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Investigação Clínica da Iniciativa do Investigador em Portugal: Identificação de Problemas e Propostas para Melhoria

Investigator-Led Clinical Research in Portugal: Problem Identification and Proposals for Improvement

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Palavras-chave: Ensaios Clínicos; Investigadores; Portugal
Keywords: Clinical Trials as Topic; Portugal; Research Personnel

Portugal tem um problema crónico de subfinanciamento da investigação científica. Apesar do investimento nacional ter vindo a aumentar nos últimos anos, este ainda é manifestamente insuficiente.[1] A Fundação para a Ciência e Tecnologia (FCT) financia anualmente projetos de investigação em todas as áreas científicas, limitando o valor máximo a €250 000 por projeto. Todavia, a área científica na qual a investigação clínica está incluída – "*Clinical Medicine, Immunology and Infection*" – financia maioritariamente projetos de matriz translacional e não tem por norma apoiar ensaios clínicos (EC) ou estudos multicêntricos epidemiológicos e de coorte da iniciativa do investigador, área onde o financiamento é hoje em dia praticamente inexistente, mesmo para estudos clínicos exploratórios e *proof-of-concept*. É importante salientar que o potencial de retorno do investimento em ensaios clínicos é enorme. Em Portugal, por cada €1 investido em ensaios clínicos obtém-se em média um retorno de €1,99, isto é, um retorno de praticamente 200%.[1]

Um relatório da APIFARMA publicado em 2019[1] retrata o panorama geral dos EC em Portugal. O relatório conclui que 1) o reconhecimento do papel estratégico da investigação clínica na melhoria dos cuidados de saúde e na economia nacional é baixo; 2) a investigação clínica não é considerada como prioridade no Plano Nacional de Saúde; e 3) a atividade de EC da iniciativa do investigador é

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subfinanciada. O presente documento foca-se no último ponto (i.e., subfinanciamento de ensaios clínicos da iniciativa do investigador) e na falta de estrutura de coordenação e apoio aos investigadores, incluindo a impossibilidade de os investigadores clínicos terem tempo dedicado para a realização dos projetos.

Em consequência desta situação, Portugal conduz uma percentagem residual de ensaios clínicos da iniciativa do investigador (cerca de 7% do total), um valor muito inferior comparativamente a outros países Europeus (entre 18% a 45% do total).[1]

Ao contrário dos EC da iniciativa da indústria farmacêutica, onde o investigador apenas executa o protocolo definido pela indústria, nos EC da iniciativa do investigador os investigadores (e as instituições académicas ou unidades de investigação que integram) são responsáveis pelo desenho, submissão às autoridades competentes, execução e conclusão do ensaio, sendo-lhes atribuída a propriedade dos dados e os direitos de propriedade intelectual.

Apesar de estarem sujeitos às mesmas normas de exigência (e.g., cumprimento de boas práticas clínicas, legislação nacional e legislação europeia), os EC da iniciativa do investigador têm habitualmente financiamento e recursos humanos muito inferiores aos EC da iniciativa da indústria farmacêutica, o que os coloca em profunda desigualdade e desvantagem.

Os EC da iniciativa do investigador são essenciais porque visam responder a questões relevantes para a prática clínica sem interesse comercial da indústria farmacêutica, desenvolvem equipas de investigação, criam redes de contacto nacionais e internacionais, melhoram a evidência clínica permitindo uma melhor prestação de cuidados à população incluindo acesso a medicamentos e dispositivos médicos e geram novo conhecimento, conduzindo a comunicações científicas e publicações em revistas de grande impacto científico, essenciais para que os centros possam ser considerados de referência.

Existem três vias possíveis para obter financiamento para a criação e realização de EC da iniciativa do investigador ou estudos multicêntricos epidemiológicos e de coorte: 1) financiamento público (atualmente inexistente); 2) mecenato ou sociedades científicas (financiamento residual e habitualmente para pequenos estudos de coorte observacionais); ou 3) financiamento através da indústria farmacêutica (na prática a única opção existente atualmente).

O investimento da indústria farmacêutica em estudos da iniciativa do investigador financia estudos que são promovidos pelas instituições públicas de ensino ou centros de investigação públicos, de forma independente da indústria, que pode constituir uma alternativa ao investimento público. Todavia, a indústria farmacêutica apenas financia projetos nos quais terá potencial interesse direto. Por exemplo, ensaios clínicos que visem reduzir o consumo de medicamentos ou a implantação de dispositivos médicos, ou que comparem estratégias ou intervenções não farmacológicas (e.g., prevenção primária e modificação de estilo de vida) dificilmente obterão financiamento, pois podem diminuir o lucro potencial da indústria farmacêutica; todavia, são obviamente estudos fulcrais para as populações e para os sistemas de saúde.

O financiamento público é pois absolutamente essencial na realização de EC independentes da indústria farmacêutica. Neste contexto, os EC da iniciativa do investigador com financiamento público são de enorme importância, pois usam uma abordagem centrada nos doentes, não tendo como objetivo o lucro ou a proteção de interesses de uma entidade comercial.

Apesar da sua elevada relevância, os EC da iniciativa do investigador enfrentam diversas dificuldades devido à falta de recursos, às restrições financeiras, à falta de infraestruturas de suporte locais, à inadequada formação em investigação clínica e translacional e à complexa e estrita regulamentação.

Igualmente importantes e sujeitos ao mesmo tipo de bloqueios estão os estudos multicêntricos epidemiológicos e de coorte (i.e., a única forma de obter uma caracterização representativa da população portuguesa) e os ensaios clínicos pragmáticos que visam a otimização de estratégias ou de recursos que já podem estar a ser usados na rotina clínica (e.g., comparação de intervenções com evidência não conclusiva em ensaios randomizados). Por estes motivos, os pontos abaixo descritos aplicam-se também a este tipo de estudos.

É assim consensual a importância da investigação clínica, capaz de criar valor não só para o individuo doente, como também valor científico e económico. São igualmente evidentes as dificuldades que a realização deste tipo de investigação enfrenta entre nós.

De modo a permitir uma discussão objetiva visando promover os EC da iniciativa do investigador, assim como os estudos multicêntricos epidemiológicos e de coorte em Portugal, identificaram-se sete pontos (“Problema” e potencial “Solução”) que consideramos serem essenciais como pontos orientadores desta discussão e que são descritos em detalhe no **Apêndice 1** (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19333/15084).

Para contornar os problemas acima expostos propomos um modelo de financiamento integrado com abertura de um concurso anual dedicado apenas à investigação clínica, favorecendo projetos multicêntricos da iniciativa do investigador que visem mudar e melhorar a prática clínica, coincidindo com os pilares estratégicos definidos no Plano Nacional de Saúde 2021 - 2030.[2]

Como acima mencionado, os projetos de investigação clínica podem incluir EC randomizados (*double-blinded*, *open-label*, e/ou pragmáticos), estudos quasi-experimentais, EC *single-arm*, estudos observacionais prospetivos e de coorte multicêntricos.

Em termos práticos propomos:

- A Agência de Investigação Clínica e Inovação Biomédica (AICIB) em conjunto com a FCT/Ministério da Saúde anunciariam uma *call* anual dedicada à investigação clínica com um orçamento próprio, idealmente entre €20 a €40 000 000/ano.
- O número de projetos a financiar deveria ser limitado entre cinco a 10 por ano.
- A *call* de Oncologia deveria ser separada das restantes áreas da Medicina. Por exemplo, atribuindo-se 10% da verba alocada a projetos da área Oncológica e os restantes 90% às outras áreas da Medicina. Esta separação é importante, pois a Oncologia é, de longe, a área da Medicina com maior investimento em ensaios clínicos e se não for colocado um limite de verba alocada à Oncologia, a *call* arrisca-se a ser 'onco-cêntrica' e a não dar oportunidade a outras áreas da Medicina.
- Cada projeto poderia obter um financiamento máximo de €5 000 000, sabendo-se de antemão que os projetos multicêntricos envolvendo múltiplas instituições nacionais visando a mudança da prática clínica e/ou a melhoria e eficiência do Serviço Nacional de Saúde serão valorizados.
- O financiamento poderia incluir projetos internacionais da iniciativa do investigador nos quais uma verba alocada a Portugal seja necessária para a implementação do estudo em território nacional, sendo para isso necessário incluir centros e investigadores portugueses no projeto.
- Os projetos seriam revistos por três revisores independentes (com experiência em investigação clínica na área médica em questão) designados pela AICIB/FCT/Ministério da Saúde, incluindo um metodologista (ver Apêndice 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19333/15085).
- A avaliação deveria ser feita em duas fases: a primeira com um *abstract* (300 palavras) e *short (draft) proposal* incluindo um orçamento sumário e um pré-acordo dos centros participantes (três a quatro páginas), e uma segunda fase onde apenas os projetos que passarem a primeira fase são convidados a submeterem a *full proposal* detalhada (10 a 15 páginas e um orçamento detalhado).
- A Rede Portuguesa de Infraestruturas para a Investigação Clínica (PtCRIN) em conjunto com a AICIB, apoiariam a submissão dos projetos às entidades competentes, já previamente informadas sobre este tipo de projetos e sobre a necessidade de lhes fornecer uma resposta célere (dois meses no máximo).
- Os vencedores de cada projeto poderiam selecionar elementos cujo salário seria parcialmente pago com verbas próprias, a quem seria atribuída redução correspondente do tempo de trabalho hospitalar; um mínimo de 12 horas semanais (i.e., 30% de um horário de 40 horas) é recomendado para a condução de um projeto de investigação clínica de larga envergadura.
- Os centros académicos clínicos e centros de investigação clínica teriam autonomia gestionária de verbas e contratação de pessoal necessário à implementação de cada projeto, seguindo um modelo de contratação transparente.
- Existiria monitorização regular de cada projeto e os resultados obtidos teriam de ser concluídos e publicados em revistas de referência.

CONTRIBUTO DOS AUTORES

JPF: Escrita do artigo original e revisões subsequentes.

ALM, ACP, CRC, CJ, CG, FJP, FS, FS, FVN, HC, HCC, IP, JP, JECF, JCP, LG, NS, TGO: Revisão crítica.

AJS: Conceptualização do trabalho, análise e interpretação de dados, revisão crítica e aprovação do manuscrito.

JFM: Conceptualização do projeto de investigação, redação do manuscrito, revisão das versões do documento, aprovação da sua versão final.

MCB: Revisão crítica e aprovação.

RFC: Elaboração do rascunho e revisão dos conteúdos.

TML: Análise e discussão do manuscrito contribuindo para a versão final do mesmo.

CRO: Análise e discussão do manuscrito contribuindo para a versão final do mesmo.

CONFLITOS DE INTERESSE

TGO recebeu bolsas ou contratos da Fundação BIAL e da Brain & Behavior Research Fountation, EUA; Tem as seguintes patentes planeadas, concedidas ou pendentes: modulação da Fosfolipase D para o tratamento dos efeitos agudos e crônicos do etanol, Di Paolo G, Oliveira TG, Wenk M, Frere SG, Chan RB, Patente WIPO WO/2011/014622A1 e modulação da Fosfolipase D para o tratamento de distúrbios neurodegenerativos, Di Paolo G, Oliveira TG, Kim TW, Patente WIPO WO/2010/138869ª1; Participou em Conselhos de Monitoramento de Segurança de Dados ou Conselhos Consultivos e detém ações ou opções de ações da Ceracuity Therapeutics.

ALM recebeu honorários de consultoria da AstraZeneca.

JECF tem concessões ou contratos com MSD, Abbvie e Janssen; Recebeu pagamento ou honorários por palestras de Lilly, Janssen e Abbvie; Participou em Conselhos de Monitoração de Segurança de Dados ou Conselhos Consultivos da UCB.

CG recebeu pagamento ou honorários por palestras da AstraZeneca, Medtronic, Bayer, Novartis, Boehringer-Ingelheim/Lillya e Servier; Recebeu apoios para reuniões e/ou viagens da AstraZeneca, Bayer, Bial, Boehringer-Ingelheim, Novartis e Servier; Participou em Conselhos de Monitoramento de Segurança de Dados ou Conselhos Consultivos para AstraZeneca, Novonordisk, Bayer, Organon, Daiichi-Sanky.

FJP recebeu pagamento ou honorários por palestras da Novartis, Servier, Philips e Vifor; É ex-presidente imediato da World Heart Federation (WHF).

Os restantes autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Nutritional Risk and Malnutrition in Paediatrics: From Anthropometric Assessment to STRONGkids® Screening Tool

Risco Nutricional e Desnutrição em Pediatria: Da Avaliação Antropométrica à Ferramenta de Rastreio STRONGkids®

Luís VIEIRA GONÇALVES✉[1], Ana Gisela OLIVEIRA[2], Mariana BARRACOSA[3], Joaquina ANTUNES[2], Joana PIMENTA[2]
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ABSTRACT

Introduction: The prevalence of malnutrition in hospitalized children is high and is associated with negative health impact. The aim of this study was to characterize the nutritional status of hospitalized children as well as comparing nutritional risk stratification using the STRONGkids® tool and anthropometric assessment.

Material and Methods: A prospective study was conducted between March and June 2019 in a paediatric unit of a district hospital. Children with ages between one month and 17 years were included. Nutritional screening (STRONGkids®) was performed, and demographic and anthropometric variables were assessed by trained doctors and nurses (z-scores for height-for-age, weight-for-age, weight-for-height and body mass index were compared to the World Health Organization reference values) and related to the underlying condition (cause of hospitalization; hospital stay; the presence of chronic disease).

Results: A total of 209 children were evaluated, 188 of whom were included. Median age was 4.6 years and median hospital length of stay was four days. Fifty-four per cent were classified with "moderate risk" and 2% with "high risk" of developing malnutrition; 25% were effectively malnourished. Of the 105 children for which it was possible to calculate the z-scores, 6% presented acute malnutrition and nearly 14% presented chronic malnutrition. The STRONGkids® score correlated positively with nutritional status on admission, disease type on admission, and presence of previous underlying disease ($p < 0.05$).

Conclusion: STRONGkids® is a simple, quick nutritional screening tool for hospitalized children that is related to nutritional status on admission. Given that a considerably high percentage of children were identified as being at risk for malnutrition, it is essential to identify this early and provide nutritional intervention during hospitalization.

Keywords: Anthropometry; Child, Hospitalized; Malnutrition/diagnosis; Nutritional Status

RESUMO

Introdução: A prevalência de desnutrição em crianças hospitalizadas é alta e associada a impactos negativos na saúde. O objetivo deste estudo foi caraterizar o estado nutricional de crianças hospitalizadas, bem como comparar a estratificação de risco nutricional através da ferramenta STRONGkids® e da avaliação antropométrica.

Material e Métodos: Estudo prospetivo realizado no período de março a junho de 2019 numa unidade de internamento pediátrica de um hospital de nível 2. Foram incluídas crianças com idades entre um mês e 17 anos. O rastreio nutricional (STRONGkids®) foi realizado e as variáveis demográficas e antropométricas (z-*scores* para altura-por-idade, peso-por-idade, peso-por-altura e índice de massa corporal foram comparados com os valores de referência da Organização Mundial de Saúde) e relacionadas com doença de base (motivo do internamento; permanência hospitalar; presença de doença crónica) foram determinadas por médicos e enfermeiros com formação prática e teórica adequada.

Resultados: Foram avaliadas 209 crianças, das quais 188 foram incluídas. A idade média foi de 4,6 anos e o tempo médio de internamento hospitalar foi de quatro dias. Dos 188 indivíduos, 54% foram classificados com 'risco moderado' e 2% com 'alto risco' de desenvolver desnutrição; 25% estavam efetivamente desnutridos. Das 105 crianças para as quais foi calculado o z-*score*, 6% apresentaram desnutrição aguda e cerca de 14% desnutrição crónica. O *score* STRONGkids® correlacionou-se positivamente com o estado nutricional à admissão, tipo de patologia à admissão e presença de doença de base prévia ($p < 0,05$).

Conclusão: O STRONGkids® é uma ferramenta de rastreio nutricional simples e rápida para crianças hospitalizadas que avalia o estado nutricional na admissão hospitalar. Devido à prevalência consideravelmente alta de crianças identificadas em risco de desnutrição, é essencial identificar e intervir precocemente durante a hospitalização.

Palavras-chave: Antropometria; Criança Hospitalizada; Desnutrição/diagnóstico; Estado Nutricional

INTRODUCTION

Adequate psychomotor growth and development are crucial for the health and well-being of children and adolescents, with nutrition playing a key role in these processes.[1,2]

The European Society for Clinical Nutrition and Metabolism (ESPEN) defines malnutrition as a state resulting from lack of uptake or intake of nutrition, leading to measurable adverse effects on tissue/body composition, reduced physical and mental function, and poor clinical outcomes.[3] Undernutrition results from deficient energy and/or protein intake or absorption.[4-6]

The prevalence of paediatric malnutrition in healthcare settings is high and often underestimated.[7-9] It is associated with longer hospitalization stays, multiple interventions, readmissions, and higher susceptibility to infections and,

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therefore, with significant morbimortality.[7-11] The resulting impact on quality of life carries great costs on a personal level, to society, and to the healthcare system.[12]

According to the literature, the prevalence of undernutrition in hospitalized patients ranges from 20% to 50%.[12] In children, studies point to a similar prevalence of 15% to 50%.[7,8,10,13-16] A study carried out in 2015 in the paediatric population of a level-three hospital unit in the Azores with a sample of 299 children showed 11.4% of the children were severely wasted and 18.1% severely stunted.[17]

Since 2005, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recommended the implementation of nutritional screening strategies to establish individualized nutritional plans in order to improve paediatric care, thus reducing the incidence of nutritional deficiencies and undernutrition during hospital stays.[18,19] Since 2018, the Portuguese government has been implementing strategies in National Health Service hospitals to optimize inpatient nutritional care and directly promote the recovery of quality of life.[17] Therefore, early identification of individuals at nutritional risk upon admission, followed by appropriate nutritional management, is essential.[7-9,13,19-21]

Nutritional risk is defined by the current nutritional status and the risk of deterioration of the current status, due to an increase in nutritional requirements caused by metabolic stress associated with the clinical condition.[22]

Since 2018, the Portuguese government has been implementing strategies in National Health Service hospitals to optimize inpatient nutritional care and directly promote the recovery of quality of life, and recommended a systematic evaluation of nutritional risk to all patients hospitalized for a period longer than 24 hours.[12]

In paediatric patients, the nutritional risk assessment tool adopted is STRONGkids® (Screening Tool for Risk of Impaired Status and Growth), a simple, safe, sensitive, specific, low-cost questionnaire which is widely used to identify nutritional risk in different populations worldwide.[12,13,23] It consists of four items: subjective assessment of nutritional status, recent weight changes, assessment of food intake and nutritional losses and presence of medical condition with risk for malnutrition.[12] Each item is assigned a score. The sum of these points identifies the risk of malnutrition and guides the necessary intervention and follow-up.[2,13] Even though there are translations of STRONGkids® into the Portuguese language, there is, to our knowledge, only one study that used this tool for the hospitalized paediatric population in the Azores.[17]

The authors aimed to characterize the nutritional status of hospitalized children admitted to the Paediatric Department of Centro Hospitalar Tondela-Viseu, as well as comparing nutritional risk stratification using the STRONGkids® screening tool and anthropometric assessment.[24,25]

MATERIAL AND METHODS

A longitudinal study was conducted on hospitalized children in a Portuguese second-level public hospital between the 15th March and the 15th July 2019, after the Ethics Committee of the hospital reviewed and approved the protocol of the present study.

Patients aged between one month and 18 years and admitted for an expected length of stay (LOS) of more than 24 hours were invited to participate in the study at the time of admission. Written informed consent was obtained. Data was collected from a questionnaire designed for the study (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16768/15025) by trained professionals (nurses and doctors). The questionnaire consisted of three groups of questions: the first was about demographic questions, the second to record anthropometric measures and the third to score the risk for malnutrition using a nutritional risk screening tool (STRONGkids®).

Data were collected from the patients' medical records, and from interviews with the patients and family members. The children's age was categorized into four different clusters: one month - one year, two - five years, six -10 years, and 11 - 17 years. The length of hospital stay (LOS) was divided into two groups: less than four days (inclusive) and more than four days; the cut-off was calculated as the median. The medical condition that led to the admission was classified according to different groups as respiratory, infectious, gastroenterological, neurological, psychiatric, cardiovascular, trauma/surgical, or other. For the purpose of comparison, the relative and absolute weight loss of body weight was also calculated such as the verification of infectious complications that were diagnosed if any one of three occurred with the clinical syndrome: (1) fever (body temperature above 38.5º C without the presence of other fever-causing factors such as surgery, blood transfusion, infusion reactions or drug fever), along with incision pain, swelling, cough, sore throat, abdominal pain, diarrhoea, frequent or urgent urination, dysuria, and other clinical manifestations, (2) presence of pathogens in incision secretions, throat swabs, sputum, urine, faeces, blood and bone marrow specimens being positive in culture; or (3) chest X-ray or another diagnostic test showing infection.

The anthropometric measurements were taken following a protocol (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16768/15026) and included weight, length/height, and mid-upper arm circumference (MUAC). Children were weighed on a calibrated electronic scale [weight < 20 kg using Oriola® data baby-scale 930 (precision 0.001 kg) and > 20 kg using SECA® 703 column scale (precision 0.1 kg)] naked and

without diaper or wearing minimal clothing (light underwear and without socks or shoes). Height was measured using an infantometer in children aged below two years (Jofre®, precision 0.5 cm), and a stadiometer included in the SECA® 703 column scale (precision 0.1 cm) in those aged over two years, with the child barefoot. The mid-upper arm circumference was measured in all children using a measuring tape.

Anthropometric data were compared with reference values for height-for-age (HFA), weight-for-height (WFH) and body mass index (BMI) defined by the World Health Organization (WHO).[26-29]

For preterm infants, Fenton curves were used up to 50 weeks of chronological age, after which the WHO curves were the reference.[4,30,31]

Malnutrition was defined according to the WHO guidelines as acute if < −2 SD of WFH or BMI for ages under five years and from five to 18 years, respectively; and chronic if < −2 SD of HFA. With regards to severity, acute malnutrition was defined as; moderate if WFH or BMI-for-age ≤ -2 SD and ≥ -3 SD of the median; and severe if WFH or BMI-for-age < -3 SD; chronic malnutrition was: moderate if HFA ≤ -2 SD and ≥ -3 SD; and severe if HFA < -3 SD. For the purpose of this article, malnutrition refers to the presence of acute and/or chronic malnutrition.[9,13,29]

The z-scores for anthropometric indices were calculated using the software WHO Anthro® and WHO AnthroPlus®, for the age group zero to five and five to 19 years, respectively.[30-32]

The nutritional risk screening tool included was STRONGkids® to score the risk for malnutrition, conducted using the Portuguese version of the questionnaire.[24] The STRONGkids® tool consists of four scored questions addressing the underlying disease, subjective clinical assessment, weight changes, food intake, and losses. At the end, the total sum of the points is calculated, with a minimum of zero and a maximum of five points, and the nutritional risk is classified as 'low' (zero points), 'moderate risk' (one to three points), or 'high' (four or five points).[13,23]

Depending on the STRONGkids® score, children were re-evaluated and when necessary, referred to a nutritionist according to the protocol. In 'low risk', reassessment was scheduled every five days; 'moderate risk', after 72 hours and if the score was maintained or changed to high, the patient was referred for nutritional support; patients diagnosed as 'high risk' were immediately referred to the nutritionist and re-evaluated after 72 hours. Patients at nutritional risk referred to a nutritionist underwent a complete assessment of their nutritional status (anthropometric measures, clinical history data, recent analytical results, and dietary history) and individual nutritional plans were established.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS®) version 26 was used for data analysis. The clinical outcomes for the different groups were compared with the Mann-Whitney U test; the chi-square and Fisher exact tests were performed to compare proportions between groups. Logistic regression analysis was used to compare 'nutritionally at risk' or low-risk STRONGkids® scores and 'nutritionally not at risk' or moderate to high-risk children in STRONGkids®. Sensitivity, specificity, negative and positive predictive values (NPV and PPV, respectively) were also calculated for the following outcome variables: acute, chronic and malnutrition (WFH/BMI < -2 SD, HFA < -2 SD or both, respectively), MUAC < -2 SD, hospital LOS over four days and weight loss over 2%. Correlation studies were demonstrated in r values provided (Spearman correlation*; p* < 0.05 was considered significant).

RESULTS

Characteristics of the study participants

During the three months, there were 283 children hospitalized of whom 210 met the inclusion criteria and were enrolled in the study. However, 22 children were excluded because the STRONGkids® score was absent or incomplete, leaving a total of 188 patients. The median age was 4.78 years, 68 (36.2%) were girls and 120 (63.8%) were boys. The median for the LOS was four days (1 to 54 days).

Risk classification and anthropometric measures

Anthropometric characteristics of patients are shown in Table 1.

There was no significant association found between STRONGkids® risk stratification and the age and sex neither comparing with LOS ($p = 0.076$ and $p = 0.747$, respectively).

Regarding the risk classification, 82 (43.6%) presented a low-risk score, 102 (56.4%) moderate risk and only four (2.1%) high risk. The moderate and high-risk patients were analysed together as a group.

Using nutritional assessment at admission through anthropometric measures: 29 (15%) were classified as malnourished (acute and/or chronic) and 129 (69%) as not being malnourished. Of these, 151 (80.3%) were classified as not acute malnourished (WFH > -2 SD), six (3%) had moderate acute undernutrition (WFH ≤ -2 SD and ≥ -3 SD) and four (2%) severe acute undernutrition (WFH< -3 SD); 143 (76%) were classified as not chronic malnourished (HFA > -2 SD), 13 (7%) as moderate chronic malnourished (HFA ≤ -2 SD and ≥ -3 SD) and 10 (5%) as severe chronic malnourished (HFA < -3 SD).

