTN11650227) aims to assess the effect of azithromycin on BPD and is ongoing[103]. The role of clarithromycin has not yet been established[94].

Future directions

Mesenchymal stromal cells (MSC) facilitate healing in injury sites and may prove to be useful against BPD, but they are still in the experimental phase[94]. Recombinant human erythropoietin (rhEPO) was shown to reduce BPD in some retrospective studies. However, a meta-analysis consisting of 17 trials, and the PENUT (Preterm Erythropoetin Neuroprotection) trial showed no significant benefit[94]. rhEpo in combination with MSC has not yet been studied in humans. Docosahexaenoic acid (DHA), clara cell protein, superoxide dismutase (SOD), pentoxifylline, citrulline, and inositol are experimental therapies and safety and efficacy still need to be established[94].

Table 5 summarizes BPD management according to current evidence and knowledge.

Conclusions

BPD is a complex and multifactorial lung disease of the preterm neonate. The lack of an objective definition makes it difficult to evaluate new treatments. Despite improvements in treatment research, only a few treatments available are supported by high-quality evidence. Several, promising, novel therapies are under study and may change the course of the disease in the future.

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Conflicts of interest

None.

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Laughing gas: nothing to laugh about

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Abstract

Trends in substance abuse are constantly evolving and therefore our awareness and knowledge as health professionals should too. Nitrous oxide (N_2O), also known as "laughing gas", "nangs", "whippits" or "hippie crack" has been used in a recreational context for almost 250 years, with a few periods of exponential growth in its use during that time, the latest occurring in the last 10 years. There is, however, a significant difference when comparing recent years to the 1970s or the Victorian era. Nowadays, N_2O is not only widely available, it is also cheap and easy to use. Adolescents who abuse N_2O are seeking quick sensations such as euphoria, relaxation, or hallucinations, unaware of, or disregarding, the potential serious adverse effects and chronic consequences. In 2014, the Global Drug Survey confirmed that N_2O had become increasingly popular as a recreational drug and Portugal, unfortunately, is no exception. In 2021, Portuguese law enforcement authorities seized nearly 400 units of canisters (N_2O containers) and 2022 followed the same trend, which led to a proposal to the Portuguese Ministry of Health to regulate N_2O sales and consumption. In September 2022, that proposal was approved and ever since, N_2O has been classified as a prohibited psychoactive substance.

Keywords: Drugs. Nitrous oxide. Adolescents. Vitamin B12. Neurotoxicity.

Gás do riso: sem razões para rir

Resumo

O forma de uso e abuso de substâncias ilícitas está em constante mutação pelo que os profissionais de saúde devem ter essa consciência e acompanhar a evolução do conhecimento nessa área. O óxido nitroso (N_2O), também conhecido como "gás do riso", "nangs", "whippits" ou "hippie crack", tem sido usado em contexto recreativo há quase 250 anos, com alguns períodos de crescimento exponencial, o mais recente ocorrendo nos últimos 10 anos. No entanto, existe uma diferença significativa ao comparar os anos recentes com os anos 1970, ou da era vitoriana. Atualmente, o N_2O não só está amplamente disponível, como também é barato e fácil de usar. Os adolescentes que abusam do N_2O procuram sensações rápidas como euforia, relaxamento ou alucinações, ignorando ou desconsiderando os potenciais efeitos adversos graves e consequências crónicas. Em 2014, o Global Drug Survey confirmou que o N_2O se tinha tornado cada vez mais popular como uma droga recreativa e Portugal, infelizmente, não é exceção. Em 2021, as autoridades portuguesas apreenderam quase 400 unidades de cartuchos (recipientes de N_2O), sento que 2022 seguiu a mesma tendência, o que levou a uma proposta ao Ministério da Saúde Português para regular as vendas e o consumo de N_2O. Em setembro de 2022, essa proposta foi aprovada e, desde então, o N_2O foi classificado como uma substância psicoativa proibida.

Palavras-chave: Drogas. Óxido nítrico. Adolescentes. Vitamina B12. Neurotoxicidade.

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Keypoints

What is known

- N_2O mixed with oxygen has been a valuable tool in pediatric emergency departments for managing pain during procedures. Its anesthesiological properties and side-effect reduction are well-documented.
- N_2O has a history of recreational use dating back to the 19th century, including "laughing gas parties" among the British upper class and usage among university students in the 1970s for euphoria.

What is added

- This paper outlines recent trends in the recreational use of N_2O, including its growing popularity among adolescents and the legislative actions taken in Portugal and other countries to address this issue. This includes the classification of N_2O as a prohibited substance in Portugal as of September 8, 2022.
- It emphasizes the need for education on the health hazards of inhalants for children, adolescents, parents, and teachers. Furthermore, it advocates for referring patients with N_2O abuse issues to specialized institutions for drug dependence treatment.

Nitrous oxide (N_2O) and its psychotropic effects have been known to the scientific community for over two centuries. In 1772, Joseph Pristley firstly synthesized N_2O and a few years later Humphry Davy investigated, by personally inhaling N_2O, the chemistry of the gas and its psychotropic properties[1]. 1844 was the year when Horace Wells, a dentist, discovered its anesthesiologic properties and used it for the first time to extract his own molar teeth[1]. From then on, several milestones followed, including the discovery that using a mixture of N_2O and oxygen helped prevent or reduce side effects such as hypoxia and nausea/vomiting. Nowadays, a mixture of N_2O and oxygen is a very useful tool in several pediatric emergency departments in managing/sedating children and adolescents who require painful procedures (fracture reductions, minor surgery, suturing or venous access, etc.).

On a different note, and following medicinal use, N_2O also began to be used recreationally. During the 19th century, members of the British upper class engaged in a peculiar form of entertainment, known as laughing gas parties, where N_2O was inhaled from silk bags[2]. Those who inhaled N_2O did so to lose their inhibitions and dance/sing. In the 1970s, the gas grew in importance as university students sourced N_2O from canisters (cylinders) for making whipped cream and used it for a quick sensation of euphoria[3]. From a cohort of 500 medical and dentals students, a study performed in 1976 found that 16% had used N_2O recreationally in the past[4].

Since then and up until 2010, other drugs attracted more attention and nitrous oxide lost its appeal to the younger generation as a recreational drug. However, the truth is that in recent years a new trend is emerging, showing a growing consumption/abuse of this gas among adolescents. In the "streets", N_2O has been nicknamed "laughing gas", "hippie crack," "whippets", and "chargers". Teenagers usually inhale it through a balloon or bulb, known as "nagging" or "nanging".

Ever since 2010, many countries around the world have documented this increase in the recreational use of N_2O. The problem became increasingly concerning from 2017, when both the supply and consumption of the gas grew[4]. The market adjusted for this substance and suppliers began to sell larger cylinders of the gas, deliberately targeting this recreational market. As a result, N_2O is now easily available and cheap. It is not only easy to find and order online, but social media has also helped encourage the use of this gas at parties, festivals, and raves, making N_2O a very common drug.

In 2014, a Global Drug Survey involving 74,864 participants from 17 countries confirmed that N_2O had gained interest among teenagers as a popular recreational drug[5]. The same group conducted another survey in 2019 involving 30 countries (including Portugal), which confirmed the popularity of this drug[6]. A survey conducted in 2020 in England, aimed at 16- to 24-year-olds, found that nine percent had used N_2O in the previous year, making the drug second only to cannabis[7].

In recent years in Portugal, a number of newspaper articles have been warning of the recent popularity of N_2O among the younger population. Unlike nearly all other drug classes, it is most-commonly used among younger adolescents with use peaking between the seventh and ninth grades[8]. In 2021, 93 confiscations of nitrous oxide (bottles or balloons) were recorded, namely in Lisbon, Setúbal and Faro[4]. Around 300 to 400 units of varying sizes of canisters and bottles were seized[4].

In 2022, up until the conclusion of the report entitled 'Recreational use of nitrous oxide: a growing concern for Europe', 35 confiscations of nitrous oxide (bottles or balloons) had already been documented by Portuguese law enforcement authorities. Following these events, the

General Directorate for Intervention on Addictive Behaviors and Dependencies (SICAD) submitted a proposal to the Ministry of Health to regulate sales and consumption of nitrous oxide[9]. The proposal was approved and ever since September 8, 2022, nitrous oxide has been classified as a prohibited psychoactive substance[9]. Despite legislative action and these regulations, N_2O remains easily accessible online and even in some convenience stores.

When inhaling the gas, users seek certain symptoms/sensations such as relaxation, a giggly mood, sound or visual distortions, and euphoria. All of these are immediate upon inhalation and disappear in a matter of 1 to 2 minutes usually, depending on the dose and concomitant drugs[2]. However, adverse effects can also occur: headache, dizziness and intense feelings of paranoia[1,2,3].