A statistically significant association was found comparing the STRONGkids® stratification and the state of

Table 1 – Patients' anthropometric characteristics

		Age cluster											
		Infant			Pre-school			School			Adolescent		
		n	Median	IQ (25^{th}; 75^{th})	n	Median	IQ (25^{th}; 75^{th})	n	Median	IQ (25^{th}; 75^{th})	n	Median	IQ (25^{th}; 75^{th})
Anthropometry	Weight (kg)	37	7.49	(5.22; 8.14)	60	12.6	(10.55; 15.34)	19	29.4	(23.1; 31.4)	51	55.7	(45.60; 62.53)
	Stature/lenght (cm)	36	61.75	(57.25; 69.00)	58	86.75	(80.00; 104.00)	19	131	(126.90; 136.25)	53	160.5	(153.88; 171.00)
	BMI (kg/m^2)	39	16.29	(14.73; 17.29)	61	15.839	(14.56; 17.12)	21	15.72	(15.09; 17.42)	61	19.63	(16.85; 22.62)
	MUAC (cm)	36	13.25	(11.88; 14.00)	56	15.5	(14.56; 16.58)	18	19.7	(17.50; 20.55)	55	24	(22.23; 27.13)
Z-scores	Weight-for-age	33	-0.69	(-1.75; 0.19)	59	-0.11	(-0.84; 0.60)	14	0.29	(-0.88; 0.92)	*	*	*
	Height-for-age	34	-1.29	(-2.09; 0.04)	59	-0.36	(-1.28; 0.60)	19	0.1	(-0.81; 0.73)	52	-0.6	(-0.56; 0.54)
	WFH and BMI/age[a]	33	-0.26	(-0.93; 0.37)	59	-0.07	(-0.46; 1.01)	19	0.12	(-1.05; 0.76)	50	0.25	(-0.35; 0.87)
	MUAC[b]	22	-0.43	(-1.50; 0.36)	49	0.167	(-0.38; 0.84)	*	*	*	*	*	*

IQ: interquartile range
[a]: Weight-for-height and body mass index/age for ages under 5 years and from 5 to 18 years, respectively
[b]: Mid-upper arm circumference
* Data excluded because of low number of cases included

malnutrition at admission (whether acute or chronic) as well as being acutely malnourished at admission (p = 0.018 and p = 0.011, respectively) (Table 2).

Clinical outcomes of patients by risk classification

Sixty-five (34.5%) children were identified at the time of admission as having an underlying disease before admission. Of those, 23 had acute conditions and 42 had chronic conditions (12.2% *vs* 22.3%). According to the existing medical conditions upon admission, 65 (34.6%) patients were classified as having an infectious disease, 45 (23.9%) respiratory, 34 (18.1%) trauma/surgical, 17 (9.0%) psychiatric and 27 (14.4%) other conditions. According to the definition of cases as medical or surgical, 154 (81.9%) were classified as medical and 34 (18.1%) as surgical.

Having underlying disease at admission, type of diagnostic categories and medical versus surgical condition on admission were all significantly different among the different risk groups (p = 0.019, p = 0.001 and p = 0.006, respectively).

For comparing terms with data from previous studies,[11,33] the children who had records of body weight at admission and at discharge, only eight (9.76%) had lost more than 2% of the total weight in the group that scored as low risk, 23 (22.55%) in the group that scored moderate risk and none in the group that scored as high risk. A statistically significant association between STRONGkids® risk stratification and weight loss was not found (p = 0.185).

Regarding infectious complications, there were 112 (59.6%) children who presented infectious complications *versus* 76 (40.4%) that did not. A significant association between STRONGkids® risk stratification and the presence of infectious complications was found (p < 0.001) (Table 2).

Concurrent and prospective validity of STRONGkids®

In our study, STRONGkids® had a sensitivity of 90%, a specificity of 44%, a PPV of 10% and a NPV of 99% for detecting acutely malnourished children, while STRONGkids® had a sensitivity of 74%, a specificity of 45%, an PPV of 18% and a NPV of 91% for detecting chronic malnourished children (Table 3).

Logistic regression

After producing a multivariate analysis and eliminating the variables sex, presence of disease upon admission and diagnostic group of disease, the logistic regression analysis showed the children that scored as moderate or high risk versus low risk had 2.23 (95% CI 0.862 – 5.779) times greater odds of being malnourished and 2.01 (95% CI, 0.38 – 10.70) times greater odds of losing more than 2% of weight upon admission. The odds of children that were scored as moderate or high risk versus low risk for children with

Table 2 – Characteristics at admission and clinical outcomes of children with risk groups of each nutritional risk screening tools analysed by the chi-squared test, fisher exact test and Mann–Whitney U-test

			STRONGKids®				
			Low risk		Moderate and high risk (only high risk)		*p* value
	n	%	n	%	n	%	
Total	188	100.0%	82	43.6%	106 (4)	56.4% (2.1%)	
Age							
Infant [1m - 1y]	42	22.3%	19	23.2%	23 (1)	21.7% (0.9%)	
Pre-school [2y - 5y]	65	34.6%	21	25.6%	44 (2)	41.5% (1.9%)	0.076
School [6y - 10y]	21	11.2%	10	12.2%	11 (0)	10.4% (0.0%)	
Adolescent [11y - 17y]	60	31.9%	32	39.0%	28 (1)	26.4% (0.9%)	
Sex							
Female	68	36.2%	24	29.3%	44 (1)	41.5% (0.9%)	0.083
Male	120	63.8%	58	70.7%	62 (3)	58.5% (2.8%)	
Weight-for-height (acute malnutrition)[a]							
Not acute malnourished (WFH > -2 SD)	151	80.3%	67	81.7%	84 (1)	79.2% (0.9%)	< 0.05*
Moderate acute malnourished (WFH < -2 SD and > -3 SD)	6	3.2%	1	1.2%	5 (1)	4.7% (0.9%)	
Severe acute malnourished (WFH < -3SD)	4	2.1%	0	0.0%	4 (1)	3.8% (0.9%)	
Height-for-age (chronic malnutrition)[a]							
Not chronic malnourished (HFA > -2 DP)	143	76.1%	64	78.0%	79 (3)	74.5% (2.8%)	0.98
Moderate chronic malnutrition (HFA < -2 DP and > -3 DP)	13	6.9%	3	3.7%	10 (0)	9.4% (0.0%)	
Severe chronic malnutrition (HFA < -3 SD)	10	5.3%	3	3.7%	7 (0)	6.6% (0.0%)	
Malnourished at admission (acute or chronic)[a]							
No	129	68.6%	58	70.7%	71 (1)	66.9% (0.9%)	< 0.05*
Yes	29	15.4%	7	8.5%	22 (2)	20.8% (1.9%)	
Previous disease upon admission[a]							
No	120	63.8%	60	73.2%	60 (0)	56.6% (0.0%)	< 0.05*
Yes, acute	23	12.2%	6	7.3%	17 (0)	16.0% (0.0%)	
Yes, chronic	42	22.3%	15	18.3%	27 (4)	25.5% (3.8%)	
Diagnostic group							
Respiratory	45	23.9%	19	23.2%	46 (1)	43.4% (0.9%)	< 0.05*
Infectious	65	34.6%	15	18.3%	30 (1)	28.3% (0.9%)	
Psychiatric	17	9.0%	9	11.0%	8 (1)	7.5% (0.9%)	
Trauma/surgical	34	18.1%	22	26.8%	12 (0)	11.3% (0.0%)	
Other	27	14.4%	17	20.7%	10 (1)	9.4% (0.9%)	
Division medical/surgical							
Medical	154	81.9%	60	73.2%	94 (4)	88.7% (3.8%)	< 0.05*
Surgical	34	18.1%	22	26.8%	12 (0)	11.3% (0.0%)	
Lenght of stay							
< 4 days	90	47.9%	37	45.1%	53 (3)	50.0% (2.8%)	0.747
> 4 days	92	48.9%	40	48.8%	52 (1)	49.1% (0.9%)	
Excluded	6	3.2%	5	6.1%	1 (0)	0.9% (0.0%)	
Weight loss							
No	157	83.5%	74	90.2%	83 (4)	78.3% (3.8%)	0.185
Yes (> 2%)	31	16.5%	8	9.8%	23 (0)	21.7% (0.0%)	
Infectious intercurrence							
No	76	40.4%	48	58.5%	28 (2)	26.4% (1.9%)	< 0.05*
Yes	112	59.6%	34	41.5%	78 (2)	73.6% (1.9%)	

[a]: Some results were not possible to display in the table because they were excluded or not measured
*: Significant for $p < 0.05$

Table 3 – Performance of the STRONGkids® tool accuracy tests in relation to the anthropometric indexes of malnourished children and those at nutritional risk

	Sensitivity	Specificity	PPV	NPV	Accuracy
Z-score WFH/BMI (acute malnutrition)	90.0%	44.4%	9.7%	98.5%	47.2%
Z-score HFA (Chronic malnutrition)	73.9%	44.8%	17.7%	91.4%	48.8%
Malnourished (either acute or chronic)	77.4%	45.8%	25.3%	89.6%	52.0%
Z-score MUAC	64.8%	53.8%	88.5%	21.9%	63.1%
Weight loss	77.8%	44.7%	6.6%	97.6%	46.3%
Infectious intercurrence	69.4%	62.3%	72.6%	58.5%	66.5%
Lengh of stay	58.9%	43.0%	50.0%	51.9%	50.8%

MUAC: mid-upper arm circumference; NPV: negative predictive value; PPV: positive predictive value

infectious complications was 3.09 (95% CI, 1.41 – 6.79) times greater odds compared with children without infectious complications and it showed a strong association (p = 0.005). Spearman's r was used to determine correlations between continuous variables) (Table 4).

DISCUSSION

Although the consequences of malnutrition in hospitalized patients are consensually recognized, nutritional screening tools – in addition to being validated – are not yet employed in Portugal on the desired scale. This study is one of the few assessing nutritional status through the use of the STRONGkids® tool Portuguese paediatric hospitalization and anthropometric measures and our data is consistent with that published by Sousa *et al*[17] and by Huysentruyt *et al*[11] and reinforced by Carter *et al*[34], in that half of paediatric patients lose weight while hospitalized and those who were malnourished on admission are being discharged without improvement of nutrition status. There is a growing need to screen nutritional status to identify malnourished children early.[11,17,34]

According to WHO cut-off values, our findings concur with those of studies from other European countries.[11,35,36] Compared with countries from Latin America and Africa, the prevalence of acute malnutrition in our study was lower.[38,39] The sensitivity of the STRONGkids® calculated in this study to detect acutely malnourished children was 90.0% and 73.9% to detect chronically malnourished children. Sensitivity is argued as being important when it comes to screening tests which leads us to consider STRONGkids® as a good screening tool when it comes to detecting acutely malnourished children but not as good for chronically malnourished children. The NPV and PPV calculated for acute malnutrition was 98.5% and 9.7% respectively, and the NPV and PPV calculated for chronic malnutrition was 91.4% and 17.7% respectively, being approximate to what is found in other developed countries. This means that in a population with this prevalence rate, 2.5% will have a probability of being acutely malnourished and 8.6% will have a probability of being chronically malnourished.[11]

There were only four children that were scored as high risk in STRONGkids®, of whom two had a history of congenital heart condition (six months and two years of age), one had a history of serious dysmorphic syndrome and the other was an adolescent with a history of autism and a severe eating behaviour disorder. We believe that the lower number of patients classified with high risk compared to the number of patients with moderate risk can be justified with two reasons 1) Only twelve cases had one of the conditions specified in the table attached to the STRONGkids® questionnaire which refers to previous conditions before the admission or 2) the observer underestimated the nutritional deficiency when carrying out the questionnaire.

Moreover, one interesting finding was that two infants that were diagnosed as having failure to thrive and scored as low nutritional risk, which suggests that the application of this questionnaire might underestimate this kind of cases probably because of its user-dependent, subjective nature. The evaluation using STRONGkids® along with the objective anthropometric evaluation seems to prevent cases like

Table 4 – Multivariate logistic analysis for predictors of higher STRONGkids® score

	Significance	OR	95% CI
Age	0.681	1.013	0.951 - 1.079
Long length of Stay (> 4 days)	0.780	0.909	0.464 - 1.780
Weight loss > 2%	0.415	2.006	0.376 - 10.703
Malnourished (general)	0.098	2.233	0.862 - 5.779
Infectious complication	0.005	3.096	1.412 - 6.789

OR: odds ratio; CI: confidence interval

these from being underestimated.

Our study found a strong correlation between the STRONGkids® screening and the state of malnutrition at admission (acute and/or chronic) and being acutely malnourished at admission but not with having chronic malnutrition at admission, which may indicate a weaker prediction of this type of patients.

Thirty-four-point six percent of the total number of children had a previous condition at admission, contrasting with 63.8% that did not. The STRONGkids® screening showed a strong correlation between the presence of a previous condition at admission, which strengthens the evidence that having a previous history of health problems predicts higher nutritional risk.

In terms of the type of condition upon admission, of the children that were scored as being at nutritional risk, 43.4% had an infectious disease on admission and 28.3% had a respiratory disease on admission – which comprises a total of 71.7% of all disease types at admission – showing a high prevalence of malnutrition in this type of diseases.

Nutritional deterioration was found in 10% of the children with low malnutrition risk and 21.7% of the children with moderate and high risk. Even though there was no statistically significant correlation found between the STRONGkids® score and nutritional deterioration, our data shows that higher-risk children might have a higher probability of developing acute malnutrition.

Our study found a strong correlation between the children scored as being at risk of malnutrition and the presence of infectious complications at admission. Compared with Cao *et al*,[39] the prevalence of infectious complications distributed in the STRONGkids® stratification is similar, as 73.6% of the children that were at risk had infectious complications.[39] Our findings show that the presence of infectious complications will affect the probability of malnutrition on admission and may validate items that are related to the presence of infection. This opens the possibility of further adaptations of this tool.

We believe that a weakness of this study was the fact that the hospital where it was performed is a second-level hospital, which made it impossible to add and assess some serious cases; it was not possible to assess anthropometric measures in a considerable percentage of surgical patients because of logistic reasons. The fact that the assessment of the STRONGkids® questionnaire and anthropometric measurements were made by different professionals may be a limitation as it can present different assessments for the same individual. In terms of opportunities, there should be studies on how the STRONGkids® Portuguese translation assessed nutritional screening and if there are changes that need to be made. It would be important to carefully evaluate the children that had nutritional intervention, how they were followed up during the intervention, and assess morbidity and mortality and possible readmission rates. It would be also interesting to assess the intrarater and interrater reliability of the process of this screening assessment.

CONCLUSION

STRONGkids® is a simple, quick nutritional screening tool for hospitalized children which demonstrates sustained evidence of being a reliable tool for assessing nutritional status on admission and all the valuable additional information related to it. Given that a considerably high percentage of children were identified as being at risk for malnutrition, it is essential to identify this early and provide nutritional intervention during and after hospitalization in order to improve individual and systematic health outcomes.

AWARDS AND PREVIOUS PRESENTATIONS:

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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The Influence of Obesity in the Autonomic Nervous System Activity in School-Aged Children in Northern Portugal: A Cross-Sectional Study

A Influência da Obesidade na Atividade do Sistema Nervoso Central em Crianças em Idade Escolar no Norte de Portugal: Um Estudo Transversal

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ABSTRACT

Introduction: Obesity is one of the most prevalent chronic diseases in childhood, being an important public health issue. Excessive weight has been associated with autonomic dysfunction but the evidence in children is scarce. Therefore, the aim of this study was to assess the effect of overweight and obesity on the autonomic nervous system activity, in children.

Material and Methods: Data from a cross-sectional study of 1602 children, aged 7 to 12 years, was used and 858 children were included in the analysis. Body mass index was calculated and classified according to criteria of the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC) and the International Obesity Task Force (IOTF). Body composition was characterized by bioelectrical impedance. Linear regression models were used to determine the association between body mass index, body composition and the autonomic nervous system activity, assessed by pupillometry.

Results: Average dilation velocity was higher among children with obesity, according to the CDC and percentage of body fat criteria (β = 0.053, 95% CI = 0.005 to 0.101 and β = 0.063, 95% CI = 0.016 to 0.109, respectively). The same trend was observed for WHO and IOTF criteria (β = 0.045, 95% CI = -0.001 to 0.091, and β = 0.055, 95% CI = -0.001 to 0.111, respectively). CDC and WHO body mass index z-scores were also positively associated with the values of average dilation velocity (rs = 0.030, *p* = 0.048; and rs = 0.027, *p* = 0.042, respectively).

Conclusion: Our findings suggest an association between body mass and changes in the autonomic activity, Moreover, this study provides proof of concept for interventions targeting the prevention/treatment of obesity in children that may offer some benefit in re-establishing the balance of the autonomic nervous system, and subsequently preventing the consequences associated with the autonomic nervous system dysfunction.

Keywords: Autonomic Nervous System/physiopathology; Child; Obesity/physiopathology; Pediatric Obesity; Portugal

RESUMO

Introdução: A obesidade é uma das doenças crónicas mais prevalentes na infância. O peso excessivo tem sido associado à disfunção autonómica, mas as evidências em crianças são escassas. Este estudo teve como objetivo avaliar o efeito da pré-obesidade e obesidade na atividade do sistema nervoso autónomo, em crianças.

Material e Métodos: Foram utilizados dados de um estudo transversal com 1602 crianças, sendo que 858 foram incluídas na análise. O índice de massa corporal foi calculado e classificado de acordo com a Organização Mundial da Saúde (OMS), Centro de Controlo e Prevenção de Doenças dos Estados Unidos (CDC) e a *Task Force* Internacional para a Obesidade (IOTF). A composição corporal foi caracterizada por impedância bioelétrica. Modelos de regressão linear foram usados para determinar a associação entre o índice de massa corporal, a composição corporal e a atividade do sistema nervoso autónomo, avaliada por pupilometria.

Resultados: A velocidade média de dilatação foi maior entre crianças com obesidade, segundo os critérios do CDC e percentagem de gordura corporal (β = 0,053, IC 95% = 0,005 a 0,101 e β = 0,063, IC 95% = 0,016 a 0,109, respetivamente). Igual tendência foi observada para os critérios da OMS e IOTF (β = 0,045, IC 95% = -0,001 a 0,091 e β = 0,055, IC 95% = -0,001 a 0,111, respetivamente). Os *z-scores* de índice de massa corporal do CDC e OMS também se associaram positivamente aos valores da velocidade média de dilatação (rs = 0,030, *p* = 0,048; e rs = 0,027, *p* = 0,042, respetivamente).

Conclusão: Os resultados sugerem uma associação entre a massa corporal e alterações na atividade do sistema nervoso autónomo Este estudo fornece prova de conceito para intervenções direcionadas à prevenção/tratamento da obesidade em crianças, podendo favorecer o restabelecimento do equilíbrio do sistema nervoso autónomo e, assim, prevenir as consequências associadas à sua disfunção.

Palavras-chave: Criança; Obesidade/fisiopatologia; Obesidade Pediátrica; Portugal; Sistema Nervoso Autónomo/fisiopatologia

INTRODUCTION

Childhood obesity is a growing public health problem. In 2016, there were 340 million obese children and adolescents worldwide.[1] It affects multiple low- and middle-income countries, especially in urban areas.[2] Childhood obesity affects children in numerous aspects of their emotional health and social life, by decreasing their quality of life, self-esteem and academic performance[2]; it also has a negative impact on their physical health, predisposing them to a greater number of comorbidities that classically would only appear in adulthood.[3,4] As such, it is of great importance to explore the mechanisms leading to its manifestation in order to develop prevention strategies and to decrease the incidence

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rate worldwide.

Recent studies have highlighted the role of the autonomic nervous system (ANS) dysfunction on weight gain and obesity development.[5,6] The ANS is comprised of two branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), each of them with opposing functions.[7,8] Several mechanisms to maintain body homeostasis are involved with the ANS, including the control of food intake and weight regulation.[7,9] Although autonomic dysfunction may be involved in the pathogenesis of obesity, the excessive weight may also lead to changes in ANS function.[6,9] People with obesity showed a sympathetic dominance and a parasympathetic withdrawal.[6,10,11] Additionally, chronic overeating in obese people may promote sympathetic activation, which increases energy expenditure and thus normalizes body weight.[12] This activation of the SNS may occur as a homeostatic mechanism to prevent fat accumulation by stimulating lipolysis.[10,13] Even though previous studies reported the role of ANS in adult obesity,[9,14] the evidence of this association in childhood is scarce. Additionally, the majority of the studies have evaluated the autonomic function through the heart rate variability (HRV), providing information on the cardiac autonomic function.[15] However, recent studies recognised pupillometry as a useful, simple, non-invasive and valuable method to assess the autonomic function.[16,17] Therefore, the aim of this study was to assess the effect of obesity on the ANS activity in school-aged children.

MATERIAL AND METHODS

Setting and design

This study included participants from a cross-sectional study. Twenty out of the 53 primary schools in the city of Porto, Portugal, were randomly selected.[18] A total of 1602 children, aged between 7 and 12 years, were invited to participate. Of those, 686 failed to provide the signed parental informed consent form and 58 refused to perform the assessments. These last 58 children had significantly higher BMI z-score values than the included children, but no differences regarding age, sex, parental education, respiratory symptoms and asthma prevalence. Therefore, data from 858 children (50.6% boys), corresponding to a participation rate of 53.6%, were analysed.

The study was approved by the University Health Ethics Committee and informed consent was obtained from each children's legal guardians.

Participants and assessments

A self-administered ISAAC (International Study of Asthma and Allergies of Childhood)-based questionnaire was filled out by the children's guardians regarding demographic, social and behavioural information, as well as questions about respiratory/allergic health. The level of parental education was used as a proxy for socioeconomic status and it was recorded as the number of successfully completed years of formal education, which was categorized into three groups: less than 9 years; between 10 years and 12 years; and more than 13 years. Sleep duration was estimated based on the question "How many hours does your child sleep, on average, most days of the week?". Physical activity was defined based on a positive answer to the question "Does your child partake in any sports activity outside of the normal school-period, at least once a week?". Dietary intake was assessed from a single 24-hour recall questionnaire[19] administered to the participants, from which total energy intake was estimated using the Food Processor®, (ESHA Research, USA) software. Participants were questioned accurately about their food and drinks consumption, consuming time and place and food brands. Asthma was defined based on the medical diagnosis of asthma, symptoms over the past 12 months and/or at least 12% and over 200 mL increase in FEV1 after bronchodilation, as previously described by Silva *et al*.[20]

Clinical assessments and anthropometry were performed by a research nurse. Weight (kg) was measured using a digital scale (Tanita™ BC-418 Segmental Body Analyzer). Height (cm) was measured using a portable stadiometer. Body mass index (BMI) was calculated by using the ratio of weight/height^2 (kg/m^2) and classified into different categories (underweight, normal weight, overweight and obesity) according to age- and sex-specific percentiles determined by the World Health Organization (WHO),[21] the Centers for Disease Control and Prevention (CDC)[22] and the International Obesity Task Force (IOTF).[23] Underweight and normal weight categories were merged into the same category (underweight and normal weight category) due to the lower prevalence of underweighted children. Bioelectrical impedance analysis was performed to characterize body composition. Body fat percentage was classified according to sex-specific centile curves for body fat in children[24] and categorized into three categories (under fat and normal fat; overfat; and obese). Different criteria were used to categorize the BMI, since the establishment of different cut-offs is generally statistical rather than based on risk or the degree of body fatness. As a result, different definitions often do not give the same results.

A portable infrared PLR-200 pupillometer (NeurOptics PLR-200™Pupillometer, NeurOptics Inc.,CA) was used to perform pupillometry. The participants had to spend at least 15 minutes in a quiet and semi-dark room, for the pupil to adjust to the low lighting level. Then they were instructed to focus, with the eye that was not being tested, on a small object three meters away, keeping their eyes wide open and head straight during targeting and measurement. The

tested eye was briefly illuminated by light-emitting diodes with a single light stimulus having a peak wavelength of 180 nm. In case of blinking, the measure was repeated. A light response curve of the pupil was recorded for each child. Each participant had recorded its pupil diameter before (initial) and at constriction peak (final), in millimetres; the relative constriction amplitude, in percentage; the maximum constriction velocity (MCV), the average constriction and dilation velocities (ACV and ADV, respectively), in mm/s; and the total time taken by the pupil to recover to 75% of the initial resting pupil size after it reached the constriction peak (T75), in seconds. No side-to-side differences were observed in the pupil responses, so all pupillary data reported were from one eye. Pupillometry is a non-invasive and simple technique that provides data from both branches of the ANS.[17] The SNS controls pupil dilation and the PNS controls pupil constriction[17]; therefore, ADV and T75 are measures of sympathetic activity and pupil diameter, MCV, ACV and constriction amplitude are measures of parasympathetic activity.

Statistical analyses

Statistical analysis was performed using the IBM® SPSS™ Statistics version 26.0.0.0 for Windows and Microsoft Office Excel® (see detailed information on statistical analyses in supplementary material). Distribution of continuous variables were analysed for normality check by the Kolmogorov-Smirnov test. Since non-Gaussian distributions were observed, non-parametric tests were performed for descriptive statistics (median and 25th and 75th percentile). The Mann-Whitney test was used to compare continuous variables between the girls and the boys. The chi-square test was used to evaluate the differences between sex and categorical variables. The Kruskall-Wallis test was used to perform the post-hoc test and study the relationship between body mass categories and ADV measures. Significant differences were reported when the α-value was less than 5% ($p < 0.05$). Linear regression models were performed to determine the association between the body mass criteria and pupillometry parameters, using linear coefficients (β) and its respective 95% confidence interval (CI). Two models were considered for the analysis: model 0, the null model and model 1, adjusted for age, sex, parental education, physical activity, energy intake, sleep duration and asthma.

RESULTS

The prevalence of overweight ranged between 15.1% and 20.4%, according to the CDC and the WHO, respectively. The prevalence of obesity varied between 7.5% (IOTF) and 16.2% (percentage of body fat criteria), and no statistically significant differences were found between girls and boys (Table 1). The amplitude and maximum velocity of constriction were significantly higher in boys compared to girls (36.0% *vs* 35.0%, $p = 0.011$; and 5.38 *vs* 5.24 mm/s, $p = 0.011$, respectively). However, no statistically significant gender differences were found for the remaining pupillometry parameters (Table 1).

Statistically significant differences were found between the ADV and all the body mass criteria [Appendix 1, Table S1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17144/15177)]. ADV was significantly higher in children with obesity compared to children with underweight/under fat and normal weight/normal fat (Fig. 1). There were no statistically significant differences between parameters related to PNS, T75 and the body mass criteria [Appendix 1, Table S1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17144/15177)].

An increase in BMI and percentage of body fat was associated with an increase in ADV, regardless of the used criteria [model 0, Appendix 1, Table S2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17144/15177)]. After adjustment for age, sex, parental education, physical activity, sleep duration, energy intake and asthma, a similar result was observed for BMI defined according to the CDC and percentage of body fat criteria and ADV. An increase in BMI and percentage of body fat was associated with higher ADV values (β = 0.053, 95% CI = 0.005 to 0.101, for CDC; and β = 0.063, 95% CI = 0.016 to 0.109, for the percentage of body fat). Although non-significant, the same trend was observed for BMI according to WHO and IOTF criteria and ADV (β = 0.045, 95% CI = -0.001 to 0.091, and β = 0.055, 95% CI = -0.001 to 0.111, respectively) (Fig. 2).

Additionally, CDC and WHO BMI z-scores were positively associated with the values of ADV (rs = 0.030, $p = 0.048$; and rs = 0.027, $p = 0.042$, respectively) [Appendix 1, Table S3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17144/15177)]. There were no statistically significant associations between the remaining parameters related to PNS, T75 and body mass criteria [Appendix1, Table S2 and Table S3 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17144/15177)].

DISCUSSION

Our findings suggested an association between body mass and changes in the autonomic activity, namely with a sympathetic dysautonomia, in school-aged children. The average dilation velocity (ADV) was significantly higher in children with obesity compared to children with underweight/under fat and normal weight/normal fat, regardless of the criteria used.

Our study has a few limitations:

- The cross-sectional design does not allow us to establish a causal relationship.
- The use of BMI may be a limitation, since it depends only on body weight, regardless of body composition,[25] and does not allow distinction between fat mass and fat-free mass.[26] Nonetheless, the majority of people with high BMI have an excessive body fat.[27]
- The use of bioelectrical impedance analysis (BIA) in children and the measurement of the percentage of body fat to classify them may be a limitation.

Table 1 – Characteristics of the participants

Characteristics	Total	Girls	Boys	*p*-value
Age, y [mean (SD)]	8.76 (0.80)	8.77 (0.78)	8.75 (0.81)	0.648
Parental education, n (%)				0.345
0 - 9 y	219 (32.10)	97 (29.60)	122 (34.50)	
10 - 12 y	201 (29.50)	103 (31.40)	98 (27.70)	
≥ 13 y	262 (38.40)	128 (39.00)	134 (37.90)	
BMI, n (%)				
CDC				0.597
Underweight and normal weight	614 (72.70)	302 (72.60)	312 (72.70)	
Overweight	128 (15.10)	67 (16.10)	61 (14.20)	
Obese	103 (12.20)	47 (11.30)	56 (13.10)	
WHO				0.057
Underweight and normal weight	553 (65.40)	265 (63.70)	288 (67.10)	
Overweight	172 (20.40)	98 (23.60)	74 (17.20)	
Obese	120 (14.20)	53 (12.70)	67 (15.60)	
IOTF				0.532
Underweight and normal weight	614 (72.70)	295 (70.90)	319 (74.40)	
Overweight	168 (19.90)	88 (21.20)	80 (18.60)	
Obese	63 (7.50)	33 (7.90)	30 (7.00)	
Percentage of body fat				0.111
Under fat and normal fat	564 (67.70)	289 (70.80)	275 (64.70)	
Overfat	134 (16.10)	63 (15.40)	71 (16.70)	
Obese	135 (16.20)	56 (13.70)	79 (18.60)	
Asthma, n (%)	80 (9.30)	49 (11.60)	31 (7.10)	**0.034**
Physical activity, n (%)	494 (64.20)	227 (60.20)	267 (67.90)	0.029
Sleep duration, hours [mean (SD)]	9.34 (0.85)	9.35 (0.85)	9.33 (0.86)	0.652
Total energy intake, Kcal [mean (SD)]	2182.46 (604.58)	2087.69 (564.78)	2273.73 (627.97)	**< 0.001**
Pupillometry parameters				
Initial pupil diameter, (mm)	5.30 (4.70 - 5.90)	5.30 (4.60 - 5.90)	5.40 (4.80 - 5.90)	0.229
Final pupil diameter, (mm)	3.40 (3.00 - 3.80)	3.40 (2.90 - 3.80)	3.40 (3.00 - 3.80)	0.888
Constriction amplitude, (%)	35.00 (32.00 - 38.00)	35.00 (32.00 - 38.00)	36.00 (33.00 - 39.00)	**0.011**
ACV, (mm/s)	4.02 (3.57 - 4.42)	3.99 (3.52 - 4.40)	4.05 (3.62 - 4.45)	0.065
MCV, (mm/s)	5.31 (4.72 - 5.89)	5.24 (4.64 - 5.83)	5.38 (4.83 - 5.96)	**0.011**
ADV, (mm/s)	1.15 (0.99 - 1.33)	1.15 (0.99 - 1.34)	1.17 (0.99 - 1.33)	0.917
T75, (s)	1.67 (1.20 - 2.13)	1.67 (1.14 - 2.09)	1.67 (1.23 - 2.16)	0.275

BMI: body mass index; CDC: US Centers for Disease Control and Prevention; WHO: World Health Organization; IOTF: International Obesity Task Force; ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; T75: the total time taken by the pupil to recover to 75% of the initial resting pupil size after it reached the constriction peak.
Data reported as median (25^{th}, 75^{th} percentile) unless otherwise stated.
Significant differences are in bold.

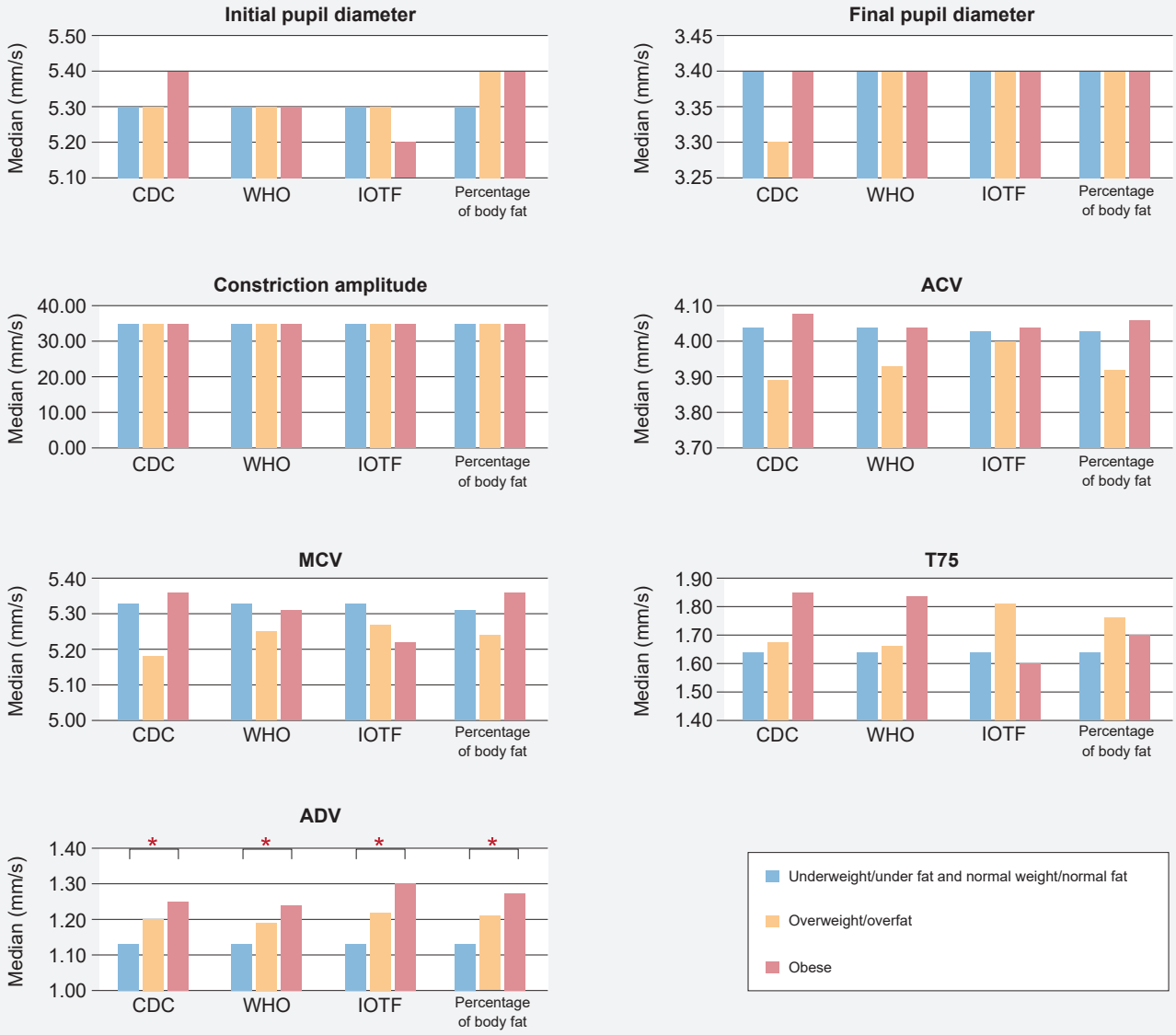

Figure 1 – Median of pupillometry parameters according to the different body mass criteria
CDC: US Centers for Disease Control and Prevention; WHO: World Health Organization; IOTF: International Obesity Task Force; ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; T75: the total time taken by the pupil to recover to 75% of the initial resting pupil size after it reached the constriction peak.
*: $p < 0.05$

Children have a considerable variation in the amount of fat mass, total body water, total body protein and osseous mineral until they reach adulthood, which challenges the assessment of body composition.[28,29] Talma *et al.* concluded that BIA was not satisfactory as a valid method to estimate of the percentage of body fat in children and adolescents, although it was a practical method for that estimation.[30] Nevertheless, an almost perfect reproducibility was found in the percentage of body fat estimation through BIA in children and adolescents,[31] and this parameter has been adopted in several recent studies.[32,33] BIA is extensively used for population-based investigations, being a non-invasive, safe, quick and relatively low cost way of assessing body composition.[28]

- The use of total energy intake does not provide information about the quality of diet. Nonetheless, evidence suggests energy intake is related with portion sizes, and is associated with an increased risk of excessive body weight.[34] In addition, 24-hour recall was found to be an acceptable assessment of total energy intake at a group level,[35] being easy to apply,

cost-effective, and having a good compliance.[19]

- Physical activity assessment was based on a single question using self-reported data, which may not reflect how active the children really were and lead to some misclassification bias. Nevertheless, indirect methods of evaluation of physical activity in childhood are moderately correlated with direct methods,[36] and are a feasible approach to collect information about physical activity.[36]
- Birth weight was not included in the analysis, which might influence the results, since low birth weight children have been previously associated with having higher sympathetic activity.[37]
- The duration of obesity was not evaluated, limiting the assessment of the function and global activity of the ANS in children with obesity over time.[38]

Our study also has important strengths. This is, to the best of our knowledge, the first study assessing the association between body mass and the ANS in a large number of schoolchildren, using pupillometry. Pupillometry allows an accurate assessment of the ANS, in an easy, fast, non-invasive way.[39] In addition, the clinical assessments were performed in each primary school, considered as the normal environment for children, which may decrease the level of stress associated with clinical and physical assessments. Height and weight were measured, avoiding the bias associated with self-perceptions of weight by parents, who tend to underestimate their children's overweight/obese condition.[40] A recent systematic review and meta-analysis assessing the validity of BMI to identify obesity in children concluded that BMI had a high specificity to detect children with obesity.[25] The existence of entities using different BMI criteria makes it harder to unify results and draw conclusions out of studies.[25] However, in this study, we used different BMI criteria as well as the percentage of body fat to characterize schoolchildren. Our results suggested that, regardless of the BMI criteria, a significant association was observed between obesity and the ADV, but the strength of the association depends on the adopted definition.

Our findings showed that obesity was associated with higher values of ADV, suggesting a change in the activity of SNS among school-aged children with obesity. Similar

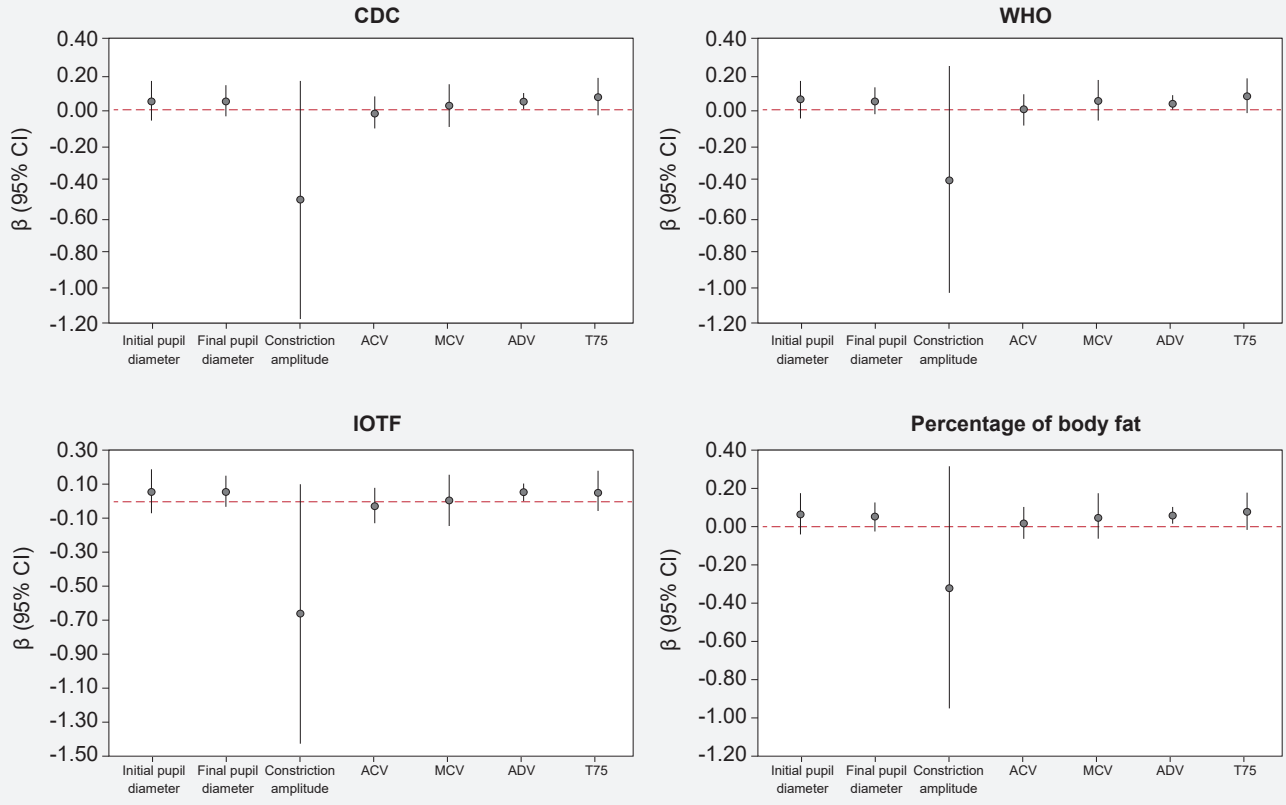

Figure 2 – Association between BMI and the percentage of body fat criteria and pupillometry parameters
CDC: US Centers for Disease Control and Prevention; WHO: World Health Organization; IOTF: International Obesity Task Force; ACV: average constriction velocity; MCV: maximum constriction velocity; ADV: average dilation velocity; T75: the total time taken by the pupil to recover to 75% of the initial resting pupil size after it reached the constriction peak.

studies reported a sympathetic dominance and a parasympathetic withdrawal among children and adolescents with obesity, using HRV to assess the ANS.[41,42] A study conducted in Germany including 149 children also demonstrated a change in ANS activity in overweight and obese children.[43] However, Baum *et al*[43] found a negative association between BMI and both pupil diameter and dilation velocity. Overweight and obese children had a lower dilation velocity and pupil diameter compared with normal weight children.[43] A Japanese study including 84 children assessed the ANS function through HRV and also found a decreased activity of the SNS and PNS in children with obesity. Interestingly, this study reported a negative correlation between HRV measures and the duration of obesity.[38] The differences between previous studies and our results may be explained by the continuous effect of obesity on ANS activity. As proposed by Nagai *et al*[38] a correlation may be observed between the activity of ANS and duration of obesity. Furthermore, a study performed in children with obesity showed an increase in sympathetic activity in participants with recent obesity (less than four years), while in participants with intermediate (four to seven years) or long (more than seven years) obesity, no changes were observed in the SNS activity, compared with participants with normal weight.[44] This decreasing trend of SNS activity suggests a biphasic behaviour of the cardiac SNS, in obesity.[44] However, our study did not evaluate the duration of obesity, not allowing the assessment of this effect on ANS activity. In addition, the categories of BMI used by the different studies may also be associated with the effect of obesity and ANS. Baum *et al*[43] classified overweight and obese participants into one category, whereas in our study these groups were classified separately, and we observed an association between children with obesity and ADV. Nevertheless, all studies suggested that obesity was associated with changes in the ANS.

The mechanisms related with sympathetic activation in obesity are still not fully understood. Landsberg[12] formulated a hypothesis advocating that the chronic overeating of people with obesity may promote a sympathetic activation intended to increase energy expenditure and normalize body weight. This activation of the SNS may occur as a homeostatic mechanism to prevent fat accumulation by stimulating lipolysis in the adipose tissue.[10,13] As a result of lipolysis, the free fatty acids (FFAs) pool will increase, contributing to insulin resistance[13] and lipotoxicity in the peripheral tissues that lead to metabolic dyshomeostasis, thus increasing the production of very low density lipoproteins in the liver, and promoting dyslipidaemia.[45] Further evidence supports the hypothesis of a sympathetic defence against obesity with an increased sympathetic activity in order to stimulate β-adrenergic thermogenesis, and to promote energy expenditure.[46] However, Guarino *et al*[9] reported that this feedback of the SNS may not favour the intended energy expenditure and, consequently, may not be associated with weight loss. The hyperactivity of the SNS may also be driven by the overexpression of several pro-inflammatory adipokines, including leptin, interleukin-6, tumour necrosis factor-α and angiotensinogen.[6,13] There are studies showing that weight loss reverses the sympathetic supremacy in people with obesity, being even associated with parasympathetic activation.[6,9] A study in children which assessed the HRV during a weight reduction program also showed a parasympathetic dominance.[47] The positive weight loss effects seem to be potentiated by the association of an hypocaloric diet with exercise.[6,48] In addition, Silva *et al* showed that a Mediterranean diet meal may also improve ANS function compared with an energetically similar fast food-like meal. The authors suggested that fast food meals may cause dysfunction of adipokines, increasing insulin secretion and, consequently, the activity of the SNS.[49]

Importantly, there is evidence showing that a dysfunction in the ANS may be implicated in the pathogenesis of obesity.[9] Guarino *et al*[9] reported a connection between the ANS and the GI system that keeps a balanced energy homeostasis. ANS is involved in the regulation of food intake and gastric emptying, by the action of gut hormones on vagal afferent neurons.[9] The exposure to a high fat diet impairs the capacity of the vagal afferents to react to GI peptides. The disruption of the GI vagal afferents causes amplified orexigenic (appetite inducer) and reduced anorexigenic signalling ability, which may be the cause for weight gain and obesity.[50] A chronic elevation of the SNS activity has been reported as being detrimental for the human body as it decreases the stimulation of the metabolism, and impairs β-adrenergic signalling, leading to changes in target tissues, which contributes to a vicious cycle of weight gain, worsening the state of obesity and associated comorbidities.[10,13] A sympathetic hyperactivity may also activate the adipose triglyceride lipase, increase the triglyceride hydrolysis, and thus promote the continuity of obesity.[9,45]

CONCLUSION

Our results suggested that childhood obesity may be associated with a change in the ANS activity, particularly a dysautonomia in the sympathetic activity. Moreover, our results highlight the need to create strategies to reduce the prevalence of obesity and, consequently, restore the balance of ANS.

AUTHOR CONTRIBUTIONS

BGT: Data analysis; conception and critical review of the manuscript.

IP, JCR: Data collection analysis and interpretation; critical review of the manuscript.

FM: Data collection and interpretation; clinical and physical evaluation; critical review of the manuscript.

MF: Data interpretation; critical review of the manuscript.

PP: Data analysis and interpretation; critical review of the manuscript.

PM: Data interpretation; critical review of the manuscript.

AM: Study design and first draft; conception of the manuscript; data interpretation; critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

PM has patents planned, issued or pending for iMC Salt Control device.

All other authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Validação da Versão Portuguesa de um Instrumento de Avaliação de Necessidades Paliativas Pediátricas: A Pediatric Palliative Screening Scale

Validation of the European Portuguese Version of a Pediatric Palliative Needs Assessment Tool: The Pediatric Palliative Screening Scale

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RESUMO

Introdução: A *Pediatric Palliative Screening Scale* (PaPaS *Scale*) foi desenhada para ajudar os profissionais a identificar as crianças/jovens com doença crónica complexa, limitante ou ameaçadora da vida que beneficiariam de cuidados paliativos pediátricos e facilitar referenciação atempada e apropriada. O objetivo deste estudo foi traduzir, adaptar culturalmente e validar a *PaPaS Scale* para a população pediátrica portuguesa.

Material e Métodos: Realizou-se um estudo metodológico quantitativo de tradução, adaptação cultural e validação de uma escala. Numa primeira fase, procedeu-se à tradução e adaptação cultural da versão original da PaPaS *Scale* de inglês para português europeu. A segunda fase consistiu na avaliação das propriedades psicométricas da versão portuguesa da Escala PaPaS.

Resultados: Numa amostra de 51 questionários referentes a crianças/jovens com doença crónica complexa, a soma das respostas aos itens da escala revelou que 84,4% dos doentes tinham indicação para ser referenciados aos cuidados paliativos pediátricos. Na análise de consistência interna obteve-se um valor do alfa de Cronbach superior a 0,80, pelo pelo que se considera a escala adequada aos dados analisados. De facto, os valores de correlação item-total indicaram que as 11 variáveis mediram com boa fiabilidade e de forma unidimensional a escala PaPaS. Na análise fatorial confirmatória, os resultados obtidos indicaram que globalmente os itens eram significativos, consistentes e apresentaram validade convergente. Apenas o item "2.2. Efeitos secundários do tratamento" obteve um valor abaixo do limiar definido.

Conclusão: A *PaPaS Scale* foi traduzida e adaptada para a versão em português europeu, o que permite a sua utilização imediata na população portuguesa. Torna-se importante o desenho de estudos, preferencialmente multicêntricos, que aprofundem as características psicométricas desta escala.

Palavras-chave: Avaliação de Necessidades; Criança; Cuidados Paliativos; Doença Crónica; Pediatria; Portugal

ABSTRACT

Introduction: The Pediatric Palliative Screening Scale (PaPaS Scale) was designed to help professionals to identify life-limiting or life-threatening children/young people with complex chronic conditions who would benefit from pediatric palliative care and facilitate their timely and appropriate referral. The aim of this study was to translate, culturally adapt and validate the PaPaS Scale for the Portuguese pediatric population.

Material and Methods: A quantitative methodological study involving translation, cultural adaptation and validation of a scale was performed. In the first phase, the translation and cultural adaptation of the original version of the PaPaS Scale from English to European Portuguese was undertaken. The second phase consisted of evaluating the psychometric properties of the Portuguese version of the PaPaS Scale.

Results: Fifty-one enquires pertaining to children/young adults with complex chronic conditions were completed and returned, the sum of the responses to the items on the scale revealed that 84.4% of the patients had an indication for referral to pediatric palliative care. The internal consistency analysis obtained a value of Cronbach's alpha above 0.80, so the scale was considered adequate for the analyzed data. In our sample, the item-total correlation values indicated that the 11 variables measured the PaPaS Scale with good reliability and unidimensionally. The confirmatory factor analysis suggested that the items were significant, consistent, and presented convergent validity globally. Only item "2.2. Treatment side effects" obtained a value below the defined threshold.

Conclusion: The PaPaS Scale was translated and adapted to the European Portuguese version, allowing its immediate use in the Portuguese population. It will be essential to design multicentric studies to expand the knowledge about the psychometric characteristics of this scale.

Keywords: Child; Chronic Disease; Needs Assessment; Palliative Care; Pediatrics; Portugal

INTRODUÇÃO

O acesso aos cuidados paliativos pediátricos (CPP) é um direito humano básico para todas as crianças/jovens[1-5] em particular para as portadoras de doenças crónicas complexas (DCC), limitantes ou ameaçadoras de vida.

Segundo a *International Children's Palliative Care Network* (ICPCN)[1], no início de 2013, Portugal era oficialmente um país sem provisão de CPP (nível 1); em março de 2013, passou para o nível 2 (evidência da capacidade de crescimento na prestação de CPP) e em outubro de 2018 atingiu o nível 4[1,6] (evidência de formação profissional disponível de prestação de CPP, com planos focados no desenvolvimento de serviços e integração nos serviços de saúde).