To date, the mechanisms of N_2O toxicity have not been fully elucidated. Clinically, its toxicity can be divided into acute toxicity and chronic toxicity[5,10]. In terms of acute toxicity, N_2O, once inhaled, diffuses across the basement membrane of the alveoli faster than oxygen and then rapidly enters the bloodstream, diluting the volume of oxygen in the alveoli. Decreased oxygen tension in the alveoli then leads to decreased oxygen delivery to the brain, and it is this hypoxia that is responsible for the sensations sought by consumers. Healthy individuals can tolerate this hypoxia in a well-ventilated space, but individuals with comorbidities such as epilepsy or heart diseases may develop seizures, arrhythmias, or even respiratory or cardiac arrest[3].

Chronic toxicity is mainly dependent on vitamin B12 deficiency. N_2O causes oxidation of the cobalt ion in vitamin B12, thereby rendering it inactive, and leading to functional vitamin B12 deficiency, even with normal stores. Without vitamin B12, homocysteine cannot be converted to methionine, thus preventing methylation of myelin proteins and ultimately promoting demyelination in the peripheral and central nervous systems. In the spinal cord, there is a predilection for demyelination in the dorsal columns, leading to a myelopathy due to 'subacute combined degeneration' of the spinal cord[10].

N_2O neurotoxicity can present with varying degrees of upper and lower motor neuron involvement. Spinal cord involvement manifests as spasticity, pyramidal pattern weakness and dorsal column sensory loss. Peripheral nerve involvement results in length-dependent large- and small-fiber sensory loss and symmetrical distal weakness. Some patients also develop visual disturbance due to optic neuropathy. Also, hyperhomocysteinemia induced by the enzymatic inhibition of methionine synthase is known to cause increased rates of thrombosis, and ischemic strokes have been linked to the recreational use of nitrous oxide in the past[11].

Some studies also suggest transient elevations in plasma homocysteine play a role in the pathogenesis of acute myocardial infarctions, via endothelial dysfunction, oxidative stress, and vascular inflammation[12]. When it comes to chronic elevations of homocysteine, these are often associated with the development of coronary artery disease via accelerated atherosclerosis[12]. A contribution of nitrous oxide on the etiology of pneumothorax and pneumomediastinum was also described[13,14].

Other complications include: mental symptoms (such as delusion, delirium, and depression), megaloblastic anemia, skin changes, and immune disorders[3]. This means that the abuse of N_2O should constitute one of the differential diagnoses in subacute-onset myeloneuropathy to explore metabolic (folic acid and copper deficiency), infectious (syphilis and HIV), vascular (spinal cord ischemia), neoplastic (compressive tumor), and autoimmune/inflammatory (Guillain-Barre syndrome and multiple sclerosis) causes.

When it comes to managing acute inhalant intoxication, maintaining cardiorespiratory function and removing the child from the source of the toxin (bottle or bag) are of primary importance. When hypoxic, supplemental 100% oxygen by a non-rebreather face mask should be administered. As to treatment in cases of neurotoxicity, this involves cessation of N_2O and immediate administration of vitamin B12. Current guidelines suggest intramuscular, rather than oral, treatment, at a dose of 1 mg on alternating days for two weeks, although it is reasonable to continue with this replacement schedule while there is ongoing neurological improvement[4,15,16].

Given the fact that adolescents will often conceal their N_2O exposure history, abuse of this gas is likely to be missed as a possible cause in emergency or medical departments, leading to misdiagnosis. Physicians, especially pediatricians, should be aware of the increasing prevalence of N_2O abuse and its potential complications. When suspected, laboratory assessments should include blood testing for vitamin B12, homocysteine, methylmalonic acid, and folic acid. Close contact with Centro de Informação Antivenenos (CIAV) should be established when nitrous oxide intoxication is suspected.

Education focused on the health hazards of inhalants and aimed at children, adolescents, parents, and teachers should be carried out in order to try and keep abreast of trending drugs. Finally, patients with either chronic or acute abuse of nitrous oxide should be referred to institutions/organizations specifically

designed to help patients dealing with drug dependence, such as the Gabinete de Prevenção Seletiva e Indicada (CLICK) and the Gabinete de Atendimento a Jovens e Envolventes (GAJE).

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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 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

Acute disseminated encephalomyelitis associated with SARS-CoV-2 in a 21-month-old: a case report

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Abstract

Introduction: Since its emergence in 2019, SARS-CoV-2 has been responsible for a myriad of symptoms affecting multiple organ systems, including the central nervous system. Although rare, especially in children, cases of acute disseminated encephalomyelitis (ADEM) associated with COVID-19 have also been described. **Case report:** We present the case of a previously healthy 21-month-old girl who presented with altered consciousness and ataxia ten days after SARS-CoV-2 infection was reported. Cranioencephalic MRI revealed hyperintense T2-weighted and hypointense T1-weighted lesions. The remaining imaging, analytical, autoimmune, and serological studies showed no alterations, allowing a diagnosis to be established. Therapy with pulses of prednisolone was initiated with excellent results. **Discussion:** This case report highlights the importance of a high index of suspicion in a child presenting with encephalopathy days to weeks after SARS-CoV-2 infection. A quick diagnosis is vital for early treatment and to improve the clinical course and long-term outcome.

Keywords: ADEM. SARS-CoV-2. Encephalitis.

Encefalomielite aguda disseminada após infeção a SARS-CoV-2 numa criança de 21 meses: um relato de caso

Resumo

Introdução: Desde o seu aparecimento em 2019, a SARS-CoV-2 tem sido responsável por uma miríade de sintomas que afetam múltiplos sistemas de órgãos, incluindo o sistema nervoso central. Embora raros, especialmente em crianças, foram também descritos casos de encefalomielite aguda disseminada (ADEM) associada à COVID-19. **Relato de caso:** Apresentamos o caso de uma criança do sexo feminino de 21 meses, previamente saudável, que se apresentou com alterações do estado de consciência e ataxia dez dias após ter sido notificada a infeção por SARS-CoV-2. A RMN cranioencefálica revelou lesões hiperintensas em T2 e hipointensas em T1. Os restantes estudos imagiológico, analítico, auto-imune e serológico não revelaram alterações, permitindo estabelecer o diagnóstico. Foi iniciada terapêutica com pulsos de prednisolona com excelente melhoria clinica. **Discussão:** O presente caso de caso salienta a importância de um elevado índice de suspeição numa criança que se apresente com encefalopatia dias a semanas após a infeção pela SARS-CoV-2. O rápido diagnóstico é importante para o tratamento precoce e para melhorar o curso clínico e o resultado a longo prazo.

Palavras-chave: Encefalomielite disseminada aguda. SARS-CoV-2. Encefalite

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Keypoints

What is known
- ADEM is a rare inflammatory demyelinating disorder of the central nervous system that usually affects children.
- ADEM is a post-infection disorder and is mostly caused by a virus vancomycin and gentamicin as a first line therapy for LOS.
- The identification of this pathology is vital for early treatment and to improve the clinical course and long-term outcome.

What is added
- Although rare, cases of ADEM associated with COVID-19 have also been described.
- The presentation and course of the disease appear to be similar to classic ADEM, although with a poorer outcome.
- This entity should be considered in a child who has had COVID-19 and presents with encephalopathy.

Introduction

Since its emergence in December 2019, SARS-CoV-2 has been responsible for a myriad of symptoms affecting multiple organ systems. Neurological involvement has been frequently reported, mainly in adults but also in children, ranging from mild symptoms to rare and severe manifestations such as meningoencephalitis, Guillain-Barré syndrome and cerebellitis[1-3]. Data that are currently available show that SARS-CoV-2 has neuroinvasive potential, that its neurotropism is limited, and that it can be neurovirulent in at least a subgroup of patients. This concurs with observations from the clinic, where the impact of SARS-CoV-2-associated central nervous system complications appears limited during the acute phase, but more prominent during the post-acute phase[4]. We report a case of a child with COVID-19-associated acute disseminated encephalomyelitis (ADEM).

Case report

A 21-month-old girl is taken to the emergency department presenting with prostration, drowsiness, and ataxia since that morning, with decreased food intake and generalized abdominal pain since the previous day. The mother reported occasional taking of herbal syrup to sleep but that it had not been administered the night before. She denied the possibility of taking other substances. She had no significant personal or family history. She had a SARS-COV-2 infection ten days before.

On admission, the child was hemodynamically stable, apyretic, awake, but with some periods of decreased responsiveness and obnubilation. She complied with some simple commands but appeared not to distinguish who was around her. Her gait was unbalanced. The remaining physical and neurological examination was unremarkable.

The patient's hematological parameters, renal function, blood glucose, electrolytes, and blood gas analysis were normal. Urine drug screening was negative. Reverse transcription polymerase chain reaction ([rRT]-PCR) for respiratory virus in nasopharyngeal secretions was negative (*Adenovirus, Infuenza A and B, Parainfluenzae 1,2 and 3, Respiratory Syncytial Virus, Methapneumovirus and Coronavirus OC43*). Magnetic resonance imaging (MRI) revealed hyperintense T2 and FLAIR lesions in the posterior left corona radiata as well as faint hypointense signal on T1 images (Fig. 1). MRI of the spinal cord showed no alterations.