Em 2018, estimava-se que a população portuguesa em idade pediátrica com necessidade de cuidados paliativos era de 7828 crianças/jovens.[7] No intervalo entre 2013 e 2018 verificou-se um decréscimo de 500 crianças/jovens com DCC no geral, mas com assimetrias por distrito. Lisboa representou o maior aumento (64 crianças/jovens) e

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Porto a maior diminuição (123 crianças/jovens).[7] Anualmente, morrem cerca de 200 crianças/jovens (50% no primeiro ano de vida) com DCC e necessidades de CPP. A maioria destas mortes acontece no hospital.[8]

A abordagem dos CPP tem como objetivos reduzir intervenções e terapêuticas excessivas em situação de DCC avançada, melhorar a qualidade de vida através do controlo sintomático eficaz e reduzir a carga emocional dos pais e da família.[9] Os CPP deveriam ser integrados na prestação de cuidados de saúde (numa articulação entre os cuidados hospitalares, primários e a comunidade) em três níveis: universais, generalistas e especializados.[5] Atualmente, os CPP caracterizam-se por elevada intervenção médica, centralização em hospitais especializados, falta de organização e coordenação da prestação de cuidados e apoio domiciliário e psicossocial precário.[4]

A nível mundial, o acesso aos CPP ainda é limitado.[4] Apesar das indicações da Organização Mundial de Saúde nesta matéria, a introdução dos CPP e a referenciação atempada para equipas especializadas ainda surge de forma tardia na trajetória da DCC.[9,10] As definições atuais de CPP não são esclarecedoras em relação ao momento de integração dos CPP e, além disso, há um conhecimento variável dos profissionais de saúde no que concerne às competências específicas dos CPP.[9] São vários os fatores que contribuem para a referenciação tardia: o benefício dos CPP ser negligenciado no início da doença, principalmente se a probabilidade de cura ou de controlo da doença estiver sobrestimada; a eventual interpretação negativa do termo 'cuidados paliativos' pela família; a pressão exercida pelas famílias sobre os profissionais de saúde para que iniciem terapêuticas que apesar de fúteis, criam esperança.[9]

Existem várias escalas para referenciação em cuidados paliativos, a maior parte desenhadas para adultos.[9] São instrumentos que se focam na avaliação do prognóstico e na estimativa da esperança de vida, especialmente nas decisões em fim de vida.[9] Um instrumento de avaliação pediátrica deve incidir nas necessidades paliativas da criança/jovem no estadio precoce da doença, tal como acontece no adulto.[9]

Bergstrasser *et al* desenvolveram em 2013 um instrumento de rastreio de necessidade de CPP, denominado *Pediatric Palliative Screening* (PaPas) *Scale*, projetado para identificar crianças/jovens que beneficiariam de CPP e facilitar o encaminhamento oportuno e apropriado.[9] Na conceptualização desta escala, os investigadores realizaram várias revisões e modificações. Atualmente os domínios[9,10] avaliados são os seguintes:

1) Trajetória da doença e impacto nas atividades de vida diária da criança/jovem;

2) Estimativa do resultado e efeitos secundários do tratamento dirigido à doença;

3) Controlo sintomático e problemas associados;

4) Preferências/necessidades da criança/jovem, família e profissional de saúde;

5) Sobrevivência.[9]

Cada domínio foi dividido entre duas a cinco questões, num total de 11 itens. Cada item incluiu várias opções que pontuam de 0 a 4. Pontuações individuais ou totais elevadas seriam sugestivas de maior necessidade de CPP. Em termos clínicos, a referenciação aos CPP seria gradual, de modo a integrar um modelo de cuidados paliativos de três fases (Fig. 1):

- Fase 1: Pontuação maior ou igual que 10 pontos - Introdução aos CPP - Considerar a introdução do conceito de CPP;

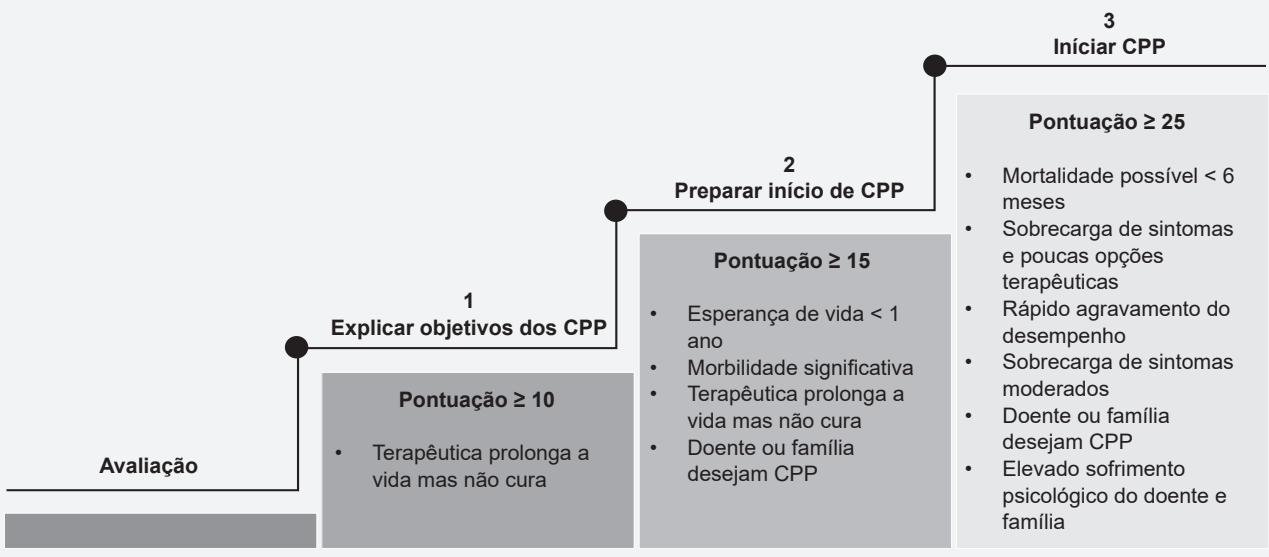

Figura 1 – Abordagem dos CPP com base na pontuação adquirida escala PaPaS

- Fase 2: CPP – Pontuação maior ou igual que 15 pontos– Preparar o início dos CPP - Controlo sintomático básico associado a tratamento da doença de base;
- Fase 3: CPP – Pontuação maior ou igual que 25 pontos– Iniciar os CPP - Os CPP são o foco do plano de cuidados.

Criou–se um instrumento heterogéneo que avalia as necessidades paliativas nas crianças/jovens com DCC com idade superior a um ano e inferior aos 19 anos. Recém-nascidos e lactentes foram excluídos porque as suas trajetórias de doença podem ser muito curtas, com dois terços das mortes a ocorrer nas primeiras semanas de vida em contexto de cuidados intensivos.[9,11,12]

A escala PaPaS é atualmente a escala pediátrica validada que identifica crianças/jovens com DCC com necessidades paliativas e permite a referenciação e orientação precoce para equipas especializadas em CPP. A classificação e estratificação dos grupos de doentes daí resultante conduz a uma abordagem integrada e cuidada de CPP. A escala PaPaS fundamenta-se na taxonomia criada pela Associação *Together for Short Lives,*[13] pelo que não se limita aos cuidados em fim de vida. É uma ferramenta educativa que pode apoiar equipas não especializadas a cuidar melhor de crianças/jovens com DCC.[9,10]

Recentemente foi proposta uma modificação desta escala e realçada a importância da sua utilização na avaliação e manutenção da continuidade de cuidados nas crianças já referenciadas a equipas de CPP.[14]

O objetivo deste estudo foi a tradução, adaptação e validação da escala para a população pediátrica portuguesa.

MATERIAL E MÉTODOS

Desenho do estudo

Realizou -se um estudo do tipo metodológico quantitativo de tradução, adaptação cultural e validação de uma escala. Na primeira fase procedeu-se à tradução e adaptação cultural da versão original da escala PaPaS do inglês para o português europeu. A segunda fase consistiu na avaliação das propriedades psicométricas da versão portuguesa da escala PaPaS.

Fase 1: tradução e adaptação cultural

Este estudo realizou-se após contacto direto por correio eletrónico com a autora da escala, Eva Bergstraesser, e respetivo consentimento. Obteve-se igualmente o parecer favorável da Diretora do Departamento de Pediatria e da Comissão de Ética do Centro Hospitalar Universitário Lisboa Norte e Centro Académico Médico de Lisboa.

Esta investigação seguiu a metodologia apresentada nas *Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures*[15] e a adaptação da versão original (língua inglesa) da escala PaPaS para a língua e cultura portuguesa europeia foi concretizada de acordo com as etapas definidas.[15]

A tradução foi realizada por dois tradutores independentes de origem portuguesa com proficiência na língua original do documento. O primeiro tinha conhecimento do tema avaliado e o segundo desconhecia os objetivos da tradução.

As duas versões traduzidas foram comparadas com o instrumento original. O seu formato foi analisado e avaliado em relação às equivalências e discrepâncias semânticas, idiomáticas, conceituais, linguísticas, contextuais e culturais, com o objetivo de se chegar a uma versão única.[16,17] As traduções foram sujeitas a uma reunião de consenso em que participaram médicos e enfermeiros, onde se realizou uma síntese das traduções, obtendo-se um documento com a versão unificada da escala PaPaS para a população pediátrica portuguesa, congruente com a versão original.

A retro-tradução, ou tradução reversa, foi realizada independentemente por outros dois tradutores diferentes com proficiência nativa na língua inglesa, e elevado nível de fluência oral e escrita em português, sem conhecimento da versão original em inglês. Compararam-se as duas retroversões independentes com o original (versão inglesa) e em reunião de consenso com os dois tradutores foi definida uma versão final adaptada à realidade portuguesa.

A comissão de especialistas (responsáveis pela validade do conteúdo) integrou profissionais de saúde (um médico e um enfermeiro), um professor de língua portuguesa, os tradutores e a investigadora. Foram analisados todos os documentos anteriores e o instrumento original até se obter um consenso. Desenvolveu-se a versão preliminar da escala adaptada culturalmente e adequada para a realização do pré-teste. Esta fase foi fundamental na identificação de expressões inadequadas e conceitos da tradução.

O estudo piloto, realizado numa pequena amostra de doentes (10%) que replicava as características da amostra/população-alvo, teve como objetivo identificar e solucionar eventuais problemas da versão portuguesa europeia deste instrumento. Os intervenientes foram informados acerca do propósito do pré-teste, tendo recebido um questionário cuja estrutura não podia ser modificada. Avaliaram-se o conteúdo, clareza e compreensão dos diversos itens da escala. Reviram-se os aspetos culturais, semânticos e conceituais[17,18] não tendo sido verificados obstáculos na sua legibilidade. Não se encontraram dificuldades na compreensão e aplicação do questionário pelo que esta passou a ser a versão final em português europeu, sem necessitar de reformulação.

Existiram vários contactos com a autora, e o documento final (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18071/15018) da versão

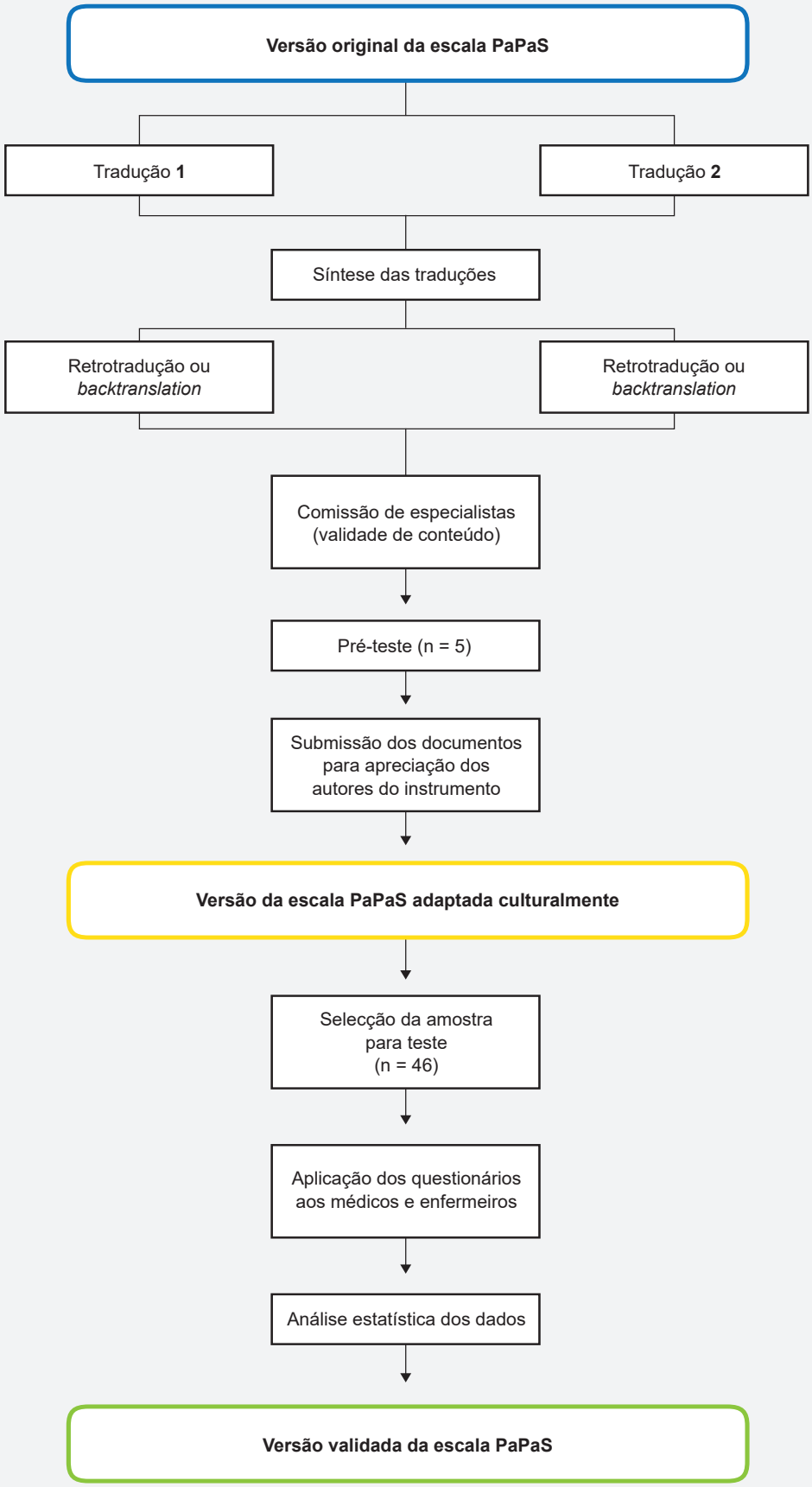

Figura 2 – Fluxograma de procedimentos adotados: tradução, adaptação cultural e de validação da escala PaPaS

portuguesa da escala PaPaS obteve a sua aprovação.

Apresenta-se no fluxograma a descrição do processo de acordo com adaptação de Beaton *et al* (Fig. 2).[15]

Fase 2: propriedades psicométricas da escala (validação da escala)

A versão final adaptada do questionário foi aplicada com uma introdução descritiva do objetivo do estudo. Os princípios éticos foram respeitados, foi garantida a confidencialidade, todos participaram de forma intencional e não houve custos nem prejuízos.

Participantes e critérios de legibilidade

A recolha de dados foi realizada de outubro a novembro de 2019. O estudo decorreu num hospital do Serviço Nacional de Saúde com autonomia administrativa, financeira e patrimonial.

A amostra foi não probabilística, de conveniência, constituída por 17 pediatras e três enfermeiros que realizaram 51 questionários referentes a crianças/jovens com DCC. Todos os profissionais tinham responsabilidade assistencial e diferenciação específica na área da DCC pediátrica, e tinham como língua materna o português europeu. Os profissionais realizaram entre um e nove questionários, de acordo com as crianças que seguiam ou por cujos cuidados eram responsáveis.

Métodos estatísticos utilizados

Os dados foram tratados e analisados estatisticamente mediante recurso ao programa informático *Statistical Package for the Social Sciences* (SPSS IBM® versão 24). A caracterização demográfica e clínica da amostra foi feita com base em vários elementos de estatística descritiva conforme apropriado[19-21]: frequência (n), percentagem (%), média, mediana, desvio padrão (SD), valor mínimo (mín.) e máximo (máx.).

A análise de consistência interna[22-27] foi verificada utilizando o coeficiente alfa de Cronbach[28] e a correlação item-total corrigida. Neste estudo, foram definidos como adequados os valores de alfa de Cronbach superiores a 0,80, e aceitáveis os coeficientes com valores entre 0,60 e 0,80.[25,26,29]

A validade da escala de medida foi verificada através de análise fatorial confirmatória.[30-37] A determinação da validade incluiu a verificação da significância estatística dos itens ($p < 0,05$),[38-47] medição elevada das saturações fatoriais (> 0,5), consistência interna e fiabilidade composta elevadas (> 0,8),[39] e grande proporção da variância extraída (> 0,5).[40] Esta análise permitiu também avaliar a escala de medida através de índices de ajustamento,[38,42,43] nomeadamente o índice absoluto (χ^2/g.l.) (< 5), o índice de discrepância (RMSEA, *root mean square error of approximation*) (< 0,08), o índice relativo (NFI, *normed of fit index*) (> 0,8) e o índice comparativo (CFI, *comparative fit index*) (> 0,8).

RESULTADOS

Estatística descritiva e resultados da escala

A escala PaPaS foi aplicada a 51 crianças/jovens com DCC (Tabela 1), com média de 11,2 anos (mediana de 10 anos), 53% do sexo feminino. Mais de metade dos diagnósticos de base correspondiam a patologia do foro neurológico e doenças metabólicas, e tinham recebido o diagnóstico no primeiro ano de vida. Quanto às categorias de necessidades paliativas, 31,4% das crianças/jovens tinham patologias do grupo IV (doença irreversível, não progressiva, de elevada morbilidade e probabilidade de morte prematura), 29,4% do grupo II (doenças que causam morte prematura, mas com longa sobrevivência se tratada) e 19,6% do grupo I (doenças potencialmente fatais, mas curáveis) e grupo III (doenças progressivas, mas sem cura possível) respetivamente (Tabela 1).

Os resultados da análise descritiva das respostas aos itens dos domínios da escala PaPaS são apresentados na Tabela 2.

A pontuação total da escala PaPaS apresentou um valor médio de 17,5, com um desvio padrão de 7,4, variando entre o valor mínimo de 6 e o valor máximo de 37. A pontuação de cada questionário foi recodificada em níveis de prestação de cuidados paliativos (Tabela 3).

Análise de consistência interna

Foi obtido um valor do alfa de Cronbach de 0,809. Todos os itens tinham um valor positivo de correlação item-total (Tabela 4), sugerindo que o questionário é uma ferramenta unidimensional. Os testes adicionais indicaram que os itens 2.2. e 3.2. contribuíram para que o valor do alfa não seja mais elevado, e apenas o item 2.2. apresentou uma correlação baixa, embora positiva (Tabela 4).

Análise fatorial confirmatória

Numa primeira análise, verificou-se que todas as saturações das variáveis (itens) medidas nas respetivas dimensões eram estatisticamente significativas ($p < 0,05$) com valor superior ou próximo de 0,5, com exceção do item 2.2. No entanto, a média das saturações fatoriais foi 0,565 (acima do limiar estabelecido). A fiabilidade composta foi 0,995 (bastante acima do limiar), e apenas o valor da proporção da variância extraída se registou um pouco abaixo do pretendido, com um valor de 0,369.

Em relação aos índices de ajustamento, o χ^2/g.l. indicou um bom ajustamento global com um valor de 2,482. Os restantes índices, embora não se encontrassem no intervalo pretendido, estavam próximos do limiar desejável, sendo que o RMSEA tinha um valor de 0,175, o NFI de 0,588 e o

Tabela 1 – Análise descritiva da amostra (n = 51)

Idade, média (DP); mediana [mín, máx]	11,2 (5,1); 10 [1,0, 18,0]
Sexo, n (%)	
Masculino	24 (47,1)
Feminino	27 (52,9)
Idade de diagnóstico (anos)[a], n (%)	
0 – 1 anos	26 (52,0)
1 – 5 anos	17 (34,0)
6 – 10 anos	6 (12,0)
11 – 15 anos	1 (2,0)
Grupo de diagnóstico de patologia de base, n (%)	
Neurologia	19 (37,3)
Metabólicas	10 (19,6)
Genética	7 (13,7)
Pneumologia	6 (11,8)
Hematologia	4 (7,8)
Nefrologia	3 (5,9)
Gastroenterologia	1 (2,0)
Oncologia	1 (2,0)
Grupo de necessidades paliativas	
Grupo I - Doenças potencialmente fatais, mas curáveis	10 (19,6)
Grupo II - Doenças que causam morte prematura, mas podem ter sobrevivências longas se tratadas	15 (29,4)
Grupo III - Doenças progressivas, mas sem cura possível	10 (19,6)
Grupo IV - Doenças irreversíveis não progressivas, que aumentam a morbilidade e probabilidade de morte prematura	16 (31,4)

[a]: um valor omisso

CFI de 0,673.

DISCUSSÃO

Este estudo tem como objetivo descrever a tradução, adaptação cultural e validação da versão portuguesa europeia da *Pediatric Palliative Screening Scale*. Este é um instrumento dirigido a profissionais de saúde que prestam cuidados a crianças/jovens com DCC e avalia as necessidades paliativas. Na literatura existem poucos estudos sobre a aplicação da escala PaPaS.[10,14,48-50] Esta é mais utilizada em países de língua de expressão inglesa com nível de prestação de CPP mais evoluído.

Este trabalho foi desenvolvido num hospital que presta cuidados especializados a crianças/jovens com DCC. O número de profissionais envolvidos foi inferior ao número de testes aplicados porque a atividade assistencial está referenciada, concentrada e limitada a profissionais específicos.

A amostra de crianças/jovens com DCC foi de pequena dimensão e revelou diversidade etária, o que é demonstrativo das características típicas da população de crianças/jovens com necessidades paliativas e que apresentam trajetórias longas e prognósticos incertos.[4,5]

Os grupos de patologias identificados foram em 70,6% da área da Neurologia, Metabólicas e Genética, o que reflete o peso importante e o impacto destas doenças crónicas nesta amostra e nos CPP em geral, concordantes com os grupos de diagnósticos mais frequentes descritos na literatura.[13,48] Esta heterogeneidade de patologias é ainda importante para os objetivos propostos, embora não tenham sido incluídas crianças com doença oncológica, responsável por cerca de 20% a 30% de doentes pediátricos com necessidades paliativas.[14] O seguimento da doença neoplásica pediátrica em Portugal está centrado em hospitais específicos com serviço de oncologia pediátrica. Contudo, isso não invalida este trabalho, pois a escala foi criada para a DCC global. A autora da escala não considerou este fator um impedimento para a progressão desta investigação.

Em metade dos casos, a idade mais frequente de diagnóstico foi o primeiro ano de vida. Este facto demonstra que grande parte das patologias identificadas são de origem congénita, com manifestações clínicas neste período

Tabela 2 – Análise descritiva das respostas aos domínios da escala PaPaS (n = 51)

Domínio 1. Trajetória da doença e impacto nas atividades da vida diária da criança/jovem	
1.1. Trajetória da doença e influência nas atividades diárias da criança/jovem (comparação com a faixa etária da criança/jovem referente às últimas 4 semanas), n (%)	
Estável	15 (29,4)
Deterioração lenta sem impacto nas atividades diárias	8 (15,7)
Instável e com impacto nas atividades diárias e restrição	14 (27,5)
Deterioração significativa com restrição grave das atividades	14 (27,5)
1.2. Aumento do nº de internamentos hospitalares (> 50% em 3 meses, comparado com períodos anteriores), n (%)	
Não	40 (78,4)
Sim	11 (21,6)
Domínio 2. Resultado esperado do tratamento da doença e efeitos secundários associados	
2.1. Tratamento direcionado para a doença (não diz respeito ao tratamento de complicações relacionadas com a doença, como ex.: dor, dispneia ou fadiga), n (%)	
É curativo	3 (5,9)
Controla a doença e prolonga a vida com boa QDV	13 (25,5)
Não cura nem controla doença, mas efeito positivo na QDV	24 (47,1)
Não controla a doença e não tem efeito na QDV	11 (21,6)
2.2. Efeitos secundários do tratamento (incluindo impacto na família e no doente, por ex.: internamentos na perspetiva do doente ou família), n (%)	
Nenhum ou ligeiros	12 (23,5)
Ligeiros	15 (29,4)
Moderados	19 (37,3)
Graves	5 (9,8)
Domínio 3. Sinais/sintomas e problemas	
3.1. Intensidade de sinais/sintomas e/ou dificuldade no controlo destes (nas últimas 4 semanas), n (%)	
Assintomático	3 (5,9)
Sinais (s)/Sintoma(s) é(são) ligeiro(s) e fácil(eis) de controlar	9 (17,6)
Qualquer sinal/sintoma é moderado e controlável	17 (33,3)
Qualquer sinal/sintoma é grave ou difícil de controlar	22 (43,1)
3.2. Intensidade de sinais/sintomas e/ou dificuldade no controlo destes (nas últimas 4 semanas), n (%)	
Ausente	20 (39,2)
Ligeiro	17 (33,3)
Moderado	8 (15,7)
Significativo (grave)	6 (11,8)
3.3. Distúrbios psicológicos (stress) dos pais ou família relacionados com os sinais/sintomas e sofrimento da criança	
Ausente	2 (3,9)
Ligeiro	11 (21,6)
Moderado	16 (31,4)
Significativo (grave)	22 (43,1)
Domínio 4. Preferências/necessidades do doente ou pais Preferências do profissional de saúde	
4.1. O doente/Os pais deseja(m) receber cuidados paliativos ou expressa(m) necessidades similares aos cuidados paliativos, n (%)	
Não	14 (27,5)
Sim	37 (72,5)
4.2. O profissional ou a sua equipa sente(m) que este doente beneficiaria de cuidados paliativos, n (%)[a]	
Não	4 (28,6)
Sim	10 (71,4)
Domínio 5. Esperança de vida	
5.1. Estimativa da esperança de vida, n (%)	
Vários anos	35 (68,6)
Entre meses a 1 - 2 anos	12 (23,5)
Entre semanas a meses	2 (3,9)
Entre dias e semanas	2 (3,9)
5.2. "Ficaria surpreendido se esta criança morresse repentinamente no prazo de seis meses?", n (%)	
Sim	24 (47,1)
Não	27 (52,9)

[a]: n = 14. QDV: qualidade de vida

Tabela 3 – Resultados e distribuição por nível de cuidados (n = 51)

Escala PaPaS, média (DP) - mediana [mín, máx]	17,5 (7,4) - 16 [6,0, 37,0]
Nível de cuidados, n (%)	
Avaliação (≤ 10)	8 (15,7)
Explicar objetivos dos cuidados paliativos (> 10 e ≤ 15)	13 (25,5)
Preparar início de cuidados paliativos (> 15 e ≤ 25)	20 (39,2)
Iniciar cuidados paliativos (> 25)	10 (19,2)

associadas a sintomas complexos de difícil gestão e que obrigam a uma abordagem diagnóstica precisa.

Em relação às categorias de patologias com necessidades paliativas, a distribuição também foi heterogénea, sendo as categorias II (29,4%) e IV (31,4%) as mais frequentes. Estas categorias de patologias com necessidades paliativas são aquelas que atingem maior tempo de sobrevivência e maior prevalência: no grupo II a morte pode acontecer entre a segunda e terceira década de vida e no grupo IV a morte surge habitualmente na segunda década de vida. No grupo I e III, a mortalidade é mais precoce,[4,13,48] pelo que a prevalência foi menor, como descrito na literatura.