Cerebrospinal fluid (CSF) analysis demonstrated 1/mcL erythrocytes, 1/mcL leucocytes, 57 mg/dL glycose, and 19.8 mg/dL proteins. The CSF (rRT)-PCR panel was negative (including *Escherichia coli, Streptococcus pneumoniae, Streptococcus agalactiae, Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus agalactiae, Neisseria meningitidis, Lysteria monocytogenes, Adenovirus, Herpes simplex virus (HSV) 1-2, Human Herpes virus 6, Parechovirus, Varicella Zoster virus, Cytomegalovirus, and Enterovirus*). CSF, blood and urine cultures were negative. Antibody serology tests were negative for *Cytomegalovirus, Epstein Barr virus, HSV 1-2, Adenovirus, Mycoplasma pneumoniae, Borrelia, and Chlamydia pneumoniae*. RT-(rRT)-PCR for SARS-CoV-2 in CSF was negative. The child was started on ceftriaxone, acyclovir, and azithromycin that were suspended after a negative CSF (rRT)-PCR and blood serologies.

Serology testing for SARS-CoV-2 resulted in IgG positive and IgM negative antibodies. The electroencephalogram showed right posterior slow activity. Tests for oligoclonal bands in CSF and serum neuronal autoantibodies (anti-NMDAR, anti-AQP4, and anti-MOG) were negative.

Given the neuroradiological findings, the temporal relationship between SARS-CoV-2 infection and the exclusion of other causes, the diagnosis of COVID-19-associated ADEM was assumed and the child was started on high-dose methylprednisolone (30 mg/kg/day id) for five days followed by tapering for four weeks.

During hospitalization, there was significant clinical improvement, with no abnormalities on neurological examination at the date of discharge. Three months

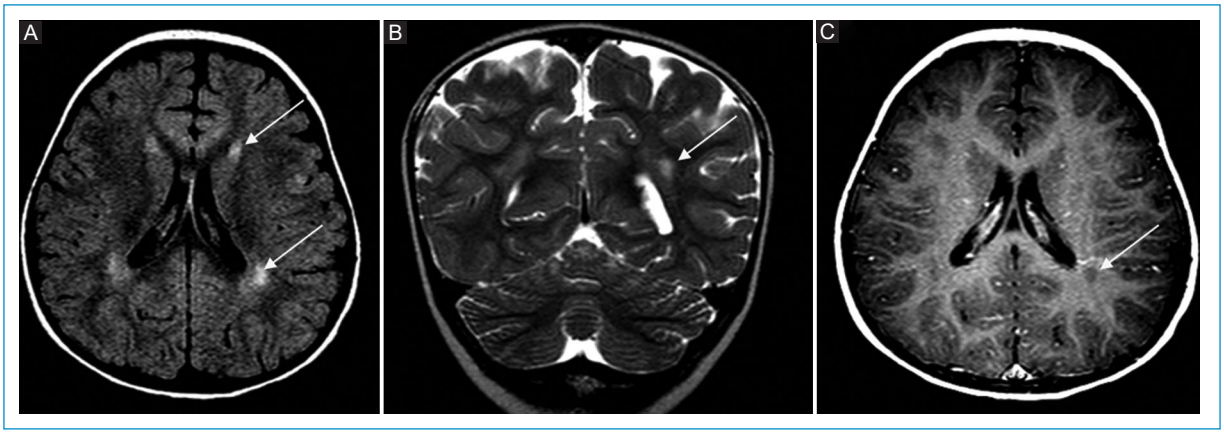

Figure 1: A: T2 FLAIR brain MRI axial image revealing hyperintense lesions in the posterior corona radiata and bilateral frontal periventricular substance. **B:** T2 coronal brain MRI revealing hyperintense lesions in the corona radiata; **C:** T1 axial brain MRI with contrast revealing hypointense lesions with no contrast uptake.

after the episode, the child remains in her usual condition, with no neurological changes and no similar episodes.

Discussion

ADEM is a rare inflammatory demyelinating disorder of the central nervous system that usually affects children and young adults[1,5]. Its etiology is often post-infectious or, more rarely, post-vaccination, with viral agents being a major culprit. Diagnosis can be difficult given the presence of several conditions mimicking ADEM and the lack of specific biomarkers[4,5]. Although rare, cases associated with COVID-19 have also been described. However, our knowledge about this entity is still scarce, since it is still based on case reports[1,6-9]. Despite classic ADEM being more frequent in pediatric age, when associated with COVID-19 it has been more frequently described in adulthood. Although extremely rare, it has also been described in pediatric patients[1,6,7].

ADEM's clinical presentation is heterogeneous. Usually, patients present with prodromal symptoms such as fever, headache, malaise, nausea, and vomiting, followed by the acute phase with encephalopathy, characterized by altered behavior and consciousness, associated with multifocal or focal neurological deficits. Diagnosis is clinical and confirmed with neuroimaging[5].

The clinical and analytical presentation of COVID-19-associated ADEM has been similar to classic ADEM, as in the presented case. However, the time gap between infection and ADEM associated with COVID-19 seems to be greater than in classic ADEM. In the typical presentation of ADEM, acute neurological symptoms develop around seven to 14 days after infection, while in ADEM post-SARS-CoV-2 infection the mean latency period seems to be around 25 days. In the case presented, the latency period was less than that described in the literature. As in the case described, the viral RNA testing for SARS-CoV-2 was negative in almost all the patients reported, reinforcing the immune-mediated character of this pathology. The treatment of classic ADEM is based on nonspecific immunosuppressive therapy, including corticosteroids, and intravenous immunoglobulins and plasma exchange for steroid-resistant patients or with contraindications to steroids[4]. The treatments used in COVID-19-associated ADEM have overlapped those recommended for classic ADEM[1]. The reported case supports this practice, having obtained an excellent clinical outcome in this child. Although the outcome of classic ADEM is usually excellent, with the full resolution of symptoms, ADEM associated with COVID-19 has been described in the literature as being associated with a poorer outcome, with an increased need for ICU, although better in the pediatric age[1,6,7]. The identification of this pathology is vital for early treatment and to improve the clinical course and long-term outcome[5], and pediatricians should consider ADEM in a child who has had COVID-19 and presents with encephalopathy.

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CASE REPORT

Bochdaleck hernia and pulmonary sequestration: case report of an unusual association

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Abstract

Introduction: Although bochdalek hernia is the most common type of congenital diaphragmatic hernia, it is still a rare condition. It can be complicated by the development of secondary pulmonary sequestration, which is subdivided into intralobar pulmonary sequestration and extralobar pulmonary sequestration. **Case report:** This study describes a case of pulmonary sequestration due to bochdalek hernia in a one-year-old girl, who underwent surgical correction. **Discussion:** Pulmonary sequestration can be confused with other more frequent pathologies, such as pneumonia or tumors, and diagnosis can be facilitated through the use of vascular imaging techniques, which confirm the diagnosis and show the vascularization of the hernia content.

Keywords: Congenital diaphragmatic hernia. Bochdalek hernia. Bronchopulmonary sequestration. Case report

Hérnia de Bochdalek e sequestro pulmonar: relato de caso de uma associação incomum

Resumo

Introdução: A hérnia de Bochdalek representa a causa mais comum de hérnia diafragmática congênita e ainda é uma condição rara. Pode ser complicada pelo desenvolvimento de sequestro pulmonar secundário, que se subdivide em sequestro pulmonar intralobar e sequestro pulmonar extralobar. **Relato de caso:** Este estudo descreve um caso de sequestro pulmonar devido a hérnia de Bochdalek em uma menina de 1 ano de idade, submetida à correção cirúrgica. **Discussão:** O sequestro pulmonar pode ser confundido com outras patologias mais frequentes, como pneumonia ou tumores, e o seu diagnóstico pode ser facilitado através da utilização de exames de imagem vascular, que confirmam o diagnóstico e mostram a vascularização do conteúdo herniário.

Palavras-chave: Hérnias diafragmáticas congênitas. Hérnia de Bochdalek. Sequestro broncopulmonar. Relato de caso.

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Keypoints

What is known

- Although rare, bochdalek hernia is the most common type of congenital diaphragmatic hernia.
- We need to be aware that congenital pulmonary abnormalities can be associated with congenital diaphragmatic hernia.

What is added

- Lobectomy or, in selected cases, segmentectomy is the treatment of choice for symptomatic and asymptomatic patients with ILPS.
- Thoracoscopy versus thoracotomy in the pediatric population showed no difference in outcomes.
- If the patient remains asymptomatic for a long time, the plan can be changed from surgery to follow-up.

Introduction

Bochdalek hernia (BH) is the most common type of congenital diaphragmatic hernia (CDH), although it is still a rare condition occurring in 1:2,500 live births[1]. A posterior defect in the pleuroperitoneal compartment allows herniation of abdominal viscera into the thorax[1], such as the stomach, omentum, liver, spleen, and intestines. Neonate liver hernia has a poorer prognosis out of all BH[2].