A análise estatística descritiva das respostas aos itens da escala PaPaS identificou a ausência da necessidade significativa de internamentos nos últimos três meses. Em cerca de dois terços dos casos a terapêutica instituída não curou nem controlou a doença. A influência dos efeitos secundários do tratamento na criança/jovem e na família foi maioritariamente ligeira a moderada, o que representa um provável viés na apreciação do profissional de saúde e desvalorização do impacto das intervenções terapêuticas. O controlo sintomático foi insuficiente em 43,1% dos casos. O impacto psicológico para as crianças/jovens foi baixo, uma vez que a maior parte dos doentes apresentavam doenças neurometabólicas que cursam com défice cognitivo e dificuldade de perceção dos efeitos psicológicos. A repercussão psicológica sobre os pais foi muito significativa e causadora de grande sofrimento. Noventa e dois por cento das respostas revelaram o benefício da integração destas crianças na tipologia dos CPP. Quanto à esperança de vida, em cerca de dois terços das respostas era esperado uma sobrevivência de vários anos. Mas a possibilidade de morte inesperada baseada na 'pergunta surpresa' ("Ficaria surpreendido se esta criança morresse repentinamente no prazo de 6 meses?") foi percetível em metade da amostra. Este facto demonstra e reforça que estas crianças com DCC têm longas sobrevivências e que a referenciação e integração na tipologia dos CPP deve ser precoce e atempada.

Tabela 4 – Correlação item-total e efeito da eliminação de cada item: escala PaPaS

Questão	Correlação item-total corrigida	Alfa de Cronbach sem o item
1.1.	0,723	0,763
1.2.	0,458	0,795
2.1.	0,389	0,801
2.2.	0,063	0,828
3.1.	0,797	0,758
3.2.	0,292	0,811
3.3.	0,500	0,791
4.1.	0,414	0,806
4.2.	0,351	0,804
5.1.	0,648	0,782
5.2.	0,677	0,779

A pontuação total da escala PaPaS permitiu classificar e estruturar o nível de cuidados a implementar em cada criança com DCC. Nesta população, 84,4% dos doentes tinham indicação para serem referenciados a uma equipa de CPP, e cerca de 60% necessitavam de um acompanhamento estruturado e integrado por uma equipa diferenciada em CPP. Estes resultados reforçam a necessidade urgente da criação de equipas de cuidados paliativos pediátricos em todos os serviços pediátricos portugueses.

A escala PaPaS é uma escala ordinal constituída por 11 itens organizados em cinco domínios. Na análise de consistência interna obteve-se um valor do alfa de Cronbach de 0,809 (superior ao limiar determinado), e todos os itens obtiveram valores positivos de correlação item-total, pelo que podemos considerar o questionário como adequado e unidimensional (as 11 variáveis mediram de forma aceitável uma única dimensão: a escala PaPaS). Os testes adicionais sugerem que a remoção do item 2.2. pode levar a uma maior consistência interna, sendo que apresenta uma correlação item-total baixa. Este item tenta capturar os 'efeitos secundários do tratamento'. A sua eliminação poderia tornar o questionário mais consistente no contexto português. No entanto, outros critérios têm de ser considerados, tais como a relevância do item e a consistência da escala com a versão original. Além disso, a eliminação do item 2.2. resultaria na perda da sua informação, o que não é compensado por nenhum outro item.

Na análise fatorial confirmatória foram também obtidos os valores dos índices de saturação fatorial, fiabilidade

composta e proporção da variância extraída que são compatíveis com uma escala de medida de validade convergente. Relativamente aos índices de ajustamento, o χ^2/g.l. indica claramente um bom ajustamento global e, ainda que os restantes índices não se encontrem no intervalo pretendido, os resultados obtidos permitem ter confiança na qualidade de ajustamento.

O conjunto dos resultados obtidos permitiu concluir que, globalmente, os itens são significativos, consistentes, apresentam validade convergente, e que o modelo tem um bom ajustamento global.

Limitação

Como principal limitação desta avaliação realçamos a falta de validação do item "2.2. Efeitos secundários do tratamento (incluindo impacto na família e no doente, por ex.: internamentos na perspetiva do doente ou família)" desta escala. Após contato com os profissionais responsáveis pelo preenchimento do questionário conclui-se que este item pode não estar suficientemente claro e explícito, tendo suscitado dúvidas na sua resposta. Shong[14] propõe uma modificação desta questão para: "Sobrecarga direta da própria doença e do tratamento (frequência e capacitação, exemplo: efeitos secundários, internamentos e consequências para o doente)". Outros possíveis fatores para a não validação deste item são a reduzida dimensão unicêntrica da amostra, escassa formação e perceção dos profissionais em CPP, e discrepância das necessidades paliativas na ótica do profissional *versus* avaliação de necessidades junto das crianças/jovens e suas famílias.

Os autores já reformularam o item após avaliação e consenso de vários especialistas e propõem-se realizar um estudo multicêntrico nacional. O objetivo desse estudo será caracterizar as necessidades paliativas da população pediátrica portuguesa e utilizar a escala na avaliação da continuidade de cuidados nas crianças já referenciadas a equipas de CPP.[14,49] A aplicação desta escala também poderá ter relevância noutros contextos clínicos, nomeadamente ao nível dos cuidados de saúde primários.[50]

CONCLUSÃO

A escala PaPaS foi traduzida e adaptada para a versão portuguesa europeia. O conjunto dos resultados obtidos na versão portuguesa desta escala permitem considerar, após análise de consistência interna, que é adequada aos dados analisados. Os valores de correlação item-total indicam que as 11 variáveis mediram com boa fiabilidade e de forma unidimensional a escala PaPaS. O conjunto dos resultados obtidos desta versão portuguesa permitem concluir que os itens são globalmente significativos, consistentes, apresentam validade convergente, e que o modelo tem um bom ajustamento global. Em suma, este trabalho legitima a utilização da escala PaPaS no contexto português.

Este trabalho é pioneiro na avaliação de necessidades de CPP em Portugal e a sua divulgação contribuirá para que as crianças/jovens portugueses com DCC e necessidades paliativas possam ser referenciados de forma mais precoce aos CPP.

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Aos membros da equipa de investigação: Inês Viegas, João Sollari Lopes e Paulo Pereira.

PRÉMIOS E APRESENTAÇÕES PRÉVIAS

Este trabalho foi apresentado em prova pública conducente ao grau de Mestre em Cuidados Paliativos pela Faculdade de Medicina de Lisboa no dia 27 de janeiro de 2021.

CONTRIBUTO DOS AUTORES

MJP: Contribuição relevante na conceção e desenho do trabalho. Aquisição, análise e interpretação de dados e elaboração do manuscrito. Aprovação da versão final a ser publicada. Responsável por todas as questões relacionadas com a precisão e integridade de qualquer parte do trabalho.

FT, MCM: Contribuição relevante na conceção e desenho do trabalho. Revisão crítica do conteúdo e aprovação da versão final a ser publicada. Responsável por todas as questões relacionadas com a precisão e integridade de qualquer parte do trabalho.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Parental Consanguinity and Risk for Childhood Hearing Loss: A Retrospective Cohort Study

Consanguinidade Parental e Risco de Surdez Infantil: Estudo de Coorte Retrospetivo

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ABSTRACT

Introduction: Genetic causes are responsible for half of the cases of hearing loss, most of them being the result of non-syndromic genetic changes resulting from autosomal recessive inheritance. Parental consanguinity might be an indicator to consider in the diagnosis of these cases. The aim of this study was to assess its importance as a risk factor for childhood hearing loss.

Material and Methods: A retrospective cohort study conducted in a district hospital, between 2014 and 2018. We included all live births born during this period and excluded those with risk factors for childhood hearing loss other than parental consanguinity and those without hearing screening. We formed two study groups: newborns with parental consanguinity and newborns without risk factors. All the participants underwent hearing screening with the primary outcome of this study being the result of the screening. Those with a not normal result or with parental consanguinity also underwent diagnostic audiological evaluation.

Results: Among 8513 live births, we studied 96 newborns with first-degree parental consanguinity and 96 newborns without risk factors. We found a statistically significant difference (p = 0.007) between the groups, with a 'refer' screening result rate of 24% in the group with parental consanguinity and 9.4% in the group without risk factors. We diagnosed one case of sensorineural hearing loss and another of mixed hearing loss in the first group and none of these cases in the second.

Conclusion: Parental consanguinity was associated with a higher risk of a refer screening result in newborns, which suggests the need to consider this as a risk factor for childhood hearing loss.

Keywords: Consanguinity; Deafness/congenital; Hearing Loss/etiology; Hearing Loss, Sensorineural/etiology; Infant, Newborn; Neonatal Screening; Parents

RESUMO

Introdução: A etiologia genética é responsável por metade dos casos de surdez, a maioria fruto de alterações genéticas não-sindrómicas decorrentes de herança autossómica recessiva. A consanguinidade parental constitui um possível indicador a considerar para o diagnóstico destes casos, pelo que este estudo pretende avaliá-la como fator de risco para a surdez infantil.

Material e Métodos: Estudo de coorte retrospetivo realizado de 2014 a 2018 num hospital distrital. Incluímos todos os nados-vivos nascidos neste período, sendo excluídos aqueles com outros fatores de risco para surdez infantil (que não a consanguinidade parental) e aqueles sem rastreio auditivo. Formámos dois grupos de estudo: recém-nascidos com consanguinidade parental e recém-nascidos sem fatores de risco. Todos os participantes realizaram rastreio auditivo, sendo o seu resultado o *outcome* primário do estudo. Aqueles com resultado anormal ou com consanguinidade parental efetuaram ainda avaliação audiológica diagnóstica.

Resultados: Entre os 8513 nados-vivos, estudámos 96 recém-nascidos com consanguinidade parental em primeiro grau e 96 recém-nascidos sem fatores de risco. Verificámos uma diferença estatisticamente significativa (p = 0,007) entre os grupos relativamente aos resultados do rastreio auditivo, tendo-se detetado uma taxa de *refer* de 24% no grupo com consanguinidade parental e de 9,4% naquele sem fatores de risco. Diagnosticámos um caso de surdez sensorioneural e outro de surdez mista no primeiro grupo e zero destes casos no segundo.

Conclusão: A consanguinidade parental associou-se a um risco significativamente superior de resultado *refer* no rastreio auditivo de recém-nascidos com consanguinidade parental e sugere a necessidade de considerar este critério como um fator de risco para surdez infantil.

Palavras-chave: Consanguinidade; Pais; Perda Auditiva/etiologia; Perda Auditiva Neurossensoria/etiologia; Rastreio Neonatal; Recém-Nascido; Surdez/congénita

INTRODUCTION

Hearing plays a crucial role in an individual's ability to communicate and interact socially. As a consequence, hearing loss can have a decisive impact on quality of life.[1-3] It is currently recognised that around 50%[1] of all cases of hearing loss have a genetic cause. Moreover, this percentage increases to 70% if we consider only the congenital cases and may become even higher due to the decreased prevalence of infectious diseases as a result of vaccination.[1]

Genetic hearing loss may present early in life or have a late onset and may be syndromic (30%) or non-syndromic (70%).[1,2] Of the non-syndromic cases, 80% are the result of autosomal recessive inheritance and in these situations, there is no parental history of the disease.[1,3] Because

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consanguineous parents are more likely to be homozygous for the same trait, parental consanguinity is an important clue to the possibility of recessive inheritance of a condition.[3] Several studies have reported a higher incidence of autosomal recessive diseases in consanguineous families, and there is also data suggesting that profound hearing loss is more prevalent in countries where consanguineous marriages are common.[1-5] These types of marriages are common practice in many Asian, African and South American communities. In Portugal, the Romani communities also present important consanguineous relationships.[2,6] Consanguinity can be defined by marriages between second or closer cousins.[2] Its effect depends on the degree of kinship between the parents: first cousins have a higher risk of disease than second cousins and more distant kinship relationships have a risk of genetic defects close to that of the general population.[4]

Hearing loss affects one to three per 1000 newborn babies (NB) with no known risk factors and 20 to 40 per 1000 NB with risk factors.[7] Currently, the risk factors specified in Portugal's *Rastreio Auditivo Neonatal Universal* (RANU - the Infant Hearing Loss Screening and Intervention Group) and international guidelines (the Joint Committee on Infant Hearing) that may be suggestive of genetic inheritance are family history of hearing loss in childhood, the presence of craniofacial anomalies or genetic syndromes associated with hearing loss.[7,8] It is therefore inferred that children with no family history of hearing loss or syndromic stigma are classified as not being at risk when they may, in fact, have an increased susceptibility for hearing loss if their parents are consanguineous. As such, given the current absence of genetic screening tests, it becomes important to identify other conditions (in addition to those currently recognised) that may effectively be risk factors for a genetic cause.

Following the empirical notion that a significant number of diagnosed cases of hearing loss were associated with a history of parental consanguinity, the coordinating team of RANU at Centro Hospitalar do Baixo Vouga (CHBV), a level II public hospital in Aveiro, Portugal, started to include first-degree parental consanguinity as a risk factor for hearing loss since 2013. In addition, we also conducted a parallel study between 2014 and 2018 regarding the RANU results at the CHBV that suggested first-degree parental consanguinity was the most frequently observed risk factor in children diagnosed with sensorineural hearing loss.

As we are unaware of the existence of national studies in this context, the aim of this study was to assess whether the history of first-degree parental consanguinity was associated with a higher risk of hearing loss in the population of the Aveiro region in Portugal.

MATERIAL AND METHODS

We conducted a retrospective cohort study at the CHBV, the main public hospital in the Aveiro region, in Portugal, between 2014 and 2018. We included all live births born in this hospital between the 1st January 2014 and the 31st December 2018. To avoid biasing the results, we excluded all those who presented risk factors[9] for hearing loss (Table 1) other than first-degree parental consanguinity as well as those who did not undergo any hearing screening test.

For the purposes of this study, and taking into account our clinical experience, we defined exposure as the existence of a history of first-degree parental consanguinity, i.e., parents in a relationship with first cousins or closer. We consecutively selected all NB with this condition in order to establish the group of exposed NBs. For each NB included in this group a NB with no known risk factors was randomly selected to establish the non-exposed group. Information regarding the existence or not of first-degree parental consanguinity and the remaining risk factors was obtained through the systematic survey of all mothers, carried out by the paediatrician responsible for each NB.

All NBs underwent neonatal hearing screening. The result of each screening test was defined as 'pass' (no changes in both ears) or 'refer' (with changes in one or both ears). The screening method used was evoked acoustic

Table 1 – Risk factors for hearing loss incorporated in the exclusion criteria

Risk factors for hearing loss
Family history of hearing loss in childhood
Prematurity ≤ 32 weeks gestation
Birth weight < 1500 g
Apgar score of 0 – 4 at the first minute or 0 – 6 at the fifth minute of life
Craniofacial malformations or stigma associated with hearing loss
Congenital infection (toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis)
Neonatal sepsis/meningitis and/or taking ototoxic medicines for five or more days
Hyperbilirubinemia (serum levels indicating the need for exsanguineous transfusion)
Intracranial haemorrhage
Hospitalisation for more than 48 hours and mechanical ventilation in Intensive Care Unit

otoemissions using a Natus® MADSEN AccuScreen device. NBs with a first 'refer' screening result were sent to a second screening evaluation using the same technique and device. All children that repeated screening were, as recommended, tested in both ears. Apart from the screening test and regardless of the results, NBs belonging to the exposed group were referred for diagnostic audiological assessment. This evaluation included a RANU consultation which comprised both an otorhinolaryngological medical assessment and a diagnostic test using the auditory brainstem potentials method (performed with an Interacoustics Eclipse EP25 device from Interacoustics®). Furthermore, NBs in the non-exposed group (without risk factors) were only referred for this assessment in case of a 'refer' in two screening tests. All screening and diagnostic tests were carried out by one of two audiologists with experience of pediatrics, in a dedicated room and in spontaneous sleep. All devices were calibrated annually by the representative companies.

We defined as primary outcome the result of the first screening test of each NB and as secondary outcomes the results of the second screening and the diagnostic tests. In order to detect a relative risk (RR) of three for a 'refer' screening result, assuming a frequency of 10% in the non-exposed population, with a confidence interval of 95% and a test power of 80%, we calculated that we would need a sample size of 59 participants in each group. This calculation was performed using the EpiTool online for sample size calculation for descriptive and analytical studies.

Data were collected through consultation and retrospective review of the electronic medical records in the database of the *Plataforma Online de Rastreio Auditivo Neonatal Universal* (Universal Newborn Auditory Screening Online Platform) created at the CHBV, which includes clinical information and data from all hearing assessments (screening and diagnostic) of all NBs born in this hospital. This platform was authorized by the *Comissão Nacional de Proteção de Dados* (National Data Protection Commission) and won a *Boas Práticas em Saúde* (Best Practices in Health) award. The study protocol received clearance from the Ethics Committee and the Data Protection Officer of the CHBV with the reference number 26-01-2022/CES. Collected data included demographic and clinical data such as gender, gestational age, type of delivery, birth weight, risk factors, audiological screening results, diagnostic audiological evaluation results and the age of the NB on the date of each evaluation. Each participant was monitored from birth to the date of the last screening assessment or, whenever necessary, diagnostic assessment in a RANU consultation. Considering the period of the study, NBs were followed for a maximum of five years for the development of hearing loss.

In the descriptive analysis we used the mean and standard deviation (SD) to characterise normally distributed quantitative variables and the median and the interquartile range (IQR) to describe quantitative variables without normal distribution. To assess the normality of distributions we resorted to the analysis of Kolmogorov-Smirnov test. Qualitative variables were expressed as absolute number and percentage. For the inferential analysis of continuous variables, we used the *t* test for independent samples or the Mann-Whitney U test, as applicable. For the analysis of categorical variables, we used the chi-square test. We defined as statistically significant a *p* value less than 0.05 for all tests performed. The data analysed was entered into Microsoft Excel® and statistical analysis was performed using IBM® SPSS® Statistics, version 27.0, for Mac®.

RESULTS

During the study period, we found 115 cases of first-degree parental consanguinity, among 8513 live births, which translates into a prevalence rate of 1.4% during the five-year period under analysis. Nineteen NBs were excluded from the study: 14 due to a family history of hearing loss; one due to an Apgar score of six at the fifth minute of life associated with craniofacial malformation; two due to the administration of ototoxic medicines for more than five days; one due to intracranial haemorrhage; and one due to the absence of screening tests. Therefore, we included a total 192 children: 96 NBs with first degree parental consanguinity, constituting the exposed group, and 96 NBs with no risk factors, constituting the non-exposed group. The results of the assessment of each group are summarised in Table 2. The birth weight variable had a normal distribution ($p = 0.200$). The gestational age, age at the date of the first screening and the age at the date of the second screening did not follow a normal distribution ($p < 0.001$).

In the group of NBs without risk factors there was a predominance of male children (57.3%) while in the exposed group there was a majority of female children (51%). The mean birth weight was 3163.9 g (SD 425.2) in the non-exposed group and 3139.2 g (SD 493.0) in the exposed group. The median gestational age was 39 weeks (IQR 38 – 40) in those without risk factors and 38 weeks (IQR 37 – 39) in the group with parental consanguinity. In both groups, there was a predominance of eutocic deliveries (63.5% in the non-exposed group and 50% in the exposed group) and vaginal delivery using forceps was more frequent (11.7%) than delivery using suction (7.4%) in the exposed group.

In the group of NBs without risk factors there was a 'refer' rate of 9.4% in the first screening while in the exposed group this percentage was 24%. In the non-exposed group, there was a predominance of right ear 'refer' results (3.1% in the left ear *vs* 7.3% in the right ear) while in the exposed group this percentage was overlapping (18.8% in the left

Table 2 – Demographic and clinical characteristics of the study groups (n = 192)

	Non-exposed Group (no risk factors)	n	Exposed Group (first-degree parental consanguinity)	n	*p*-value
Gender		96		96	0.247[a]
Female	42.7%	41	51.0%	49	
Male	57.3%	55	49.0%	47	
GA (weeks)	39 (IQR, 38 – 40)	94	38 (IQR, 37 – 39)	94	0.107[c]
Type of birth		96		94	0.017[a]
Eutocic	63.5%	61	50.0%	47	
Caesarean section	14.6%	14	30.9%	29	
Forceps	7.3%	7	11.7%	11	
Suction cup	14.6%	14	7.4%	7	
Weight (grams)	3163.9 (BW, 425.2)	94	3139.2 (BW, 493.0)	94	0.712[b]
First screening		96		96	0.007[a]
'Pass'	90.6%	87	76.0%	73	
'Refer'	9.4%	9	24.0%	23	
First screening LE		96		96	< 0.001[a]
'Pass'	96.9%	93	81.3%	78	
'Refer'	3.1%	3	18.8%	18	
First screening RE		96		96	0.029[a]
'Pass'	92.7%	89	82.3%	79	
'Refer'	7.3%	7	17.7%	17	
Age at first screening (days)	2 (IQR, 2 – 3)	96	2 (IQR, 2 – 4)	96	0.322[c]
Second screening		9		22	[d]
'Pass'	88.9%	8	81.8%	18	
'Refer'	11.1%	1	18.2%	4	
Age at second screening (days)	19 (IQR, 16 – 33)	8	33 (IQR, 24 – 54)	22	[d]
Diagnostic assessment		1		36	[d]
Normal	0%	0	58.3%	21	
Conductive HL	100%	1	36.1%	13	
Sensorineural HL	0%	0	2.8%	1	
Mixed HL	0%	0	2.8%	1	

SD: standard deviation; IQR: interquartile range; LE: left ear; RE: right ear; **a**: chi-square test; **b**: *t*-test for independent samples; **c**: Mann-Whitney U test; **d**: variables with an insufficient number of cases for a reliable inferential analysis to be carried out; HL: hearing loss

ear *vs* 17.7% in the right ear). In both groups the median age at first screening was two days. Of the 'refer' NBs in the first screening, all those belonging to the group without risk factors underwent a second screening in which a 'refer' result rate of 11.1% was found. In the group of NBs with first degree parental consanguinity there was one NB who missed this assessment and a 'refer' rate of 18.2% was found. The median age at the date of the second screening was 19 days for the group of non-exposed and 33 days for the group of exposed NBs.

The diagnostic assessment in the group of NBs without risk factors was only carried out in the one child who presented 'refer' in two screening tests and in whom conductive hearing loss was detected. In the group of NBs with first degree parental consanguinity, there was a 62.5% rate of absenteeism in the diagnostic assessment and this analysis was only carried out in 36 children. Most of these children presented normal results (58.3%), with one case of sensorineural hearing loss and one case of mixed hearing loss.

There were no statistically significant differences regarding gender, birth weight, gestational age or age at the date of the first screening. On the contrary, regarding the type of delivery, the difference between the groups was statistically significant (p = 0.017). A statistically significant difference was also found in the results of the first screening, both when considering the overall screening result (p = 0.007)

and when analysing the result separately for each ear ($p < 0.001$ for the left ear; $p = 0.029$ for the right ear). As for the results of the second screening, the age of each child at the time of the screening and the diagnostic assessment, it was not possible to carry out an inferential analysis, as we did not have a minimum sample size to allow for reliable statistical tests.

As for measures of association and impact, we calculated a relative risk of 2.6 (95% CI, 1.2 – 5.2) for a 'refer' result at first screening in the group of NB with first-degree parental consanguinity, an attributable risk of 61% and a number required to cause harm of 9.

DISCUSSION

This study found that having first degree parental consanguinity was associated with a three times higher risk of having a 'refer' hearing screening result compared to children without risk factors. When we analysed the proportion of screenings attributable to consanguinity, we found that first degree parental consanguinity accounted for 61% of the risk of a 'refer' result, meaning that if this factor did not exist, this risk would decrease by 61%. We also determined that, for every nine NBs with first degree parental consanguinity, there was an additional case of a 'refer' result in the screening. No other studies were found with a similar design analysing the results of screening between consanguineous children and those without risk factors.

While hearing screening does not guarantee the diagnosis of hearing loss and, therefore, does not establish a direct relationship between its result and diagnosis, we estimate that a higher number of 'refer' screening results corresponded to a higher risk of hearing loss. The fact that the CHBV is a district hospital and, as such, serves a small population, limits the number of diagnosed cases of hearing loss. This reality made it impossible for us to carry out a cohort study with the results of a diagnostic audiological assessment instead of screening results as the outcome. A national multi-centre study could have overcome this limitation. Still, several reports in the literature suggest that first-degree parental consanguinity is associated with a higher risk of sensorineural hearing loss. Almazroua *et al* found a 3.5 times higher risk of sensorioneural hearing loss in consanguineous marriages than that non-consanguineous.[3] Some authors investigated the cause of this association and Kavitha *et al* performed a prospective MRI study that suggested that genetic defects resulted in a cochlea with normal morphology but abnormal function.[10] A study carried out in Qatar, a country with one of the highest rates of consanguinity in the world, showed a strong correlation between parental consanguinity and hearing loss.[4] In a study from Pakistan, a country with a high rate of consanguinity, there was a positive association between consanguinity and profound sensorineural hearing loss.[2] A study in Oman, a Middle Eastern country, showed an association between the incidence of severe hearing loss and consanguineous marriages.[11] These reports appear not only in Middle Eastern countries but also in European countries. Although consanguineous marriages are not culturally frequent in the West, globalisation and migration give rise to small communities in which consanguinity is a frequent practice.[11,12]

In this context, a study has shown that the prevalence of hearing loss in British children of Bangladeshi origin is at least 2.3 times higher than the British average, with consanguinity contributing towards the increase in prevalence along with other environmental factors.[12] The results presented in different studies are so relevant that a Belgian guideline developed by consensus of several experts suggests not only screening but also diagnostic audiological assessment during the neonatal period for this group of children.[13] In Portugal, parental consanguinity is still an existing practice, in particular within the Romani community.[6]

In our study, first-degree parental consanguinity showed a prevalence rate of 1.4% in the studied population. In another study carried out in parallel at the CHBV, first-degree parental consanguinity was the third most common risk factor among children with risk factors for hearing loss, the second most frequent risk factor in children referred at the first hearing screening and the one most that was found more often in the group of children diagnosed with sensorineural and mixed hearing loss (two had parental consanguinity, two had family history and two had both). We thus perceive that although it is not a common practice in Portugal, parental consanguinity has a significant impact on the population of the Aveiro region.