About 50-60% of affected individuals have isolated CDH; the remainder have complex CDH, that is, CDH occurring with additional malformations[3]. One of the more common pulmonary anomalies found with CDH is extralobar bronchopulmonary sequestration (BPS)[4]. More than 50% of cases with CDH are detected prenatally through ultrasound examination[3].

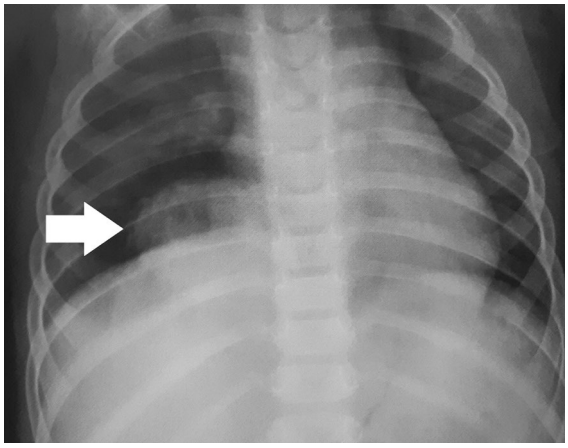

Figure 1. Chest X-ray in a posteroanterior view showing opacity in the right lung base (white arrow).

Case report

A one-year-old girl was seen at the pulmonology department to evaluate an opacity in the right lung base on a chest X-ray (Fig. 1) performed four months after treatment for bacterial pneumonia. The patient had no related symptoms and presented with normal physical examination. Her mother reported normal prenatal examinations and no postnatal complications.

A chest CT scan was performed, which detected opacity in the right lung base with anomalous vascularization from the descending aorta with Bochdaleck diaphragmatic herniation of hepatic content. MRI confirmed right Bochdaleck diaphragmatic herniation with hepatic content (Fig. 2) in addition to associated pulmonary intralobar sequestration (Fig. 3). The patient was referred for surgical treatment, but due to the pandemic the surgery was postponed for two years. During these years the patient remained asymptomatic. Thus, the plan was changed from surgery to follow-up.

Discussion

Pulmonary sequestration (PS) is a congenital malformation consequence of nonfunctioning lung tissue with no tracheobronchial tree communication. PS accounts for 0.15% and 6.5% of all congenital pulmonary malformations[5] and is subdivided into intralobar PS (ILPS) and extralobar PS (ELPS). ILPS has a higher incidence (about 80% of all PS) and is characterized by a blend of the hernia with the normal lung, whereas ELPS is separated from the normal lung by its distinct visceral pleura[6]. The sequestrated lung is supplied by an anomalous artery arising from the aorta and its venous drainage is via the azygous system, the pulmonary veins, or the inferior vena cava. In some cases, the mass effect sequestration is speculated to have a protective effect in concomitant CDH, delaying the herniation of abdominal contents until after delivery and allowing prenatal lung development[3].

Lobectomy or, in selected cases, segmentectomy is the treatment of choice for symptomatic and asymptomatic patients with ILPS, through thoracotomy or thoracoscopy. Recent reviews of thoracoscopy versus thoracotomy in the pediatric population showed no difference in outcomes[7].

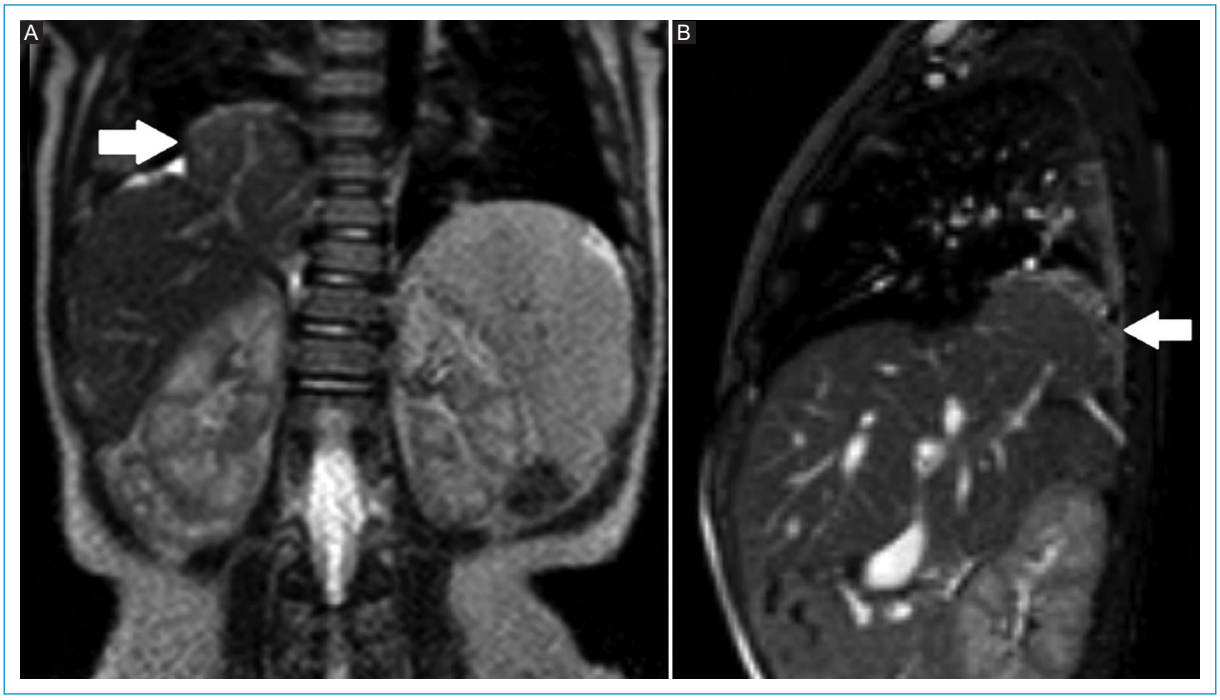

Figure 2. Magnetic resonance in the T2 sequence in **A:** the coronal plane and **B:** sagittal showing Bochdaleck diaphragmatic herniation of hepatic content (white arrows).

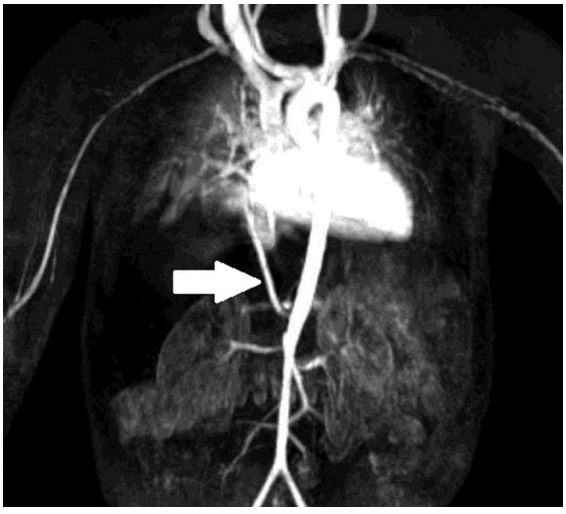

Figure 3. 3D arterial magnetic resonance angiography in the coronal plane showing the arterial vessel originating from the descending aorta supplying the lower lobe of the right lung (white arrow).

The Ramsport et al. systematic review reported that 86% of cases of Bochdalek hernia are treated surgically[8]. All of the patients treated conservatively were asymptomatic[8]. Laparotomy and laparoscopy are the preferred surgical procedures, followed by thoracotomy, thoracoabdominal approach, and thoracoscopy[8]. Some of these procedures are already being performed by robotic surgery[8]. The most common complications of surgical treatment are lung abscess, empyema, pleural effusion, broncho-pleuro-colonic fistula, hemothorax, and pneumonia[8].

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CASE REPORT

Autism spectrum disorder and PTEN hamartoma tumor syndrome – Child and adolescent psychiatric perspective

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Abstract

Introduction: Autism spectrum disorder is a neurodevelopmental disorder characterized by impairments in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities that negatively impact social, occupational, or other domains. Certain clinical features in autism spectrum disorder patients could raise suspicions of a syndromic form, such as *PTEN* hamartoma tumor syndrome, which is also associated with cancer predisposition in adulthood, in child and adolescent psychiatric appointments. **Case report:** Three pediatric patients with autism spectrum disorder presented clinical features in their physical examination that elicited a suspicion of *PTEN* hamartoma tumor syndrome. Their autism spectrum disorder profile was indistinguishable from idiopathic autism spectrum disorder and did not contribute to clinical pre-test suspicions of *PTEN* hamartoma tumor syndrome. **Discussion:** *PTEN* hamartoma tumor syndrome features should be screened in autism spectrum disorder patients to provide further medical care, including appropriate cancer screening.

Keywords: Autism spectrum disorder. Macrocephaly. *PTEN* hamartoma tumor syndrome.