Our study used a non-random sampling for the establishment of the group of NBs with parental consanguinity. However, what could be seen as a limitation turned out to be an advantage, since the use of a consecutive sample ensured the selection of all cases of consanguinity throughout the study period, which meant a representative sample of the population being studied and contributing to the internal validity of the study. The comparison of consanguineous children with others without risk factors also minimised the risk of bias. Collectively, the performance of screening and diagnostic tests by an experienced paediatric audiologist helped to limit the number of false-positive screening results but we can not rule out the risk of bias because they knew which NBs had risk factors for hearing loss. The homogeneity between the groups in terms of gestational age, birth weight and age at the time of screening reinforces their comparability. As for the statistically significant differences between the groups regarding the type of delivery, some authors suggest that caesarean deliveries are associated with a higher risk of referral for screening due to greater

fluid retention in the ear, although others suggest that these differences are related to the timing of the screening.[15,16] In our study the median age at first screening was the same between the two groups so the differences do not correlate with this fact. As far as variation in screening results and diagnosis according to the use of forceps or suction is concerned, we found no data in the literature to suggest differences in outcomes.

As for the rate of absenteeism regarding diagnostic audiological assessment found in the group of NBs with parental consanguinity, we noticed that it is higher than the already significant absenteeism rate detected in our hospital (62.5% *vs* 44.56%). This fact may be due to a reduced perception by parents of the harmful effects of consanguinity, and the association between parental consanguinity and illiteracy. This knowledge highlights the importance of parental education on this issue.[1,14,17]

CONCLUSION

Children with first degree parental consanguinity had a three times higher risk of having a 'refer' hearing screening result which probably corresponds to a higher risk of hearing loss. Knowing this, we intend to draw attention to the evidence suggesting a significant association between parental consanguinity and the prevalence of childhood hearing loss. Failure to consider this criterion as a risk factor may lead us to include children with increased risk of hearing loss in a non-risk group, limiting not only the type of assessment performed but also the observation of these children. Further national studies are necessary in order to confirm the cost-effectiveness of considering this criterion as a risk factor in Portugal. Regarding the practice at our hospital center, given the data collected, it seems prudent to maintain first-degree parental consanguinity as a risk factor for hearing loss.

AUTHOR CONTRIBUTIONS

BL: Literature research; study design; data collection; statistical analysis; draft of the manuscript.

ACL: Literature research; data collection and interpretation; draft of the manuscript.

DP, LC: Data collection; draft of the manuscript.

MMA, MAB: Study design; critical review.

JV: Data collection and processing.

MLA: Critical review.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

MLA has received consulting fees, payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, support for attending meetings and/or travel from Sanofi, and participated on a Data Safety Monitoring Board or Advisory Board for Sanofi.

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Resurgence of Respiratory Syncytial Virus in Children: An Out-of-Season Epidemic in Portugal

Ressurgimento do Vírus Sincicial Respiratório em Crianças: Atividade Epidémica Fora de Época em Portugal

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ABSTRACT

Introduction: An out-of-season increase in respiratory syncytial virus (RSV) incidence was observed in Portugal from June 2021 onwards, revealing a continuing surge in cases throughout 2021/2022 autumn/winter. We aimed to describe this out-of-season epidemic and define its epidemic period, by analysing RSV incidence from week 40 of 2020 (2020-W40) to week 18 of 2022 (2022-W18).

Material and Methods: Surveillance data on weekly RSV laboratory confirmed cases, in Portugal, was used to monitor RSV incidence using CUSUM test methodology for count data.

Results: In 2021-W23, the CUSUM score identified a significant increase in the risk of RSV. By that time, the percentage of RSV positive tests rose from 1% in 2021-W22 (3/265) to 6% in 2021-W23 (18/298). Despite a sharp decrease in RSV incidence on 2021-W33 and on 2022-W02, the CUSUM score stayed over the limit up to 2022-W07, indicating that the RSV activity remained at an epidemic level. Distinct peaks of RSV cases were observed between 2021-W30 and 2021-W32 (average of 77 RSV cases per week) and between 2021-W39 and 2021-W41 (average of 79 RSV cases per week) with positivity rates around 60%.

Conclusion: An out-of-season RSV epidemic was identified, with a longer epidemic period compared with previous seasons. Possible reasons include relaxation of COVID-19 physical distancing measures and a greater proportion of population susceptible to disease. As several factors may change the pattern of RSV activity, countries should implement year-round surveillance RSV surveillance systems. These findings might have an impact on public health planning regarding future RSV surges, namely, on the palivizumab prophylaxis period for high-risk infants.

Keywords: Child; Palivizumab; Respiratory Syncytial Virus Infections/epidemiology; Respiratory Syncytial Virus Infections/prevention and control; Respiratory Syncytial Virus, Human

RESUMO

Introdução: A partir de junho de 2021, registou-se um aumento na circulação do vírus sincicial respiratório (VSR) em Portugal, continuando a observar-se um elevado número de casos ao longo do outono/inverno de 2021/2022. O objetivo deste estudo foi descrever esta epidemia fora de época e definir a sua duração, analisando a incidência deste vírus desde a semana 40 de 2020 (2020-40) até à semana 18 de 2022 (2022-18).

Material e Métodos: O número semanal de casos de VSR confirmados laboratorialmente em Portugal foi utilizado para monitorização de incidência, utilizando a metodologia de teste CUSUM para contagens.

Resultados: Na semana 2021-23, foi identificado um aumento significativo no risco de VSR, tendo a proporção de testes positivos aumentado de 1% na semana 2021-22 (3/265) para 6% na semana 2021-23 (18/298). Apesar de ter sido observado um decréscimo acentuado na incidência de VSR nas semanas 2021-33 e 2022-02, o *score* do teste de CUSUM permaneceu acima do limiar epidémico até à semana 2022-07. Foram observados picos distintos na incidência de VSR entre as semanas 2021-30 e 2021-32 (média de 77 casos de VSR por semana) e entre as semanas 2021-39 e 2021-41 (média de 79 casos de VSR por semana), com taxas de positividade em torno de 60%.

Conclusão: Foi identificada uma epidemia de VSR fora de época, com um período epidémico superior ao observado noutras épocas de vigilância. Entre as razões possíveis para esta ocorrência inclui-se o relaxamento de medidas implementadas no âmbito do combate à pandemia de COVID-19 e uma maior proporção de população suscetível à doença. Uma vez que vários fatores podem interferir na sazonalidade do VSR, recomenda-se que os países implementem sistemas de vigilância ao longo de todo o ano. Estes resultados poderão ter impacto no planeamento de medidas de saúde pública em futuros surtos de VSR, nomeadamente, no período de administração de palivizumab para prevenção de infeção em crianças de alto risco.

Palavras-chave: Criança; Infecções por Vírus Respiratório Sincicial/epidemiologia; Infecções por Vírus Respiratório Sincicial/ prevenção e controlo; Palivizumab; Vírus Sincicial Respiratório Humano

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INTRODUCTION

Respiratory syncytial virus (RSV) is considered a major pathogen causing severe lower respiratory tract infections, in infants and young children.[1] In 2015, RSV was associated with 33.1 million acute lower respiratory tract infections, 3.2 million hospital admissions, and an overall mortality of 118 200 in children under five years of age worldwide.[1]

With no existing vaccine, prevention methods include passive immunization through the monthly administration of the monoclonal antibody (mAb) palivizumab during the RSV season, in the first year of life in high-risk infants.[2] The IMpact-RSV study, a placebo-controlled trial conducted in the United States, the United Kingdom and Canada, found that palivizumab prophylaxis was associated with a 55% reduction in hospitalization attributable to RSV.[3]

Therefore, for prevention methods to be deployed effectively, an understanding of the seasonality of RSV is required. Previous studies have found that temperate countries in the Northern Hemisphere experience a distinct peak in RSV cases per season, with the start of the RSV season between September and January, in line with colder temperatures.[4–6] In particular, between the 2013-2014 and the 2019-2020 seasons, all RSV epidemics in Portugal that started in December had a median epidemic duration of 10 to 11 weeks, and low or inexistent circulation was registered in summer months.[4,6,7]

However, unlike previous seasons, and similarly to many countries worldwide, an unprecedented low incidence of respiratory viral infections, including RSV, was reported during the 2020-2021 autumn/winter in Portugal.[7] Probable reasons for this low incidence include viral competition and non-pharmaceutical interventions (NPIs) implemented to fight the COVID-19 pandemic, since March 2020.[8–11] As transmission pathways of RSV include aerosols, inhalation of virus-laden liquid droplets, close contact with infected individuals and contact with contaminated surfaces, NPIs affecting daily activities such as stay-at-home mandates, school closures and gathering bans would have a direct impact on reducing infectious social contacts.[12] On the other hand, the high incidence of COVID-19 could induce viral competition between SARS-CoV-2 and RSV through multiple mechanisms, such as antibody-driven cross-immunity and a reduced susceptible pool due to isolation.[13,14] In fact, a change in RSV activity had already been observed during the 2009 pandemic influenza A(H1N1), in France and Hong Kong, thus supporting this hypothesis.[15,16]

From June 2021 onwards, in the setting of relaxed COVID-19 measures in Portugal, an out-of-season increase in RSV incidence was observed, revealing a continuing surge in cases throughout the 2021-2022 autumn/winter. To our knowledge, no study described this epidemic in Portugal, assessed its magnitude, or discussed its implications. RSV surveillance data has the potential to assist informed decision-making in public health by: (1) providing baseline data and a comprehensive assessment of the epidemics; (2) aiding governments in prioritizing healthcare investments and targeting interventions, and considering in particular that RSV protection conferred by monoclonal antibodies or maternal immunization may be short lasting; (3) guiding healthcare services in demand-side planning; (4) aiding the pharmaceutical industry in planning for effective RSV vaccines and new monoclonal antibodies; (5) guiding diagnostic testing and information for parents of vulnerable children.[17–19] Consequently, in this context, we aimed to describe this uncommon RSV epidemic and define its epidemic period by analysing RSV incidence from week 40 of 2020 to week 18 of 2022.

MATERIAL AND METHODS

Setting

The study was implemented in hospitals from the Portuguese Laboratory Network for the Diagnosis of Influenza Infection. The network comprises 20 non-sentinel public hospital-based laboratories, in three mainland regional health administrations (North, Center and Lisbon and Tagus Valley) and the Azores Islands, and is coordinated by the Portuguese Reference Laboratory for Influenza and other Respiratory Virus. Every site reports RSV aggregated data to the Portuguese Reference Laboratory for Influenza and other Respiratory Virus on a weekly basis. The information is collected in a standardized Excel form including the epidemiological week, number of tests performed, number of positive tests and age group. In order to increase data completeness, report timings were adapted according to data availability and to the capacity of paediatricians and laboratories capacity to ensure the reports.

Study population

The study population comprised children aged 0 to 4 years living in the geographically defined catchment area of the non-sentinel hospitals (catchment population). The catchment area of the surveillance hospitals is the area which attracts the individuals who usually seek healthcare at the sites when they get sick.[20] In order to estimate the catchment areas and respective population, we reviewed the hospital discharge registry database that covers all admissions in public hospitals in Portugal, and for each site we prepared a hotspot map based on the residential address of children aged 0 to 4 years who were hospitalized due to severe acute respiratory infections (SARI). This map corresponded to a least of 85% SARI cases in children aged 0 to 4 years hospitalized at each non-sentinel site, in the years between 2018 and 2020. For each selected

municipality within the hotspot map we computed the proportion of SARI in children aged 0 to 4 years admitted by participating hospital, among all SARI admissions in children aged 0 to 4 years registered in the municipality. Finally, to estimate the individual contribution of each selected municipality to the catchment population, we applied previously estimated proportions to most recent resident population estimates for municipalities regarding children aged 0 to 4 years.[21] This resulted in a total catchment population of 187 068 individuals which corresponds to 43% of the resident population aged 0 to 4 years in Portugal. Detailed information on the catchment population for each non-sentinel hospital is provided in the supplementary material [Appendix, Fig. 1 and Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)].

Study period

All data was updated on the 12th May 2022 and data for the period between week 40 of 2020 (2020-W40) and week 18 of 2022 (2022-W18) (28 September 2020 to 8 May 2022) was used as observation period for our analysis.

Testing strategy

According to the standard 19/2020 issued by the Directorate-General of Health (DGS), all children attended in hospitals and presenting acute respiratory infection symptoms (acute onset of at least one of the following four respiratory symptoms: cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection) should be tested for SARS-CoV-2, Influenza and RSV.[22] The study included outpatients and inpatients aged 0 to 4 years tested for RSV. Tests for RSV detection during the analysis period were performed using a multiplex assay, allowing for the simultaneous detection of RSV, influenza and SARS-CoV-2. The most used kit for the detection of RSV was the Allplex™ SARS-CoV-2/FluA/FluB/RSV (ASFR, Seegene Technologies Inc; Seoul, South Korea). According to recent research, the sensitivity of Allplex™ SARS-CoV-2/FluA/FluB/RSV ranges between 92.0% and 98.7%, while the specificity ranges between 99.5% and 100%.[23] Only one laboratory reported using the antigen-based MariPOC® respi test (ArcDia International Ltd; Turku, Finland). The sensitivity and specificity reported by the manufacturer were 88.6% and 100%, respectively.[24] The choice of MariPOC® respiratory test over other rapid detection tests, was made due to the multiplexing feature that allows the simultaneous detection of viruses that have a major impact on healthcare systems.

Outcome measures

The primary outcome of interest was the weekly number of RSV laboratory confirmed cases in paediatric 0-to 4-year-old outpatients and inpatients, in Portugal. Secondary outcomes of interest included the number of RSV tests performed in children aged 0 to 4 years and the distribution per region of RSV laboratory confirmed cases.

Timeline of public health measures

In order to mitigate transmission and severe consequences of SARS-CoV-2 infection, in addition to avoiding the collapse of the healthcare system in Portugal, a coordinated public health response was issued, including NPIs enforced by the government with different stringency levels and duration periods.[25–28] In the second COVID-19 epidemic wave in Portugal (October - December 2020), tiered NPIs based on local epidemic assessment were set. Along with the mandatory use of face masks in outer spaces (mandatory use of masks in inner spaces was already in place since April 2020) and a nationwide curfew between 23.00 pm and 5.00 am, in mainland Portugal, weekend lockdowns were implemented in municipalities classified as extremely high risk (14-day incidence rate of COVID-19 ≥ 240 cases per 100 000 population). In the third epidemic wave (late December 2020 - March 2021), stricter NPIs were issued. Such NPIs included stay-at-home mandates, closure of schools and all non-essential businesses, individual movement restrictions for non-essential activities, international borders closed for non-residents, banning of mass gatherings, visitation restrictions in long-term care facilities and working from home However, the stay-at-home mandates along with the closure of kindergartens and elementary schools were revoked in March 2021, while some NPIs, such as working from home and bans on mass gatherings, were in place until June 2021 (Fig. 1).[28]

Statistical analysis

As we did not have a long series of surveillance historical data (minimum of five years), the method used in this study to specify the epidemic alert thresholds for RSV was chosen taking into account: (1) prospective surveillance methods, based on short-term data[29]; (2) methods tested for respiratory virus surveillance.[30]

The weekly incidence of RSV was monitored using CUSUM test methodology for count data.[31,32] This test computes, for each week n, a score S_n defined by: (1- ascending CUSUM) $S_n = max(0, S_{n-1} + W_n)$ where $S_0 = 0$ and W_n is the log-likelihood ratio sample weight. This weight is a measure of the deviation of the observed count from the target or expected count. For each week, the CUSUM tests the null hypothesis: 'RSV activity is at a baseline level (in control)', against the alternative hypothesis: 'RSV activity is at an epidemic level (out-of-control)' (i.e., $H_0 : \lambda = \lambda_0$ *vs* $H_1 : \lambda > \lambda_0$, where λ_0 is the mean of the process under in control state).

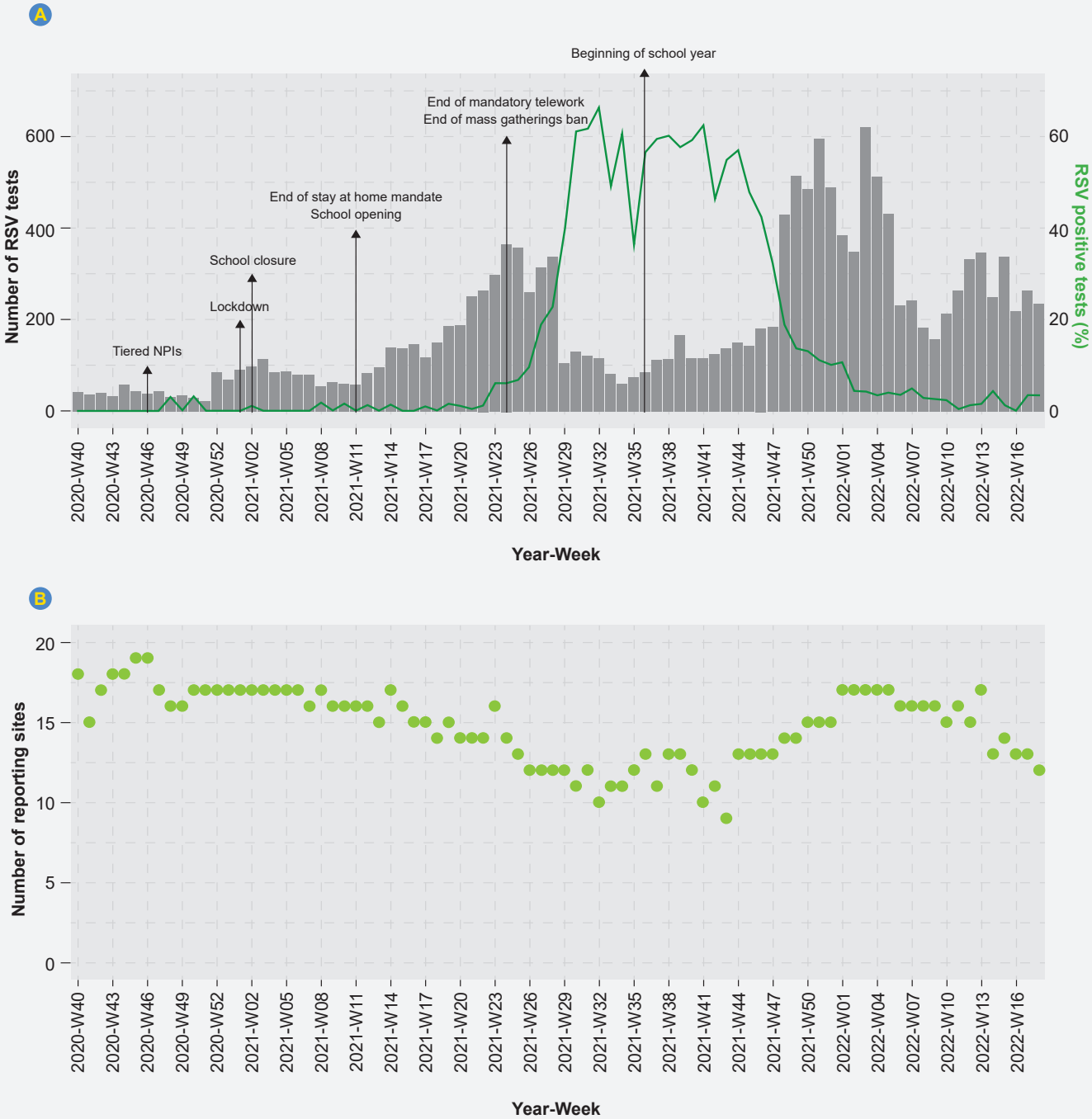

Figure 1 – Weekly number of RSV tests, weekly proportion of RSV positive tests and timeline of NPIs implemented in Portugal (A). Weekly number of reporting non-sentinel sites (B).

The null hypothesis is rejected when the CUSUM score crosses a decision limit h.

The sample weight was computed as: (2) $W_n = X_n - \{(\lambda_1 - \lambda_0) : [(log\ (\lambda_1) - log\ (\lambda_0)]\}$ where X_n is the RSV count for week n, and λ_0 is the mean weekly numbers of RSV cases expected if the incidence is in control and and λ_1 is smallest out-of-control mean of RSV cases we want to detect. We estimated the baseline level of RSV activity, λ_0, as the average of weekly RSV counts recorded when the RSV positivity rates were below 10%. The 10% threshold was set according to Centre for Disease Control (CDC) guidelines.[33] We designed the CUSUM test to detect a four-fold increase

in RSV incidence (relative risk of 4).

Based on these values, we determined the decision limit h that controls type I error rate. The analogous of type I rate for a CUSUM test is the average run length (ARL) under the null hypothesis, i.e., the expected number of weeks until the CUSUM test detects an out-of-control level of RSV given that the incidence is in control. The limit h was set to 2, to ensure an ARL about 400 weeks if the process is in-control. For this purpose, ARL was first approximated using existing tables and then a more precise determination of h was estimated using computer software.[31,34]

Determining the period when a process returns to its in-control state can be difficult if the recorded deviation was significantly high, either from a long out-of-control period or the presence of a particularly large epidemic. These situations cause the CUSUM statistic to rise steeply, and it may take some time after the end of an epidemic for the CUSUM statistic to return to previous levels.[35]

Therefore, if the CUSUM test detected an epidemic level for the RSV activity, the hypotheses were reversed, and we tested for a decrease in the monthly incidence from the out-of-control situation (λ_1) to the in-control situation (λ_0). In this case, the score S_n test was defined by:

(3 – descending CUSUM) $S_n = min(0, S_{n-1} - W_n)$

All analyses were performed using 4.1.2 statistical software.[36] For computing the decision interval (h) for CUSUM test, we used the 'CUSUMdesign' package.[34]

Ethics statement

The aggregated data used within this study were anonymised and collected in the scope of epidemiological surveillance for which submission to an ethics committee was not required.

RESULTS

Between 2020-W40 and 2022-W18, among a population of 187 068 individuals aged 0 to 4 years under surveillance, 15 614 RSV tests were performed, resulting in 1986 laboratory confirmed cases of RSV [Fig.1 and Table 2 of the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)]. Almost 90% of the laboratory confirmed RSV cases were detected in the North (52.0%) and Lisbon and Tagus Valley (36.6%) regions. Only 9.1% and 2.4% of RSV cases were from the Center region and the Azores islands.

Although, the number of RSV tests varied during the analysis period, the number of weekly reporting sites was fairly constant: on average 14 hospitals per week (minimum of nine hospitals on week 43 of 2021 and maximum of 19 hospitals on weeks 46 and 47 of 2021) reported data [Fig.1 and Table 2 of the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)].

CUSUM analysis showed no significant deviation from the expected weekly number of RSV cases between 2020-W40 and 2021-W22 (Fig. 2). In 2021-W23, the CUSUM score crossed the decision limit, i.e., identified a significant increase in the risk of RSV. By that time, the percentage of RSV positive tests rose from 1% in 2021-W22 (3/265) to 6% in 2021-W23 (18/298), coinciding with the end of the mass gatherings ban and mandatory working from home) (Fig. 1).

Despite a sharp decrease in RSV incidence on 2021-W33 (followed by a steep rise in 2021-W36 aligned with the beginning of the school year) and on 2022-W02, the CUSUM score stayed over the limit up to 2022-W07, indicating that the RSV activity remained at an epidemic level. A significant decrease was identified in 2022-W08. From 2022-W08 onwards, no significant increase in RSV cases was identified, thus supporting the hypothesis of a return to the baseline situation (Fig. 2).

Two distinct peaks of RSV cases were observed during the analysis period: between 2021-W30 and 2021-W32 (average of 77 RSV cases per week) and between 2021-W39 and 2021-W41 (average of 79 RSV cases per week) with positivity rates around 60% (Figs.1 and 2).

DISCUSSION

We reported an out-of-season RSV epidemic in Portugal, with a longer epidemic period comparing to previous seasons, after easing of COVID-19 restrictions.

During the 2020–2021 autumn/winter season in Portugal, the RSV epidemic (which usually starts in December)[4,6,7] remained at baseline levels while an out-of-season epidemic starting in June 2021 (2021-W23) was observed. This surge was coincident with the relaxation of COVID-19 NPIs and may have been facilitated by increased levels of travel due to the start of the summer holidays, along with a decrease in COVID-19 risk perception and lesser use of protective measures.[37] Similar out-of-season epidemics and on a different scale to previous trends, after easing of COVID-19 physical distancing measures, were also experienced in several countries worldwide.[8,9,38–42] As socioeconomic activity and movement were re-established, the overall risk for respiratory infections in all population, but specially in infants and young children who had less chance to have a previous contact with common respiratory viruses, increased as a consequence.