Perturbação do espetro do autismo e síndrome tumores hamartosos associados ao PTEN – Perspetiva da pedopsiquiatria

Resumo

Introdução: A perturbação do espectro do autismo é uma perturbação do neurodesenvolvimento caracterizada por comunicação e interação social precária e padrões repetitivos de comportamento, interesses ou atividades com impacto negativo nos domínios social, ocupacional e outros. Determinadas características clínicas em pacientes com perturbação do espetro do autismo devem fazer, o pedopsiquiatra, suspeitar de uma forma sindrómica, como a síndrome de tumores hamartosos associados ao *PTEN*, também associada a predisposição para cancro na idade adulta. **Relato de caso:** Três casos pediátricos de perturbação do espetro do autismo com características clínicas ao exame físico que levantaram à suspeita de síndrome de tumores hamartosos associados ao *PTEN*. Operfil de perturbação do espetro do autism foi indistinto dos casos idiopáticos, não permitindo suspeita dirigida d síndrome de tumores hamartosos associados ao *PTEN*. **Discussão:** A síndrome de tumores hamartosos associados a *PTEN* deve ser considerada em determinados pacientes com perturbação do espetro do autismo para que estes usufruam a cuidados médicos personalizados, incluindo o rastreio oncológico.

Palavras-chave: Perturbação espero autismo. Macrocefalia. PTEN

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Keypoints

What is known

- Heterozygous deleterious variants in *PTEN* cause *PTEN* hamartoma tumor syndrome (PHTS).
- The exact prevalence of PHTS in patients with autism spectrum disorder is uncertain, with expected prevalence rates ranging from 1 to 7%.
- An occipital frontal circumference > 3 SD should elicit the suspicion of a PHTS diagnosis in patients with ASD.

What is added

- Despite the variability of the neurodevelopmental profile of PHTS-ASD, it is not currently possible to distinguish it from idiopathic ASD at a child and adolescent psychiatry observation.
- A diagnosis of PHTS-ASD adds to parents' anxiety and fear of the risk of additional health problems, mainly cancer predisposition.
- In cases where a PHTS diagnosis has a negative impact on patients, referral to a child and adolescent psychiatrist should be considered.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social communication and social interaction and the presence of restricted, repetitive patterns of behavior, interests, or activities that negatively impact social, occupational, or other domains[1-3]. It typically occurs early in life, often before the age of three, and is four to five times more common in boys than in girls. It is a complex developmental and behavioral disorder for which prevalence has tripled since 1970[2,3]. The etiology of ASD remains elusive; however, investigations in recent years have hypothesized that environmental and genetic factors contribute to ASD[4-9]. In 0.22-10.02% of ASD cases, a monogenic or copy number variant is identified as a major contributor to ASD, and *PTEN* is an example of a major contributor[10,11].

Deleterious germline *PTEN* variants cause *PTEN* hamartoma tumor syndrome (PHTS), which is characterized by neurodevelopmental disorders, multiple hamartomas, benign skin lesions, and increased susceptibility to cancer, such as breast, thyroid, renal cell, endometrium, and colon cancer, as well as melanoma[1-4]. Neurodevelopmental disorders and macrocephaly are early manifestations of PHTS. Benign skin or oral lesions are common and usually appear in early adulthood. The most common types of benign skin lesions seen are lipomas, acral keratosis, papillomatous skin papules, mucosal papillomas, trichilemmomas, and fibromas[3,4]. The neurodevelopmental profile of individuals with PHTS has a wide range of cognitive features including executive function impairments, elevated rates of intellectual disability, and a high prevalence of ASD[1].

A link between *PTEN* variants, macrocephaly, ASD, intellectual disability, and neurodevelopmental delay, has been demonstrated in several studies. Previous studies have also indicated that a detailed profile of ASD-related behaviors may differ between different genetic syndrome groups and from that seen in idiopathic ASD[12-14].

Since child and adolescent psychiatrists monitor multiple children with ASD, a better knowledge of the clinical features of PHTS-ASD could facilitate the identification of red flags that could elicit further testing.

Materials and methods

From a cohort of 13 patients diagnosed with PHTS and monitored at our center, three pediatric-age cases with ASD were selected.

PubMed research was carried out on June 6-8 using the MeSH terms *"macrocephaly", "autism spectrum disorder"*, and *"PTEN"*. The exclusion criteria were as follows: publication date of more than five years ago. The OMIM platform was consulted and the project was approved by the local ethics committee (017-DEFI/017-CE).

Case reports

Case 1

A male infant born at 34 weeks gestation, with a weight of 2350 g (percentile [P] 57, +0.16 standard deviation [SD]), a height of 46.5 cm (P70, +0.51 SD), and a head circumference (HC) of 36.3 cm (P89, +1.25 SD) to healthy non-consanguineous parents with a healthy younger sibling. At the age of four, the parents brought him for his first medical genetics appointment with concerns about his gait and language regression, which occurred at twelve months of age, and an increased HC. They also reported axial hypotonia since the first month of life and developmental delays in achieving milestones, such as cephalic control at seven months, sentences at five to six years of ages, and diurnal sphincter control at seven years of age. His first words were uttered at thirteen months, but he later regressed.

Upon physical examination, he was found to be macrosomic with a weight and height above P95 and a HC of more than 6.4 SD above the mean. He also presented

with facial dysmorphisms, including frontal bossing, a high forehead, downward-slanted palpebral fissures, a high-arched palate, short neck, 2-3 syndactyly in the hand, frontal angioma, and two lipomas (suprascapular and inguinal regions). Multiple trichilemmomas and arteriovenous malformations were also noted in the leg and glabellar region.

His behavior was disorganized, with increased sensory demand that conditioned his short attention span and task permanence. He required adult supervision to perform tasks and had expressive language impairment, only pronouncing simple vocalizations or isolated words. He displayed limited reciprocal social interaction, except for activities of interest to him, such as sensorimotor activities. His interests were restricted to letters and numbers, and he had a low frustration tolerance. He had received support from speech, occupational, and psychological interventions since age three.

At the age of 53 months, the Ruth Griffiths Mental Developmental Scale showed a psychometric profile below the expected level for his age, with lower results in the locomotor, personal/social, practical reasoning, and eye-motor coordination sub-scales. He was diagnosed with ASD on the basis of suggestive findings in the autism diagnostic observation-scale (ADOS) and Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. He also fulfilled the criteria for attention deficit hyperactivity disorder (ADHD) and was treated with methylphenidate (MPH), with good tolerance and therapeutic response.

The diagnosis of PHTS was confirmed through the identification of a *de novo* heterozygous pathogenic nonsense variant, c.388C > T (p.Arg130*) in *PTEN*. At his last appointment at nine years of age, his behavior had improved and he was more autonomous in daily activities. He still did not have nocturnal sphincter control, and there was evidence of precarious fine motor skills. Although he was able to read, his understanding and prosody were poor. His working memory and attention levels had improved with MPH. However, he still had deficits in social communication and interaction, difficulties with environmental transitions, and problems with behavior adjustment.

Case 2

A female patient, born at 39 weeks with a birth weight of 3600 g (P76, +0.71 SD), a height of 49 cm (P42, –0.2 SD), and a HC of 37.5 cm (p > 99, +2.95 SD) showed increased HC in the third trimester of gestation. There was no relevant family history of note. Developmental delays were observed, including the ability to sit at nine months, and her first words were uttered at three years of age.

At her first appointment at five years of age, the patient presented with macrocephaly and lipomas on her torso and limbs. During observation, she spent most of the time lying down, visually inspecting her hands while moving them in a stereotyped way and refraining from eye contact. It was challenging to capture her attention even for short periods, and she did not explore toys, except for a game with sounds and lights. She reacted with frustration when interrupted, vocalizing and crying. The patient displayed sensory issues such as displeasure with touch and soap bubbles and appreciated vestibular stimulation.

The Vineland Adaptive Behavior Scales (VABS) indicated a level of adaptive behavior lower than expected for her age. She had a limited range of vocabulary, communicating mostly through gestures and vocalizations of like or dislike. The patient showed considerable difficulty in understanding language and did not have any relationships with peers or adults. She struggled with handling toys and pencils in terms of manual dexterity, balance, hand-eye coordination, and graphomotricity.

A multigene panel for neurodevelopmental disorders was performed to elucidate the etiology of the developmental delay, which revealed a *de novo* heterozygous frameshift pathogenic variant in *PTEN*, c.264del, p. (Pro89Leufs*10), diagnosing this patient with PHTS.

During the last observation at seven years of age, the patient presented high levels of psychomotor agitation and significant motor stereotypes, which made clinical assessment difficult. She was in the first year of school at a special educational unit, where it became evident that her attention parameters were impaired, resulting in poor academic performance. Therapy with MPH was proposed but was refused by her parents. The patient was beginning to show auto- and hetero-aggressive behavior in a context of frustration and difficulties in task or routine transitions.

Case 3

We observed a male born at 39 weeks with macrosomia, weighing 4213 g (P96 +1.72 SD), and measuring 55 cm (P99 +2.6 SD) in length and 39 cm (p > 99, +3 SD) in head circumference (HC). There was no relevant family history. The patient had normal psychomotor development until the age of two, after which he experienced developmental regression. Upon examination, the patient exhibited facial dysmorphic features, including a broad forehead, frontal bossing, macrocephaly, and a depressed nasal bridge. He demonstrated poorly modulated eye

contact, limited communicative intentionality, and a preference for sensorimotor play. The patient's daily routine was hampered by increased vestibular, proprioceptive, and tactile demand, as well as oral hypersensitivity. He vocalized only minimally and showed limited communication abilities.

Genetic testing was conducted to determine the cause of macrocephaly and developmental regression, which revealed a heterozygous, likely pathogenic, missense variant in PTEN, c.139A > G (p.Arg47Gly), confirming the PHTS diagnosis. The patient benefited from therapeutic interventions, including speech therapy, occupational therapy with sensory integration, and psychology. However, he did not cooperate with the development/cognitive standardized assessments.

In his last appointment at six years of age, he presented with impairments in all life contexts, with a clinical diagnosis of ASD with intellectual disability according to the DSM-5 criteria.

Discussion

ASD is a highly heterogeneous disorder with environmental and genetic factors contributing to its etiology[12,13]. The exact prevalence of PHTS in patients with ASD is uncertain, with expected prevalence rates ranging from 1 to 7%[14,15]. Even though the same *PTEN* deleterious variants in different individuals lead to different phenotypes, missense mutations were predominantly reported in PHTS-ASD[16,17]. In our cohort, the type of variants found were heterogenous with one missense, one nonsense, and one frameshift deleterious *PTEN* variant.

The literature stated that individuals with PHTS show a broad neurodevelopmental phenotype with reduced performance in measurements of attention, impulsivity, working memory, reaction time, processing speed, motor coordination, visual-spatial abilities, auditory immediate memory, adaptive function, and more severe intellectual disability compared to idiopathic ASD. It should be noted, however, that reported cognitive abilities varied greatly, with some papers reporting individuals with IQs of over two SD above the population mean (IQ range of 80-135)[1]. In our cohort, all three patients presented intellectual disability. It has been postulated that defects in processing speed and working memory associated with PHTS may be related to poorly-developed white matter[6,8]. People with PHTS and ASD showed frontal deficits in the moderate to severe range accompanied by moderate to severe impairments in intellectual functioning and moderate deficits in both expressive and receptive language suggesting the involvement of a wider region of the brain[6,8]. The literature also suggests that PHTS-ASD patients show deficits in sensory functioning, with the most notable issues on the under-responsive/seeks sensation, low energy/weak, and taste/smell sensitivity subscales of the Short Sensory Profile[18]. Three patients demonstrate a sensory search profile.

The literature reported emotional difficulties only sporadically, but the prevalence of these difficulties may be higher. Hansen-Kiss et al. identified these issues in 34% of their participants, citing anxiety, bipolar disorder, and obsessive-compulsive disorder. "Disruptive" or "problematic" behavior was also reported; however, the precise relationship between different *PTEN* variants and psychological corollaries is yet to be delineated. Evidence showed that those with PHTS-ASD have more difficulties than those with ASD and macrocephaly of different etiology, suggesting that the combination of *PTEN* deleterious variants and ASD may be particularly associated with lower abilities[19-22]. Taken together, this suggests that children with PHTS-ASD might have a distinct neurobehavioral phenotype in multiple aspects of their clinical presentation from patients with idiopathic ASD. These manifestations strongly suggest the importance of reliable genotype-phenotype studies to help with patient management, prognosis, and therapeutic selection by identifying key genetic variants associated with ASD phenotypes[23]. However, this variability of the neurodevelopmental profile associated with PHTS-ASD does not allow child and adolescent psychiatrists to distinguish from idiopathic ASD during clinical behavioral observation. In our PHTS-ASD cohort, the neurodevelopmental profile was indistinguishable from idiopathic ASD.

The macrocephaly associated with ASD is an important "red flag" for diagnosis. Careful physical examination and clinical scoring could increase the clinical suspicion of PHTS, with genetic testing confirming the diagnosis[24]. An occipital frontal circumference > 3 SD should elicit the suspicion of a PHTS diagnosis in patients with ASD or intellectual disability and warn about further features: lipomas, trichilemomas, oral papillomas, arteriovenous malformations, or hemangiomas, with mandatory referral to a physician with experience in this syndrome. This referral would aim to diagnose patients early on and establish an adequate monitoring program given the increased lifetime risk of a wide variety of cancers (thyroid, breast, endometrial, melanoma, colorectal, and renal cell cancer) in patients with PHTS, with specific guidelines for cancer screening[25].

If idiopathic ASD brings with it a requirement for multiple follow-ups, PHTS-ASD adds an anxiety and fear

surrounding the risk of additional health problems, mainly cancer predisposition. Genetic counseling is needed to guide the follow-up and alleviate the psychosocial anxiety of their parents regarding this cancer predisposition. It is also helpful for other family members who may also be at risk of PHTS and would benefit from the knowledge of their reproductive options in positive cases. If the news of the diagnosis has a functional negative impact, referral to a child and adolescent psychiatrist is mandatory.

Funding

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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 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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Hepatopulmonary syndrome: an incidental radiological finding in a child with signs of portal hypertension

Síndrome hepatopulmonar: achado radiológico incidental numa criança com sinais clínicos de hipertensão portal

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Keypoints

What is known

– Hepatopulmonary syndrome is a rare condition, affecting children with portal hypertension/chronic liver disease. It is an important cause of morbidity, demanding early recognition of signs/symptoms and prompt diagnosis, including imaging studies, to allow for adequate treatment.

What is added

– We present an atypical case study of highly-symptomatic children due to portal hypertension, showcasing all the characteristic imaging findings of accompanying abdominal consequences, and a simultaneous subclinical intrapulmonary vascular dilation, resulting in hepatopulmonary syndrome.

A 10-year-old boy was transferred to our hospital from his native country, Guinea-Bissau, due to sustained pancytopenia, ascites, hepatosplenomegaly, and grade III esophageal varices of unknown origin. Symptoms started when he was 8 years old, presenting with an increased abdominal perimeter, and a palpable liver and spleen. Over the last two years, he suffered repeated episodes of hematemesis, requiring multiple blood transfusions. Two months before admission, he began to show periorbital and lower limb edema.

At our hospital, a physical examination added the presence of subicterus. Peripheral oxygen saturations were normal (SpPO2 > 98%). The ultrasound showed a liver of normal dimensions (9 cm) and heterogeneous texture, splenomegaly (16 x 8 cm), ascites, and decreased main portal vein (MPV) peak systolic velocity (15 cm/s), suggesting portal hypertension (Fig. 1). An abdominal computed tomography (CT) scan also revealed portal vein cavernoma (20 mm) and normal permeability in all arterial segments evaluated. There were also varices in splenic (spleno-renal shunt), inferior mesenteric, and superior rectal veins (Fig. 2).

A thoracic CT suggested the presence of esophageal varices. In this exam, a nodular image on the lower lobe of the left lung was discovered. It was in the subpleural region, with a bi-lobulated shape and slight contrast retention (Fig. 3). A serpiginous structure visualized inside the nodule, suspected of corresponding to a vessel, was better characterized by ultrasound, confirming the vascular nature of the lesion (Fig. 4). Endoscopy showed esophageal varices (grade III), gastric varices (GOV1 and GOV2), and congestive gastropathy, and some were simultaneously treated with elastic ligation.

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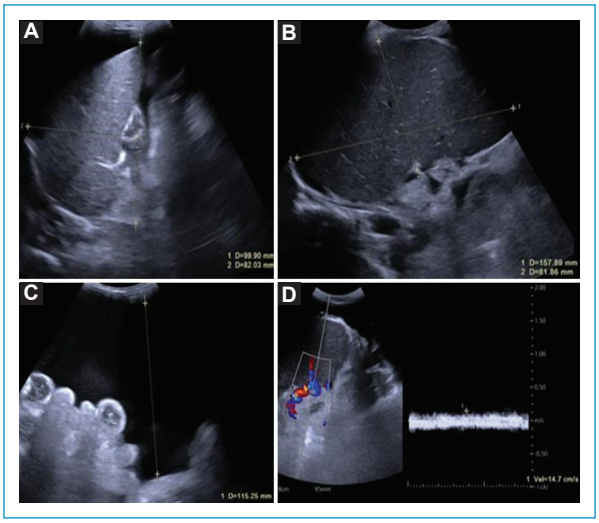

Figure 1. Ultrasound showing normal dimensions of the liver (9cm) with heterogeneous texture **(A)**, splenomegaly **(B)**, and ascites **(C)**, associated with decreased main portal vein peak systolic velocity **(D)**.