Contrary to previous years, two distinct peaks of RSV cases were observed during the analysis period: between 2021-W30 and 2021-W32 and between 2021-W39 and 2021-W41 with positivity rates around 60%.[4,6,7] A sharp decrease in RSV cases was registered in 2021-W33, followed by a steep rise in 2021-W36. Even though the number of tests performed during these three weeks (average of 73

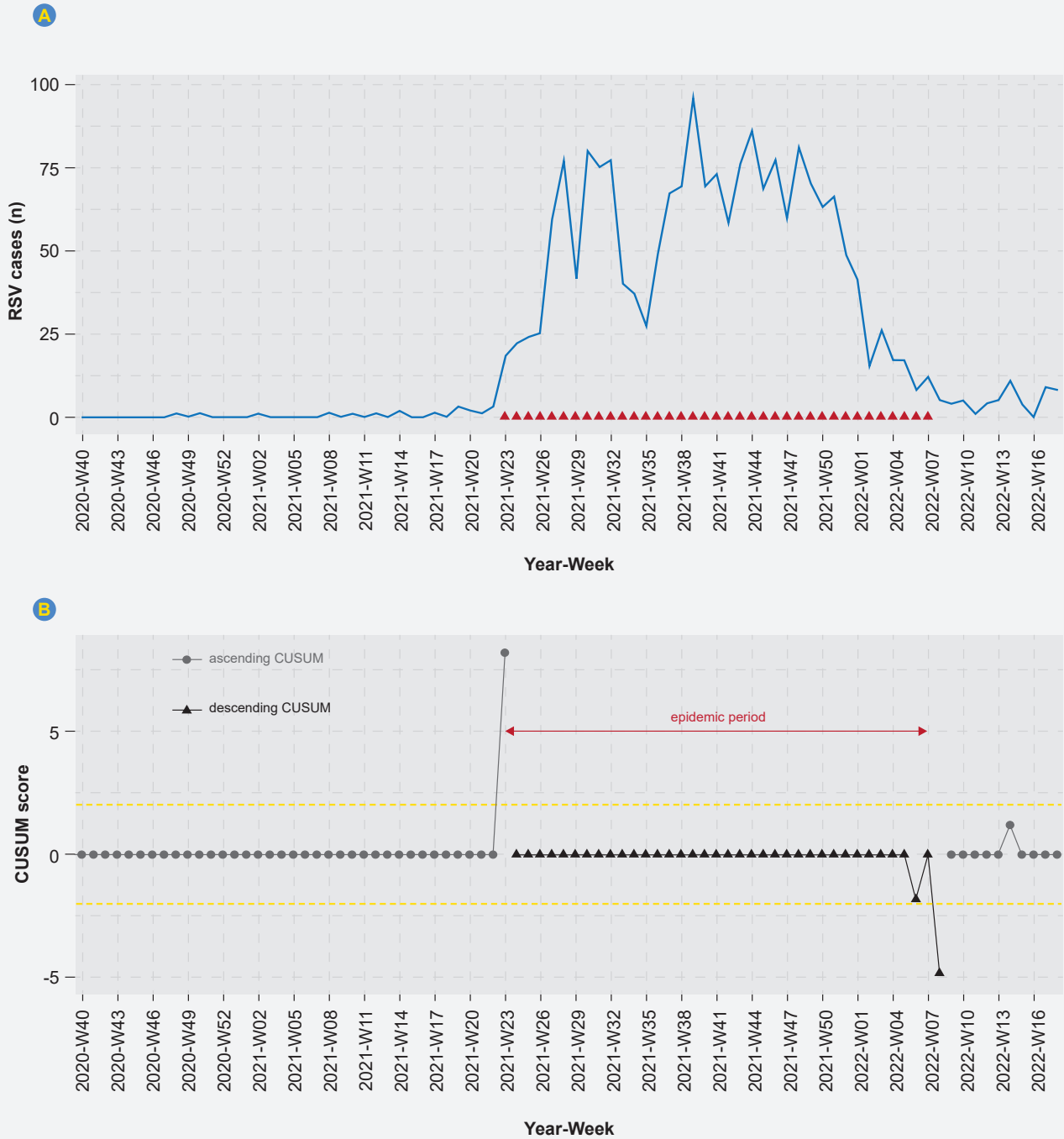

Figure 2 – Distribution over time of RSV cases between 2020-W40 and 2022-W18. Weekly report of RSV cases (A). Red triangles denote incidence is out-of-control. Cumulative sums (CUSUM). Horizontal yellow dashed lines represent the test limits (B).

tests per week) was lower than in the previous three weeks (average of 123 tests per week), the number of reporting sites remained the same (average of 11 reporting sites per week). Therefore, although we cannot exclude the influence of testing capacity in the number of RSV positive samples detected, we postulate that this decrease was mainly due a disruption in RSV transmission because of the summer holidays, as it was a period that coincided with an increase in mobility in parks, retail and recreation.[43] The increase in RSV cases in 2021-W36 was time aligned with the end of

the summer holidays and the restart of school activities for children. We postulate that primary school and day care facilities had an important impact on this RSV transmission, which is in line with other studies.[38,44] Additionally, we note that the main RSV transmission routes are aerosols, droplets (generated during coughing, sneezing or talking), direct contact (from an infected person to a susceptible individual) or indirect contact (fomite transmission).[12] As wearing masks was mandatory in schools for children over 10 years of age, but these social distancing measures did not apply to infants and young children, the latter were at higher risk of RSV infections.

RSV incidence remained at epidemic levels from 2021-W23 until 2022-W07, in a total of 37 weeks. This epidemic period was considerably longer than in previous years, considering a median epidemic duration of 10-11 weeks from 2013-14 to 2018-2019.[4] In light of these results, some public health implications should be emphasised. In Portugal, five doses of palivizumab, in the period between October 15th and February 15th, are recommended for young children with congenital heart disease, pulmonary comorbidities, or with T-cell immunodeficiency, as well as for premature infants or infants with pulmonary comorbidities.[45] In 2021, due to the exceptional circulation of RSV in the summer, the Directorate General of Health in Portugal decided to anticipate the administration of palivizumab to September 15th.[46] This recommendation also stated that monitoring of the RSV epidemic (with the support of the Portuguese Laboratory Network for the Diagnosis of Influenza Infection) would be required to determine the timing of the administration of the last dose of palivizumab. As a result, following a sharp decrease in RSV circulation in January 2022, the timing of the last dose of palivizumab was set to February 15th.[47]

Therefore, our findings suggest that climate characteristics cannot be used as a definitive predictor for the timing of RSV epidemics and highlight the need to take into account the country's surveillance data when defining the prophylaxis period for palivizumab, as the COVID-19 pandemic might have an effect on RSV activity in the following seasons. Several modelling studies analysed how the build-up of immunity debt due to COVID-19 NPIs could result in earlier and larger outbreaks of RSV and possibly affect seasonality for some years to come.[48,49] Moreover, a study conducted in the setting of a delayed surge of RSV in the USA showed a more severe disease course, explained by decreased immunity from lack of previous exposure.[50] Nonetheless, even in countries where an increase in seriousness of disease was not observed, the burden on the healthcare system was substantial: surveillance data from New Zealand, for children aged 0 to 4 years showed that, in 2021, the RSV-associated hospitalization and ICU incidence rates were, respectively, 3 times and 2.8 times higher than the average of peaks between 2015 and 2019.[40] Similar trends were observed in Italy and Germany in 2021, where the out-of-season RSV epidemics were characterized by an extraordinary burden on paediatric hospitals.[41,42] On the other hand, a Canadian study had already demonstrated the added value of prospective surveillance data in aiding decision-making regarding prophylaxis periods: compared to using a predetermined date for the palivizumab prophylaxis period onset, the prospective method involved the administration of less five palivizumab doses, thus minimizing excess healthcare expenditure.[51]

As COVID-19 NPIs are relaxed, it is necessary to adapt currently existing surveillance systems, in order to guarantee the identification of new threats, increase in epidemic activity or the emergence of serious forms of disease, with the proportional use of resources, and without increasing pressure on healthcare services. Systematic RSV surveillance data will allow targeted intervention strategies for better management of infections and prevention of severe illness, and will save costs, thus allowing maximum benefit from prophylaxis and ultimately, will protect children lives.[17–19]

This study has several limitations. As we assessed RSV activity using CUSUM test methodology for count data our results have the potential to be biased if testing strategies change. However, according to the DGS guideline 19/2020, testing strategies remained stable in the period under analysis and included RSV testing for every children with an acute respiratory infection.[22] Even though the number of RSV tests varied within the analysis period, as the number of reporting sites remained relatively stable, we postulate that testing differences were mainly due to the COVID-19 epidemiological situation in Portugal: as RSV tests were performed in multiplex with SARS-CoV-2 and influenza, periods with a higher incidence of COVID-19 should have a positive effect in RSV testing and vice-versa.[52] Nevertheless, we cannot exclude the possibility that, according to epidemiological context and clinical situation, individual testing might differ from this standard. Before 2020-W40, testing strategies differed and therefore, previous periods could not be used for direct comparison.

Additionally, underreporting of RSV cases could cause the algorithm to miss an epidemic. The number of reporting sites was constant during the analysis period, apart from a decrease on 2022-W43 due to the start of the autumn/winter season and consequent re-organization of healthcare services in hospitals. Nonetheless, as the CUSUM score crossed the decision limit in 2021-W23 and stayed over the limit up to 2022-W07, the potential underreporting on 2022-W43 does not have an impact in the epidemic detection for this period. We cannot exclude, however, the possibility that the true number of RSV detected cases might be of higher

magnitude, especially during epidemic peaks, as healthcare professionals who participate in the surveillance might see data reporting as time-consuming during times of increased workload.[53,54] We surveyed the focal points of each non-sentinel site on their willingness to participate in the surveillance system and on the simplicity of data reporting. All answers perceived the public health relevance of RSV disease and emphasized the importance of participation and inclusion in a national epidemiological study. However, 38% of sites reported difficulties in filling the surveillance Excel form. Keeping this in mind, and in order to improve the feasibility of the surveillance system, from October 2022 onwards, reporting will be made through an online platform, which we expect to improve reporting timeliness and data completeness. Furthermore, an attempt should be made to engage in the surveillance system hospitals from the regions of Algarve, Alentejo and Madeira islands. However, our surveillance system has the advantage of including a large study population, corresponding to 43% of the Portuguese children aged 0 to 4 years, and therefore, it provides useful information on RSV epidemiology.

Finally, we lacked clinical data regarding the severity of RSV reported cases (e.g., need for intensive care, mechanically assisted ventilation, or death) and, therefore, we cannot conclude if this out-of-season epidemic has an increased severity compared with previous epidemics. However, we are currently working on a paediatric RSV sentinel surveillance system in hospitals, with the aim to provide disease incidence estimates, identify associated risk factors and assess RSV-related illness severity. Previous studies showed RSV subtype A to be associated with a more severe disease compared with subtype B.[55] Among cases reported within the paediatric RSV sentinel surveillance system, between June 2021 and February 2022, more RSV subtype A (67%) than RSV subtype B (33%) virus were detected. As such, more research is needed on whether viral characteristics in interaction with host susceptibility factors increased severe illness in the 2021-2022 RSV epidemic.[56]

CONCLUSION

An out-of-season RSV epidemic was identified, with a longer epidemic period compared with previous seasons. Possible reasons include relaxation of COVID-19 physical distancing measures and a greater proportion of population susceptible to disease, arising from an extended period of low exposure to RSV. As several factors may change the pattern of RSV activity, and risk of infection or pressures on the healthcare systems may occur at different times, countries should implement year-round surveillance RSV surveillance systems in order to be prepared for uncertain times. These findings might have an impact on public health planning regarding future RSV surges, namely, on the palivizumab prophylaxis period for high-risk infants.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Not all Nodules Are Cancer and not all Fungal Infections Are Aspergillus

Nem todos os Nódulos São Cancro e nem todas as Infeções Fúngicas São Aspergillus

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ABSTRACT

Pithomyces, a dematiaceous fungus, is a common colonizer of dead leaves and stems of many different plants and is associated with facial eczema in some animals. We report a case of invasive fungal pulmonary disease by *Pithomyces chartarum* in a healthy, non-immunocompromised patient. We aim to demonstrate our diagnostic and therapeutic approach and focus on the major challenges arising from the lack of scientific evidence regarding infection by this fungus in humans.
Keywords: Fungi; Humans; Lung Diseases, Fungal; Solitary Pulmonary Nodules

RESUMO

Pithomyces, um fungo demáceo, é um colonizador comum de folhas e caules de diferentes plantas e está associado a eczema facial em alguns animais. Neste trabalho, descrevemos um caso de infeção fúngica invasiva pelo fungo *Pithomyces chartarum*, numa mulher não imunocomprometida. O nosso objetivo é descrever a abordagem diagnóstica e terapêutica deste caso, realçando os principais desafios que surgem devido à falta de evidência científica relativamente à infeção deste fungo em humanos.
Palavras-chave: Fungos; Humanos; Nódulo Pulmonar Solitário; Pneumopatias Fúngicas

INTRODUCTION

Pithomyces chartarum (*P. chartarum*) is a saprophytic fungus, member of the *Pleosporales* order.[1] Apart from one case of fungal peritonitis caused by a *Pithomyces* species in association with *Curvularia geniculate*,[2] this fungal species has not been reported to be implicated in any human infection. Most reports are limited to those of facial eczema or pithomycotoxicosis in ruminants developing after ingestion of vegetation bearing *P. chartarum* which produces a specific family of mycotoxins named sporidesmins.[3,4] As far as we know, we present the first case of *P. chartarum* pulmonary infection in an immunocompetent patient.

CASE REPORT

A 33-year-old woman was admitted to the emergency department with significant haemoptysis lasting a couple of hours. She was a hairdresser, non-smoker, with no recent travels, no animal contact and no humidity or mold at home. Past medical history included conization of the cervix because of cervical dysplasia five years ago. She had no history of respiratory disease or previous similar episodes. On admission, she had no fever, dyspnea or cough. On examination, she was hemodynamically stable, with good peripheral oxygen saturation and no other findings. Blood workup showed no haemoglobin drop and no coagulation test changes. Chest computed tomography (CT) was performed, revealing a single peripheral spiculated nodule with the largest diameter of 3 cm on the left lower lobe, and no other changes (Fig. 1). Bronchoscopy was also performed, revealing serohematic secretions with no signs of active bleeding. Because of lung cancer suspicion, a transthoracic needle biopsy (TTNB) was performed and a brain magnetic resonance imaging (MRI) and a positron emission tomography - computed tomography (PET-CT) were scheduled for the outpatient setting.

No signs of malignancy were found on bronchoalveolar lavage (LBA) or on TTNB histology, but septate hyphae were identified in the latter (Fig. 2). LBA cultures were negative, even though mycological analysis was not performed, as fungal infection was not suspected at first. MRI showed no lesions and PET-CT revealed fluorodeoxyglucose (FDG) high uptake by the left lower lobe nodule previous known (qSUV max 11.6), with no other findings.

Given these results suggesting a fungal infection, a more exhaustive workup was conducted. HIV serologies were negative, serum lymphocyte populations and immunoglobulin levels were normal. *Aspergillus fumigatus* IgG specific antibody, serum galactomannan *Aspergillus* antigen and fungal DNA detection by PCR on histology were negative.

At this point, an otherwise healthy, young, non-immunocompromised woman, with no lung structural abnormalities, was found to have a suspicious pulmonary nodule. Even though there was evidence of fungal hyphae, there was no other test supporting fungal infection and there were no

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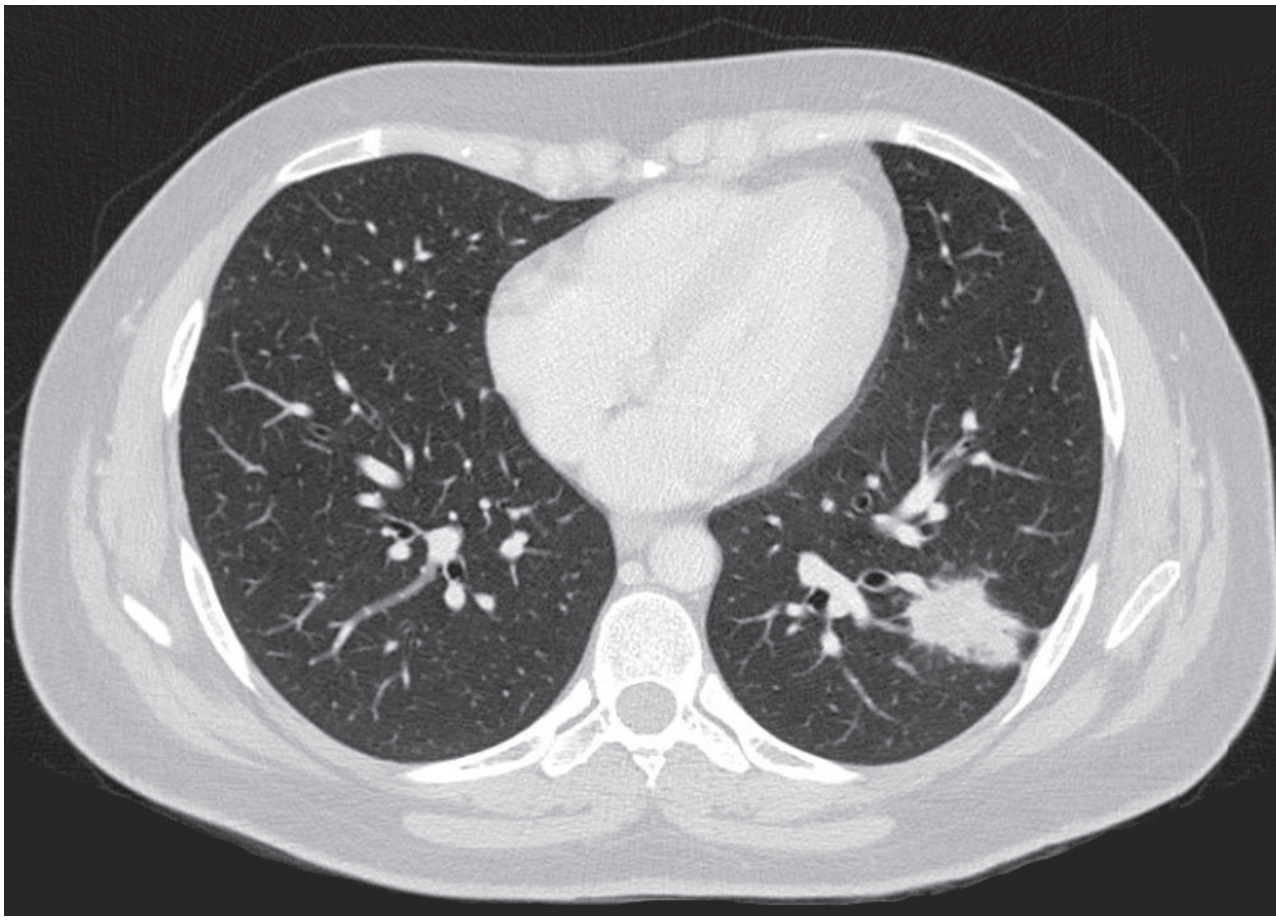

Figure 1 – CT scan revealing a single peripheral spiculated nodule with 3 cm on the left lower lobe

signs of malignancy on cytologic or histologic analyses. In face of a reasonable doubt pending on the differential diagnosis between lung cancer and fungal infection, the thoracic multidisciplinary tumour board decided to propose a left lower lobectomy to the patient.

Left lower lobectomy via uniportal video-assisted thoracic surgery (VATS) was performed and the histological examination of the surgical specimen revealed filamentous septate fungi with tissue damage without vascular invasion, which suggested the diagnosis of chronic necrotising aspergillosis; there were no signs of malignancy. Detection of fungal DNA by PCR on the specimen from surgery revealed *Pithomyces chartarum* with 98% homology and no other fungal DNA detected.

Soon after the surgery, the patient integrated a pulmonary rehabilitation program and resumed her regular personal and professional life. Three months after surgery, the patient was found to be asymptomatic, with no other episodes of haemoptysis and no constitutional symptoms. Follow-up chest x-ray and chest CT scan showed no signs of recurrence (Fig. 3). Regarding the evidence of a localized lesion without signs of systemic infection, it was discussed and decided between peers not to start antifungal agents as evidence was lacking in regard of this fungal infection in humans and the possibility of antifungal adverse effects. The patient kept close clinical, and imaging follow-up.

DISCUSSION

In light of a suspicious lung nodule, with no clinical or laboratory signs of infection, the main differential diagnosis is lung cancer. Therefore, our diagnostic approach followed this direction. Once fungal hyphae suggestive of fungal infection were identified on TTNB, our diagnostic approach was broadened. In fact, there are several cases of fungal diseases mimicking lung cancer described in the literature, most frequently by paracoccidioidomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis, mucormycosis and blastomycosis.[5,6]

Since *Aspergillus* is a filamentous septate ubiquitous fungus that causes a variety of clinical syndromes, we were faced with chronic pulmonary aspergillosis (CPA) as differential diagnosis, more specifically with an *Aspergillus* nodule, an unusual and less severe form of CPA. CPA generally affects immunocompetent patients with a pre-existing

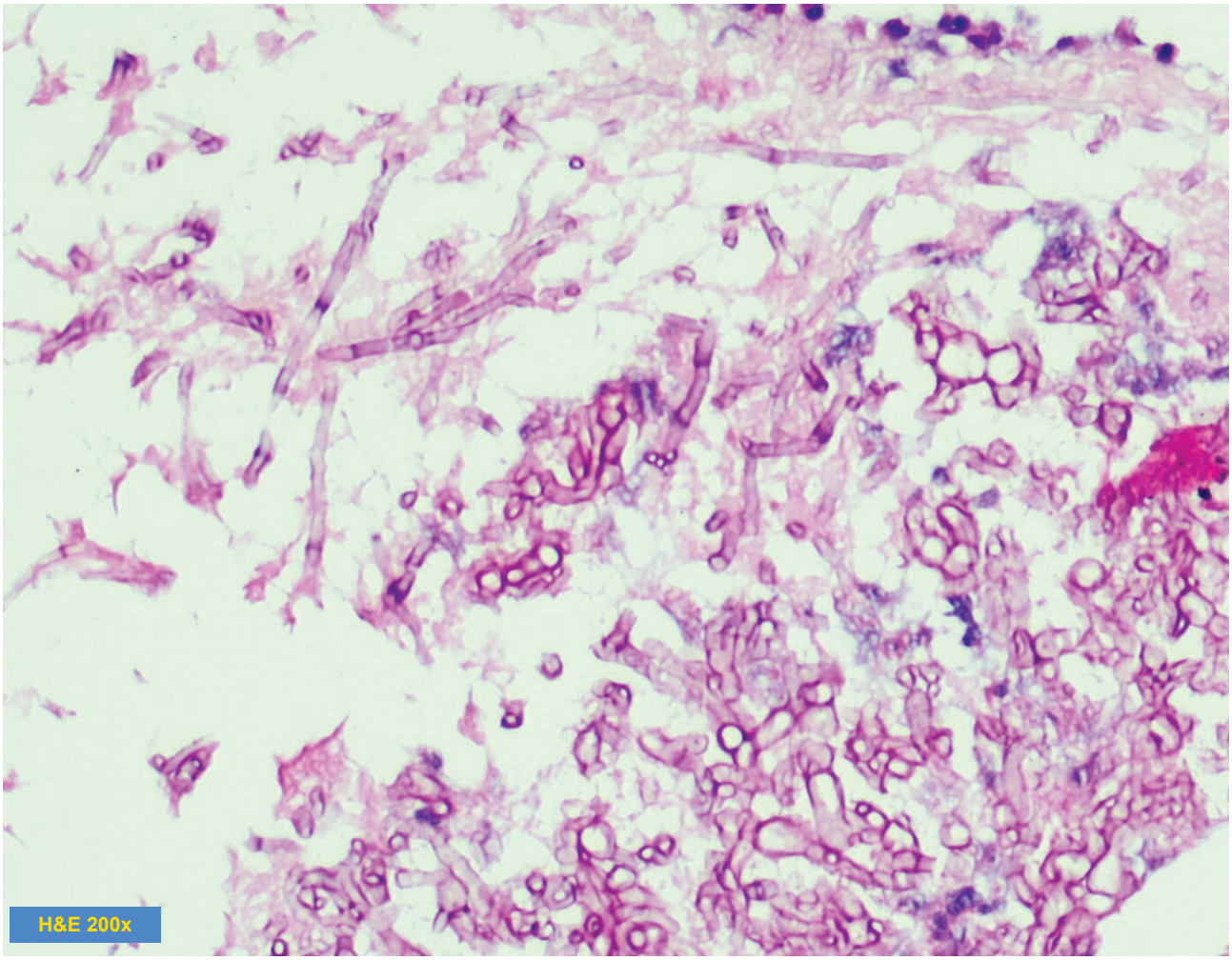

Figure 2 – Pathological findings of lung biopsy specimen. On 200X hematoxylin and eosin staining, abundant fungal colonies with sparsely septated hyphae and barrel-shaped spores were identified.

pulmonary condition. Our patient was indeed immunocompetent but had no history of previous pulmonary diseases and no structural abnormalities on chest CT scan.