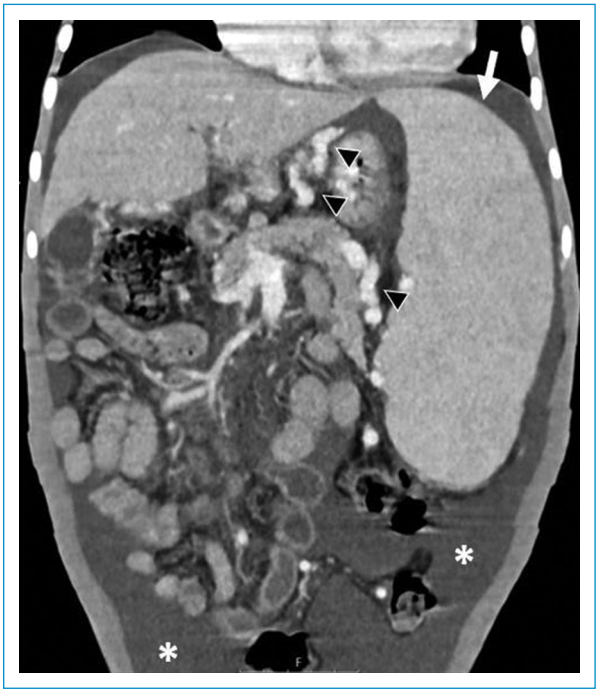

Figure 2. Abdominal coronal computed tomography with ascitis (asterisk), splenomegaly (arrow) and perigastric and perisplenic varices (arrowheads).

Throughout hospitalization, the patient remained free from respiratory symptoms. His serial SpO2 measurements were stable and he had no need for supplemental oxygen. During the follow-up, the patient remained free from any additional complications, and the current status involves awaiting liver transplantation.

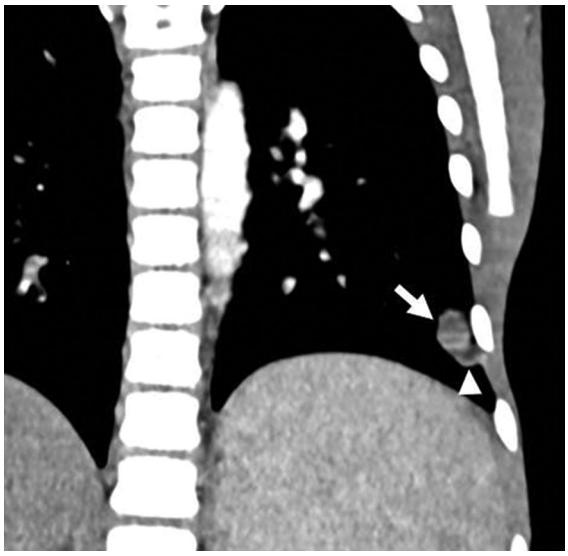

Figure 3. Thoracic coronal computed tomography with a nodular image on the inferior left lower lung lobe, in the subpleural region, with a bi-lobated shape and slight contrast retention (arrow). There was a serpiginous structure visualized inside the nodule (arrowhead), suspected of corresponding to a vessel.

Hepatopulmonary syndrome (HPS) is characterized by the triad of abnormal arterial oxygenation caused by intrapulmonary vascular dilation (IPVD) in the setting of liver disease, portal hypertension, or congenital portosystemic shunts. The estimated prevalence of HPS among children with chronic liver disease is around 4-5%[1-3]. Subclinical HPS occurs when there is IPVD without hypoxemia[4].

The pathophysiology of HPS is still unclear, but evidence suggests it occurs owing to an excess of endogenous vasodilators such as nitric oxide (NO) and endothelin (ET-1)[5]. Symptoms are related to the underlying liver disease and oxygenation impairment, when present.

The diagnosis of HPS is clinical, and the presence of a shunt is usually confirmed by pulmonary scintigraphy, a diagnostic imaging modality. Excluding other causes for a shunt and conditions that present with hypoxemia is also essential.

Liver transplantation remains the only treatment for HPS[5-7]. In the pre-transplant evaluation of pediatric patients, ultrasound, and mainly CT scans, are essential imaging tools, providing crucial information about the liver, other abdominal structures, and vascular anatomy. These radiological modalities may also demonstrate

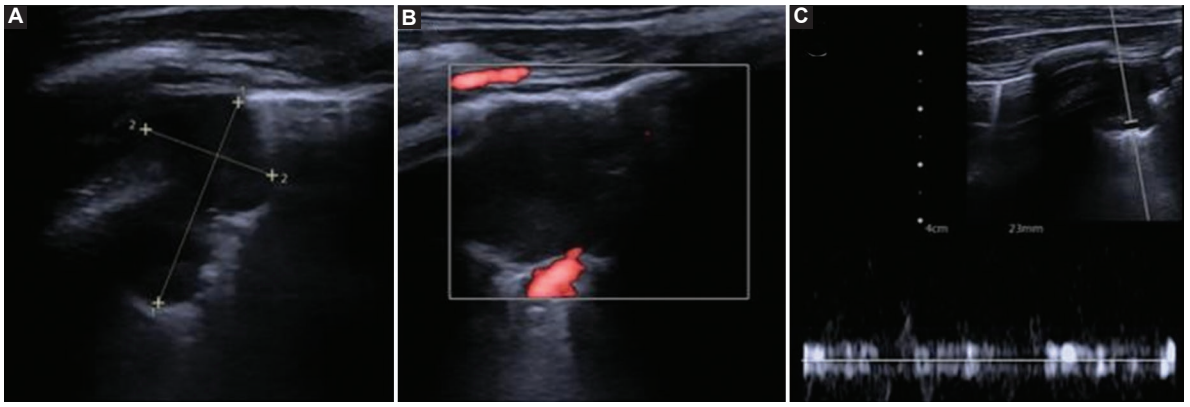

Figure 4. A-C: ultrasound of the lung nodular structure, confirming the vascular nature of the lesion.

some suggestive findings of HPS in this setting. In our patient, HPS diagnosis was made incidentally, in an atypical scenario, from images obtained during the evaluation of portal hypertension in a child without hypoxemia.

Early recognition of HPS is fundamental since it is an urgent criterion for listing patients for liver transplantation, and early action may lead to a shorter recovery period following the procedure.

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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 they have followed the protocols of their work center on the publication of patient data.

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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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Pediatric onychodystrophy: is it always a fungal infection?

Onicodistrofia pediátrica: será sempre uma infeção fúngica?

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Keypoints

What is known

- Lichen striatus is a rare dermatosis whose etiology and pathogenesis are not well defined.
- Treatment with topical corticosteroids or calcineurin inhibitors seems to ameliorate pruritus.

What is added

- Nail involvement is rare and can be misdiagnosed as fungal infection.
- A high index of suspicion is needed to avoid unnecessary treatments.

A healthy, dark-skinned four-year-old female presented with a three-month history of asymptomatic linear red-brown papules on the left forefinger and left thumb which extended to the periungual area of the thumb with consequent changes to the nail. There was no history of recent trauma, viral infections, allergy, new medications, or vaccines. The patient revealed multiple millimetric flesh-colored papules along Blaschko's lines on the lateral side of the left forefinger and on the medial side of the left thumb extending to the periungual area, with onycholysis, longitudinal ridging and nail splitting and subungual hyperkeratosis of that nail (Fig. 1). The examination was otherwise unremarkable. The lesion was diagnosed as lichen striatus with nail involvement. She initiated topic tacrolimus ointment 0.03%, showing nail improvement at the 4-month follow-up (Fig. 2).

Lichen striatus (LS) is a rare, benign, acquired dermatosis with a predilection for females[1-5]. The etiology is unknown, but it has been hypothesized to be derived from cutaneous mosaicism caused by a postzygotic somatic mutation[3,4]. Triggering events such as trauma, viral infections, vaccinations, and medications, can initiate an autoimmune response[3,4] which will produce a linear dermatosis, characterized by pink to flesh-colored or erythematous, millimetric flat-topped papules that follow Blaschko's lines[1-5]. Papules often coalesce to form a hyperpigmented continuous or interrupted linear band over weeks (occasionally months)[1,3]. It is typically unilateral, most commonly involving the extremities with a proximal to distal progression[1-3]. Although rare, there is sometimes involvement of the nail leading to onychodystrophy, characterized by nail pitting, longitudinal ridging, nail plate thinning and subungual hyperkeratosis[1,4]. Usually only the lateral or medial portion of the nail plate of a single nail is affected and is sometimes mistaken for fungal infection[1,3,4].

LS is generally asymptomatic although it may be pruritic[3,4]. Diagnosis is based on clinical features and in doubtful cases, a skin biopsy can be made[3].

Topical corticosteroids or topical calcineurin inhibitors may improve pruritus. However, in view of its

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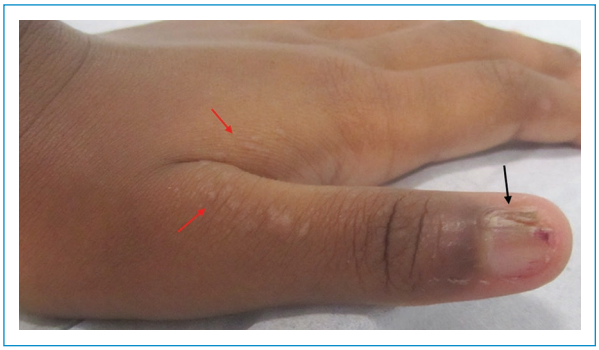

Figure 1. Flesh-colored papules along Blaschko's lines on the lateral side of the left forefinger and thumb (red arrows) with involvement of the medial portion of the nail plate (black arrow).

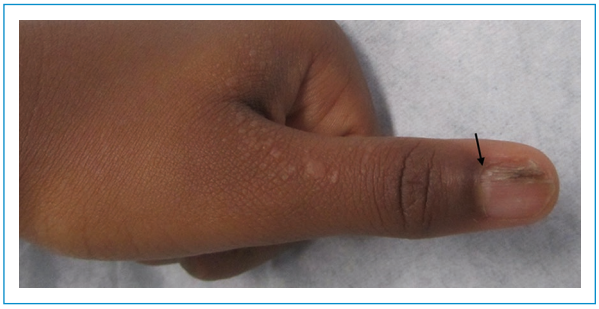

Figure 2. Slight improvement of the proximal edge of the nail plate at the 4th month of topic tacrolimus ointment 0.03% (black arrow).

self-limiting nature, parents should be reassured about spontaneous resolution within six months to three years[2-4].

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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 they have followed the protocols of their work center on the publication of patient data.

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Poland syndrome – Atypical neonatal presentation

Síndrome de Poland – Apresentação neonatal atípica

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Keypoints

What is known

- Poland syndrome is a rare congenital disease characterized by the absence or hypoplasia of the pectoralis major muscle.
- The condition is benign, non-progressive, and may be asymptomatic, depending on the clinical defects.

What is added

- Patients can present with a wide phenotypical presentation and multiple combinations of defects.
- Although defects are more frequent on the right side, left-side and bilateral defects are also reported.
- Early diagnosis allows for appropriate treatment and psychological follow-up is also necessary due to the visible physical malformation.

Poland syndrome (PS) is a rare congenital condition. The estimated incidence is 1:30,000 live births[1,2]. Most cases are sporadic, with a higher prevalence in males[3]. PS diagnosis is clinical and the cardinal feature (essential for diagnosis) is the agenesis or hypoplasia of the pectoralis major muscle[3]. Other associated features include anomalies of the thoracic cage, agenesis or hypoplasia of the breast, areola and nipple, abnormalities of the upper limb and shoulder, genitourinary malformations, cardiac malformations, and hepatic or biliary tract malformations[3].

We describe a male infant born at 40 weeks and 5 days. The parents are not consanguineous and have no other children. The mother is a 25-year-old woman with generalized anxiety disorder, medicated with valerian root extract and ethyl loflazepate, and no other relevant family history.

Antenatal ultrasounds were described as normal. Maternal serologies were negative. The third-trimester urine culture and group B streptococcus test were negative. Assisted birth with vacuum extraction. Apgar score 8/9/10. Birth weight was 3010 g (P15-50; 0 < SD < –2 [WHO Growth Charts]), length was 50 cm (P50; SD 0 [WHO Growth Charts]) and head circumference was 36 cm (P85-97; 1 < SD < 2 [WHO Growth Charts]).

The newborn was admitted to the Special Neonatal Care Unit (UCEN) four hours after birth, with transient tachypnea of the newborn. Physical examination showed left thoracic asymmetry, hypoplastic homolateral nipple (Fig. 1), left hand brachydactyly (Fig. 2) and abnormal implantation of the 5th toe, bilaterally. There were no other associated congenital anomalies.

Thoracic ultrasound showed anterior thoracic muscle plan asymmetry and a left-hand X-ray confirmed the agenesis of the distal phalanx of the 2nd finger and hypoplasia of the middle phalanges of the 2nd and 3rd fingers (Fig. 3). A transthoracic echocardiogram revealed the median position of the cardiac apex, by the pushing of the left rib cage. Brain, abdominal, renal, and pelvic ultrasounds were normal.

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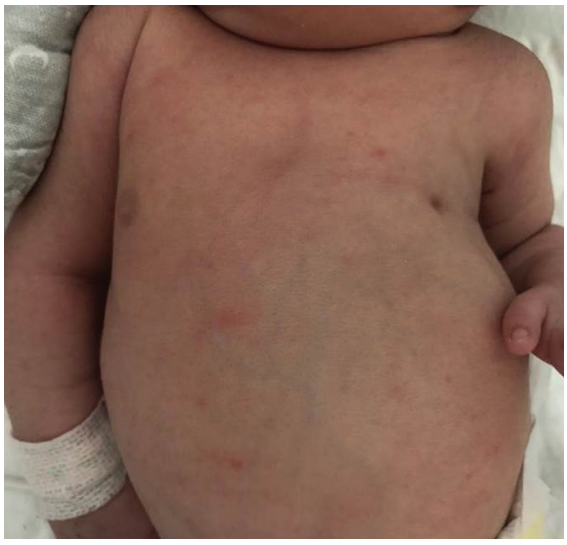

Figure 1. Left thoracic asymmetry and hypoplastic nipple.

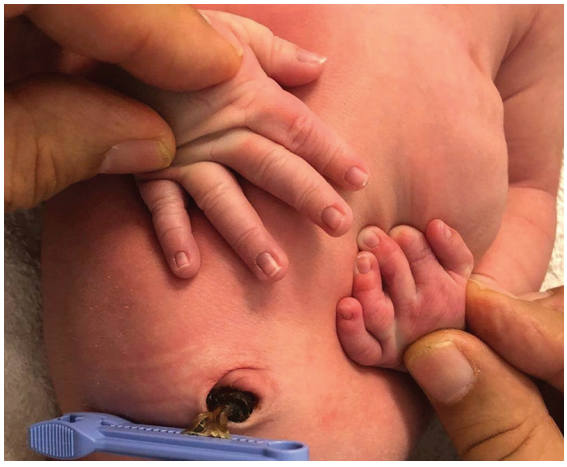

Figure 2. Left hand brachydactyly.

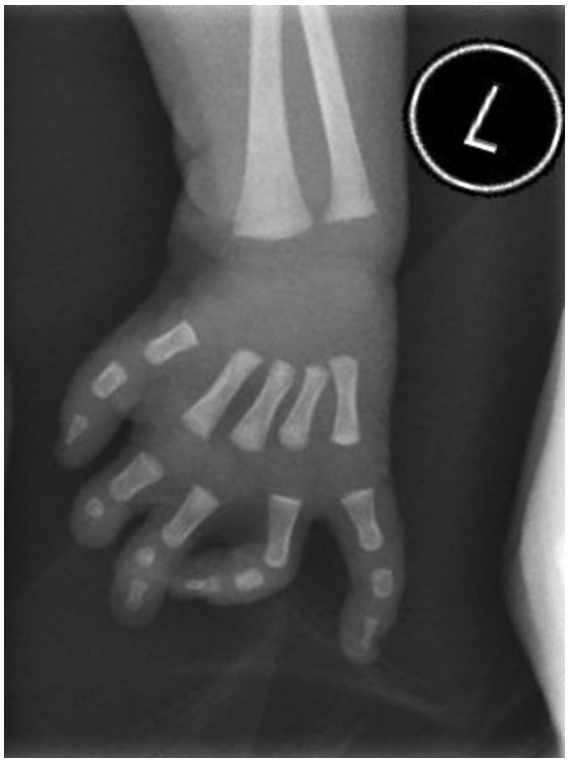

Figure 3. Left-hand x-ray showing hypoplasia of the middle phalanx and agenesis of the distal phalanx of the 2nd finger and hypoplasia of the middle phalanx of the 3rd finger.

The newborn was admitted for 7 days, due to the need for oxygen therapy in the first hours of life, followed by feeding difficulties with the need for nasogastric tube feeding.

Currently twelve months old, the patient weighs 12 kg (> P97; SD 2 [WHO Growth Charts]), has a length of 76.2 cm (P50; SD 0 [WHO Growth Charts]) and head circumference of 50.4 cm (> P97; SD 3 [WHO Growth Charts]). The patient has normal psychomotor development and is under close monitoring by a multidisciplinary team (pediatrics, physiatry, orthopedics, and genetics), with a conservative approach and no genetic testing for now.

Although the etiology is unknown, it has been suggested that a disruption in blood supply to the embryonic tissues that give rise to the chest wall and hand may play a role in the physiopathology of PS[1,4].

The phenotypical presentation of PS is wide and multiple combinations of clinical defects are possible[1]. According to the classification proposed by Romanini et al. in 2018[2], three types of PS are identifiable, based on the presence or absence of upper limb and rib cage abnormalities. Our patient presented with pectoral muscle defect associated with upper limb anomalies (with no rib anomalies), representing a type-2a or upper limb variant of PS.

Our patient's defects are located on the left hemithorax and hand, a less frequent location. The right side is usually more affected than the left (ratio 1.6 to 1) and there are also bilateral cases described[2].

It is important to underline that PS is not progressive and, in the absence of severe rib cage malformations, its survival rate is comparable with the general population. A normal psychomotor development is expected[3]. In some patients, plastic surgery may be performed to rebuild the chest wall or to construct a breast, and physical therapy may be beneficial in improving restricted mobility[4]. Due to the visible physical malformation,

which might be a source of distress, early psychological evaluation and follow-up is also important.

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