The diagnosis of CPA requires a combination of thoracic imaging and direct evidence of *Aspergillus* infection or an IgG antibody response to *Aspergillus*.[7] In clinical situations like this, in which the criteria of CPA are not fulfilled nor there is evidence of infection by any other fungi, but there is still a suspicious nodule, the best approach is not straightforward. It was decided that a left lower lobectomy via uniportal VATS was the best approach in this patient. With the presence of septate hyphae and tissue damage on two sterile samples and PCR detection of *P. chartarum* in the surgical specimen, two criteria for invasive fungal disease were met, according to the revision and update of the Consensus Definitions of Invasive Fungal Disease.[8]

The *Pithomyces,* order of *Pleosporales*[1] is a dematiaceous fungi (i.e. which have melanin-like pigment in the cell wall of hyphae or spores) with species commonly colonizing dead leaves and stems of many different plants. Some species have been isolated from mammals with various symptoms. Its fungal spores are part of a significant fraction of the atmospheric bioparticles (bioaerosols) and capable of inducing the production of specific immunoglobulin E, aggravating the clinical symptoms of allergic respiratory diseases in sensitized individuals.[9] *Pithomyces chartarum*, the most widespread species, has been reported to cause facial eczema in some animals (i.e., sheep, cattle, goats, and deer) due to liver damage caused by a mycotoxin (sporidesmin) produced by the fungus.[3,4] There is only one report in humans of an unidentified *Pithomyces* isolate in association with *Curvularia geniculate* as the aetiology of peritonitis in a patient with vulvar cancer.[2]

Due to the lack of evidence on how to manage this kind of infection, we decided to keep our patient under surveillance. Whether antifungals should be started or not, one

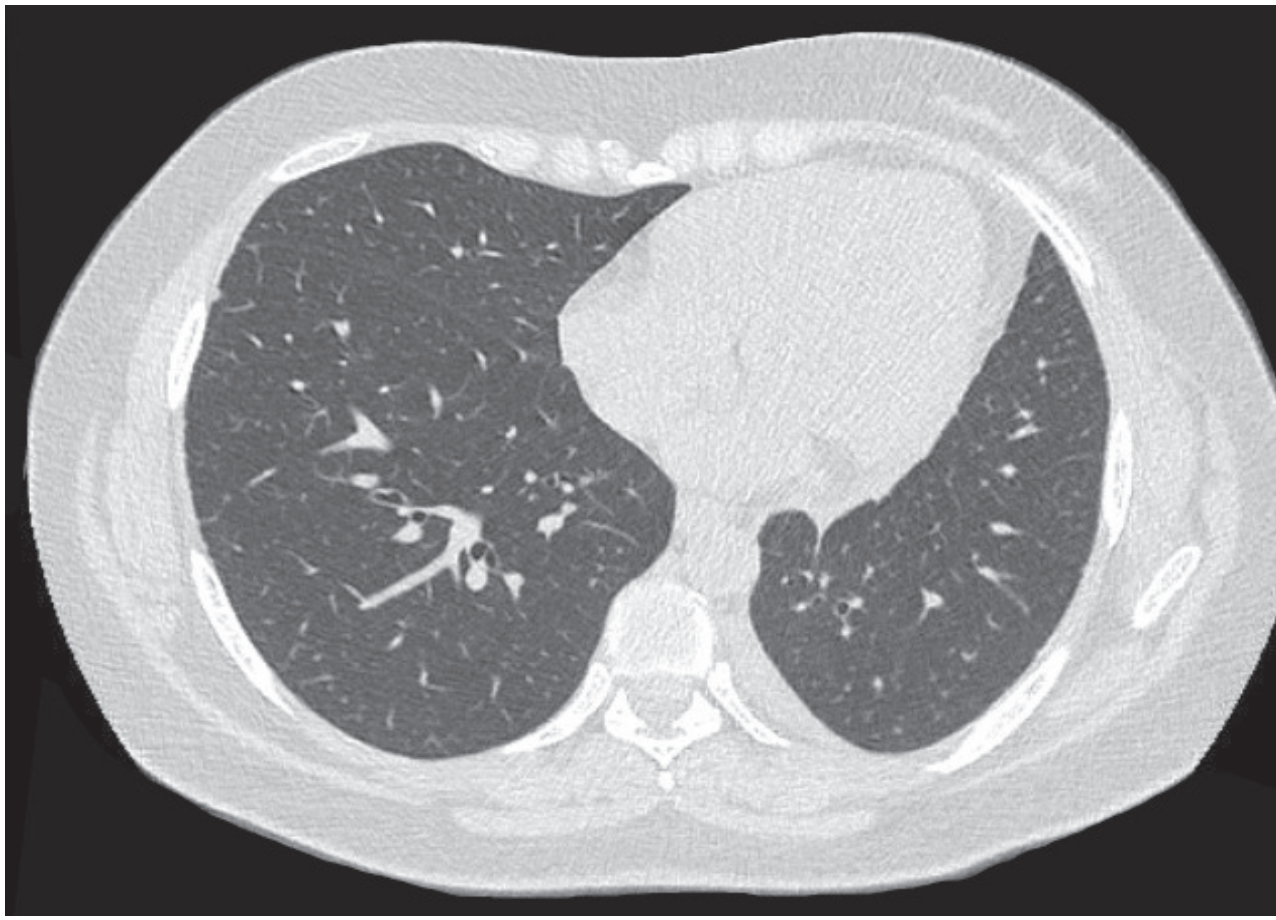

Figure 3 – CT scan with signs of lower left lobectomy, no other changes

study showed potent *in vitro* activity of most of the antifungal drugs against *Pithomyces* species, which could offer different therapeutic options for the treatment of infections caused by these fungi.[10]

In conclusion, there are countless species of fungi, and most of them are ubiquitous. This clinical case shows how important it is to have a high suspicion of a pulmonary fungal infection, even in immunocompetent patients and with no lung structural abnormalities. Not all nodules are cancer and not all fungal infections are *Aspergillus*.

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AUTHOR CONTRIBUTIONS

AF: First draft and literature review.
DAJ: Data review and image collection.
GA: Literature review.
DC: Critical review of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association published in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

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COMPETING INTERESTS

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ACTA MÉDICA PORTUGUESA
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Priapism Secondary to Low-Molecular-Weight Heparins: A Case Report

Priapismo Secundário a Heparinas de Baixo-Peso-Molecular: Um Caso Clínico

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ABSTRACT

Priapism may be a side effect of low-molecular-weight heparins, and its mechanism remains unknown. The authors present a clinical case of a 51-year-old male patient with oligodendroglioma. The patient presented ischemic priapism on the third month after starting tinzaparin, without other recent changes to his medication and he denied the use of other new medicines. The patient went through surgery and the erection was resolved but presented fibrosis of the cavernous body which left him with erectile dysfunction. Since this event, the patient is no longer receiving heparin and has had no other episodes of priapism. The prompt recognition of this side effect may decrease its morbidity and consequent impact on the quality of life. More studies are needed to better understand its pathophysiology.
Keywords: Heparin, Low-Molecular-Weight/adverse effects; Priapism/chemically induced

RESUMO

O priapismo pode ser um efeito adverso das heparinas de baixo peso molecular, cuja fisiopatologia não é totalmente compreendida. Os autores apresentam o caso de um doente, do sexo masculino, 51 anos, com diagnóstico de oligodendroglioma. O doente apresentou um episódio de priapismo, no terceiro mês sob tinzaparina, sem nenhuma outra alteração recente da sua medicação habitual e com consumo de outros medicamentos negado. Foi submetido a cirurgia, com resolução do priapismo, mas apresentou fibrose sequelar dos corpos cavernosos, com consequente disfunção eréctil. Desde então o doente não retomou heparina e não apresentou novos episódios de priapismo. Um célere reconhecimento do quadro pode contribuir para menores sequelas, com consequente diminuição da morbilidade e impacto na qualidade de vida. Mais investigação é necessária para aumentar o conhecimento sobre a fisiopatologia desta situação.
Palavras-chave: Heparina de Baixo Peso Molecular/efeitos adversos; Priapismo/induzido quimicamente

INTRODUCTION

The word priapism comes from Priapus, a Greek god of fertility renowned for his large phallus.[1] Priapism is a prolonged penile erection in the absence of sexual desire.[2]

Priapism associated with the use of low-molecular-weight heparins (LMWH) treatment has been described.[3,4] The pathophysiology is not fully understood and there are few published cases of LMWH-induced priapism.[5,6] As a case of ischemic priapism, its consequences may be permanent and severe, which explains why erection resolution is an urologic emergency. Ischemic priapism may lead to necrosis of erectile tissue and penile fibrosis,[7] which could then cause significant psychological and social sequelae.[1]

In the future, more cancer patients will receive anticoagulants due to an increased incidence of DVT. This increase could be the result of better overall survival of the cancer population, the prothrombotic effect of anticancer treatments and better accuracy of imaging tests (increasing mainly incidental DVT).[8] The number of cancer patients receiving anticoagulants is expected to be higher too due to an increase in thromboprophylaxis, as a result of recent guidelines updates recommending primary thromboprophylaxis for ambulatory cancer patients at higher risk for DVT (defined as a Khorana score higher than two) in the absence of contraindications. Because of this, LMWH-induced priapism may increase in this population.[9] By being familiar with the potential risks associated with medication, physicians can inform the patients of the right attitude if it occurs and make a more rapid diagnosis.[6]

We present a case report of ischemic priapism associated with tinzaparin in a cancer patient.

CASE REPORT

This article reports the case of a 51-year-old male with a medical history of left frontal anaplastic oligodendroglioma, isocitrate dehydrogenase (IDH) 1 mutated, World Health Organization (WHO) grade III, diagnosed in 2005 and a Deep Vein Thromboembolism (DVT) identified in January 2018. The patient was receiving treatment with prednisolone 10 mg daily, phenytoin 100 mg daily, levetiracetam 10 mg twice a day, and temozolomide 225 mg/day for five days, in cycles of 28/28 days, and started tinzaparin 10 000 U daily in January 2018. There were no relevant prior medical conditions, he presented preserved sexual function and had no history of drug allergies or other conditions.

On the 24th May 2018, the patient presented to the Emergency Department with a persistent, painful penile

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erection lasting 35 hours. He was not receiving treatment with phosphodiesterase type five inhibitors (PDE5I) or other medicines apart from his usual medication. The physical examination showed a penile erection, soft glans, and no ischemic signs. The penile blood gas analysis revealed a pH of 6.7 (reference range: 7.35 – 7.45), pO2 of 30 mmHg (reference range: 80 – 100 mmHg) and pCO2 of 66 mmHg (reference range: 35 – 45 mmHg), and all other laboratory tests were within the normal range. He went through emergent surgical treatment with lavage with saline solution and phenylephrine, without success, and then an Al Ghorab type shunt was performed (semi-lunar incision on the dorsal side of the gland, dissection, incision of cavernous bodies with blood drainage and abundant lavage -without apparent blood clot washout -, partial penile detumescence and cutaneous closure of the penile gland). After surgery, the rigid erection was resolved without signs of compartment syndrome and pain. He recovered with fibrosis of the cavernous body. Since this event, the patient is no longer under LMWH, and he had no further episodes of ischemic priapism.

The patient currently presents erectile dysfunction, which is non-responsive to PDE5I, and is aware of his irreversible clinical condition and of the possibility of penile prosthesis implantation. He is under the fourth line of antineoplastic palliative systemic treatment with temozolomide (200 mg/m^2/day for five days, in cycles of 28/28 days) associated with bevacizumab (10 mg/kg every 14/14 days) after having presented multiple progressions of oligodendroglioma.

DISCUSSION

A penile erection involves a complex coordination of signals including parasympathetic and sympathetic inputs and smooth muscle to control vasorelaxation and vasoconstriction[10] which allows for increased arterial blood flow and trabecular cavernous tissue distension.[11] Diverse causes of priapism have been described, including neurological, pharmacological, trauma and idiopathic causes.[12]

The mechanism by which LMWH may induce ischemic priapism is not completely known and its low frequency makes it harder to study.[13] Some hypotheses are that heparin causes vasodilatation,[14] while another is that it stimulates rebound thrombosis[15] or increases platelet aggregation by heparin-induced antiplatelet-antibodies (seen *in vivo* and *in vitro*).[16] Nowadays, there is an increase in cancer-associated thromboembolism treatment and prophylaxis, so this adverse effect might be more commonly observed.[8]

Priapism is divided into non-ischemic and ischemic, the latter comprising around 95% of the cases and it is the one associated with LMWH.[17] It is also known as veno-occlusive or low-flow priapism because it is associated with decreased or absent cavernous blood flow, corpus rigidity, and pain.[7] It represents a form of compartment syndrome characterized by increased pressure within the enclosed cavernous space and compressed circulation.[17] Histopathologic studies show time-dependent erectile tissue damage with irreversible corporal damage occurring in episodes lasting six hours (major priapism).[11] Beyond 24 hours, tissue necrosis and fibroblast proliferation could lead to erectile dysfunction (ED), with estimated rates of 90%. Therefore, it is a medical emergency.[1]

For the diagnosis of priapism, it is essential to take a comprehensive medical history, that covers the patient's previous medical conditions (namely hemoglobinopathies), usual medicines and other drugs as well, the occurrence of previous similar episodes, the recent history of trauma (mainly pelvic), the duration of an episode of priapism and whether there is pain.[7,11] Performing a penile arterial blood gas test is essential. The presence of acidosis, hypoxia, and hypercapnia indicates ischemia. The penile blood gas levels in ischemic priapism are pH < 7.25 (reference range: 7.35 – 7.45), pO2 < 30 mmHg (reference range: 80 – 100 mmHg) and pCO2 > 60 mmHg (reference range: 35 – 45 mmHg).[9] In non-ischaemic priapism, cavernous blood gases are similar to arterial blood.[7] Urine and blood toxicology can aid in determining pharmacotherapeutic or recreational drug use.[1] Regarding treatment, the objective is to re-establish venous blood return and relieve pain.[11] Priapism urges the use of stepwise, from least to more invasive, techniques.[18] The initial treatment is conservative (early corpus aspiration and phenylephrine injection) followed by surgery which would shunt cavernous blood return to the corpus spongiosum or local veins, or early placement of a penile prosthesis.[1] The approach of these patients represents a challenge and should involve a multidisciplinary approach.[18]

The existence of several possible risk factors for priapism is a limitation of this case report. The patient presented a central nervous tumour and was under tinzaparin, levetiracetam and phenytoin. Because of the temporal relation and the absence of new episodes with heparin withdrawal, priapism was considered as being most likely caused by LMWH. Nonetheless, priapism may have not occurred again due to cavernous fibrosis and consequent penile erectile dysfunction.

This article describes a case of priapism as a side effect of LMWH. The pathophysiology is not yet fully understood, so more studies aimed at unveiling the mechanism behind it are needed, which would enable improvements in treatment and prevention. As the number of cancer patients under LMWH increases, clinicians should be aware of the existence of this entity that requires prompt and multidisciplinary management.

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AUTHOR CONTRIBUTIONS

JLP, ND: Design and conception of the work.

MB, MS: Design, critical review and approval of the work.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association published in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

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ACTA MÉDICA PORTUGUESA
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Multifocal Bullous Fixed Drug Eruption

Eritema Pigmentado Fixo Bolhoso

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Keywords: Drug Eruptions; Etoricoxib; Non-steroidal Anti-inflammatory Drugs; Skin Diseases
Palavras-chave: Anti-inflamatórios Não Esteróides; Doenças da Pele; Erupções por Medicamento; Etoricoxib; Medicamentosa

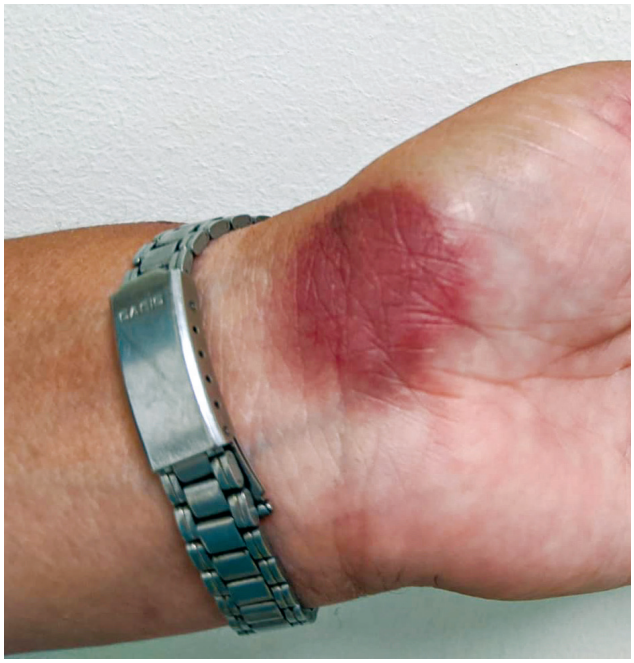

Figure 1 – Round, well circumscribed, edematous erythematous-violaceus plaque

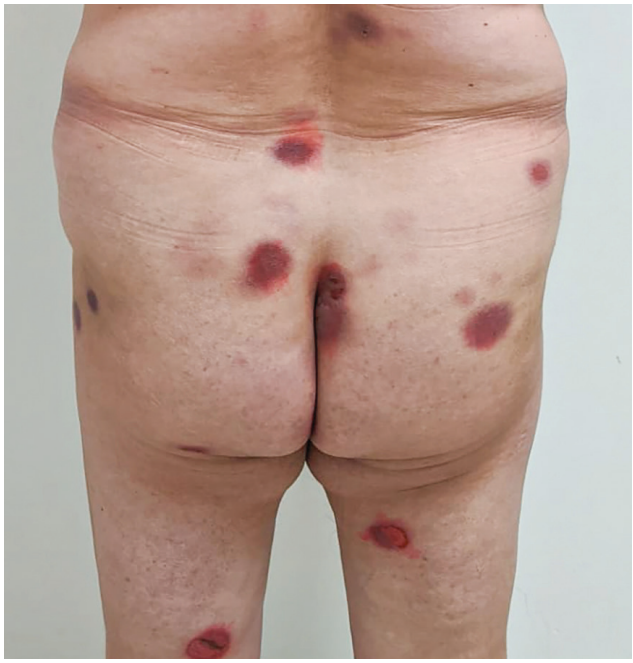

Figure 2 – Multiple lesions on the trunk and lower limbs

We report a case of a 58-year-old woman with multiple round, well circumscribed, edematous erythematous-violaceus plaques on the trunk and both upper and lower limbs (Figs. 1 and 2) which appeared about 24 hours after taking etoricoxib for dental pain. She denied taking other drugs. She mentioned a similar episode in the past, after etoricoxib as well. The biopsy confirmed the diagnosis, but the patch test with etoricoxib on the lesional skin was negative.

Multifocal bullous fixed drug eruption is an adverse drug reaction that is characterized by multiple plaques with frequently central bullous detachment.[1,2] They can be located anywhere on the body surface, including on the genitalia and oral mucosa. The lesions appear several days after the intake of the drug, but can emerge in less than 24 hours on the same anatomical sites, if there is a re-exposure. The most common culprit agents are non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics.[3]

AUTHOR CONTRIBUTIONS

CRO, GCV: Clinical history, draft of the paper.
MAR: Clinical history, draft of the paper, images.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

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Protocolo de Abordagem Diagnóstica e Terapêutica da Hipotensão Intracraniana Espontânea

Guidelines for the Diagnosis and Treatment of Spontaneous Intracranial Hypotension

Maria João PINTO✉*[,1,2], Luís BRAZ*[,1,2], José FONSECA[3], Paulo PEREIRA[2,4], Paula TRIGO BARBOSA[5], Armanda GOMES[5], Joana GUIMARÃES[1,2]
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RESUMO

A hipotensão intracraniana espontânea (HIE) é uma síndrome caracterizada por cefaleia ortostática incapacitante, fruto de uma redução do volume de líquido cefalorraquidiano (LCR) provavelmente causada por uma fístula de LCR. Afeta sobretudo mulheres em idade ativa, estando provavelmente subdiagnosticada. Este protocolo visa apresentar uma proposta de abordagem prática ao diagnóstico e tratamento da HIE. Após uma secção descritiva das manifestações clínicas da HIE, apresentamos um modelo de atuação passo-a-passo para a confirmação do seu diagnóstico e tratamento, considerando diferentes cenários clínicos. Pretende-se, assim, facilitar a decisão clínica através de uma conduta sistematizada e individualizada, visando o melhor interesse do doente.
Palavras-chave: Hipotensão Intracraniana/diagnóstico por imagem; Hipotensão Intracraniana/tratamento; Perda de Líquido Cefalorraquidiano/diagnóstico por imagem

ABSTRACT

Spontaneous intracranial hypotension (SIH) is a syndrome characterized by disabling orthostatic headache, due to reduced cerebrospinal fluid (CSF) volume probably caused by a CSF fistula. It affects mostly women of working-age, although it is probably underdiagnosed. The aim of this article is to present a practical approach to the diagnosis and treatment of SIH. After a description of its symptoms and signs, we present a step-by-step approach to the confirmation of the diagnosis and treatment, considering different clinical scenarios. This is intended to guide clinical decision making, through a systematized and individualized management, aimed at the best interest of the patient.
Keywords: Cerebrospinal Fluid Leak/diagnostic imaging; Intracranial Hypotension/diagnostic imaging; Intracranial Hypotension/therapy

INTRODUÇÃO

A hipotensão intracraniana espontânea (HIE) caracteriza-se pela presença de um volume de líquido cefalorraquidiano (LCR) inferior ao normal, presumivelmente devido à perda de LCR através de uma fragilidade na dura-máter (fístula de LCR). Diferencia-se de outras situações em que se conhece o motivo pelo qual existe hipotensão intracraniana por fuga de LCR (p.e., punção lombar, anestesia espinhal, trauma ou cirurgia cranioespinhal), daí ser considerada 'espontânea'.[1,2] Ainda que tenha sido mantida a nomenclatura original, uma parte significativa dos casos não apresenta redução da pressão de abertura de LCR, a qual é normal em aproximadamente 30% a 60% dos casos. Assim, a manometria de LCR para comprovar a existência de hipotensão de LCR é geralmente dispensada.[1,3]

Na maioria dos casos, existe um ponto de fuga de LCR a nível espinhal, mais frequentemente torácico. As fístulas de LCR podem ser classificadas em três tipos: laceração dural (tipo 1), divertículo meníngeo (tipo 2) ou fístula LCR-venosa (tipo 3). Contudo, os meios imagiológicos atualmente disponíveis apenas permitem detetar sinais de extravasamento de LCR em cerca de dois terços dos casos de HIE e, mesmo nessas situações, poderá não ser possível identificar o local exato do ponto de fístula. As síndromes de Marfan e de Ehlers-Danlos ou a presença de osteófitos podem contribuir para a fragilidade da dura, facilitando a formação de uma fístula de LCR.[1,2]

Pensa-se que os sintomas neurológicos, incluindo cefaleia incapacitante, resultam da deslocação caudal das estruturas cerebrais pela perda de LCR e sua consequente tração/compressão (p.e., terminações nervosas sensíveis à dor na dura-máter craniana). O reconhecimento precoce da HIE permite o tratamento atempado da sintomatologia e prevenção de complicações.[2]

Embora provavelmente subdiagnosticada, estima-se que a HIE tenha uma incidência anual de 4 a 5 casos/100 000 habitantes/ano. Afeta sobretudo mulheres (numa

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proporção de 2:1) entre os 35 e os 55 anos, mas pode ocorrer em qualquer idade.[1,2,4,5]

Este protocolo pretende apresentar uma abordagem sistematizada e prática ao diagnóstico e tratamento da HIE, facilitando a decisão clínica perante diferentes cenários, com benefício para o doente.

MATERIAL E MÉTODOS

Este protocolo resulta de uma iniciativa conjunta dos serviços de Neurologia, Neurorradiologia, Neurocirurgia e Anestesiologia (Unidade de Dor Crónica) do Centro Hospitalar Universitário de São João (CHUSJ), no Porto.

Foi dividido em duas secções. Na primeira, "Clínica da HIE", são descritos os sinais e sintomas associados, os critérios de diagnóstico e possíveis complicações desta patologia. Para tal, foi efetuada uma revisão da literatura em inglês, recorrendo à base de dados PubMed, utilizando como termo de pesquisa "intracranial hypotension" e selecionando os artigos que se referissem à HIE.

A segunda secção, "Abordagem Diagnóstica e Terapêutica da HIE", resultou da descrição da prática realizada no CHUSJ, suportada pela evidência e após discussão conjunta entre os quatro serviços supracitados. A literatura citada foi recolhida após pesquisa na PubMed, usando os critérios de pesquisa já mencionados, com foco no seu diagnóstico e tratamento. São descritos os exames complementares de diagnóstico que consideramos indispensáveis para confirmar o diagnóstico e, se necessário, orientar o tratamento dirigido. Apresentamos, também, os vários tratamentos possíveis, numa atuação passo-a-passo e perante o tipo de resposta do doente. No final, expomos um diagrama-resumo da nossa proposta de atuação.

Clínica da HIE

Tipicamente, a HIE apresenta-se com cefaleia ortostática (sintoma cardinal), que agrava com o ortostatismo (imediatamente, ao fim de segundos/minutos, ou horas – 'cefaleia da segunda metade do dia') e tende a melhorar marcadamente com o decúbito. É, geralmente, holocraniana ou bi-suboccipital, mas pode ser unilateral ou pulsátil, simulando uma enxaqueca. Pode agravar-se com a manobra de Valsalva e tende a resolver-se após normalização da pressão de LCR ou do encerramento da fístula de LCR. Ressalva-se que o componente ortostático da cefaleia tende a atenuar-se com o tempo de evolução, razão pela qual a anamnese se deve focar nas características iniciais da mesma. Raramente, o doente pode apresentar uma cefaleia não posicional, inespecífica, ou até com componente postural inverso (i.e., agrava com o decúbito e melhora com o ortostatismo) e, em 3% dos casos, a HIE pode cursar sem cefaleia.[1,2,4,6]

De acordo com 3.ª edição da Classificação Internacional de Cefaleias,[6,7] o diagnóstico de 'cefaleia atribuída a HIE' é feito quando são preenchidos todos os seguintes critérios:

1. Qualquer cefaleia associada a hipotensão de LCR (< 6 cm H_20) e/ou evidência imagiológica de fístula de LCR;
2. Ausência de trauma ou procedimento que possa causar uma fístula de LCR;
3. A cefaleia ocorre em estreita relação temporal com a hipotensão ou perda de LCR, ou conduziu à sua descoberta;
4. Não melhor explicada por outro diagnóstico.

Assim, depreende-se que o diagnóstico desta síndrome assenta primariamente em aspetos clínicos e imagiológicos, não implicando obrigatoriamente a realização de punção lombar para manometria do LCR, caso o doente apresente manifestações clínicas e sinais imagiológicos sugestivos.[2,3,6] Nas séries mais recentes é inclusivamente descrita uma pressão de abertura do LCR < 6 cm H_20 em menos de um terço dos doentes com HIE.[3,5] Além disso, existe um risco de agravamento da HIE, pelo que o seu uso deve ser ponderado em situações em que o estudo imagiológico [ressonância magnética (RM) cerebral e vertebromedular] seja inconclusivo, mas com suspeita clínica elevada.[1,8]

A cefaleia da HIE associa-se, muitas vezes, a cervicalgia/rigidez cervical, acufenos, perturbação da audição, foto e/ou fonofobia, náuseas/vómitos. Menos frequentemente, o doente pode apresentar diplopia (por paresia do sexto nervo craniano, mais frequentemente), tremor/parkinsonismo ou queixas inespecíficas, como fadiga e dificuldades de concentração.[1,2,4]

A HIE pode ter diversas complicações, algumas das quais potencialmente fatais, incluindo: hematoma subdural (a mais frequente, em 20% a 25% dos casos), trombose venosa cerebral, herniação uncal, isquemia do tronco cerebral e coma. Também foram reportados casos de siderose superficial, amiotrofia bibraquial e/ou alterações da personalidade/comportamento.[2,4,5]

Abordagem diagnóstica e terapêutica da HIE

Perante a suspeita clínica de HIE, deverá proceder-se à realização de RM cerebral com gadolínio. Os achados imagiológicos sugestivos de HIE incluem: realce paquimeníngeo difuso, coleções subdurais, ingurgitamento venoso, alargamento e hiperemia da hipófise, redução do espaço subaracnoideu da bainha do nervo óptico e deslocação caudal das estruturas cerebrais (*brain sagging*).[1,2] O *score* de Bern conjuga a presença destes sinais imagiológicos, de forma ponderada, permitindo exprimir de forma quantitativa o grau de certeza diagnóstica de HIE.[8,9] A maioria das alterações clínicas e imagiológicas da HIE é explicada pelo

aumento do componente vascular, compensando a perda de LCR (hipótese de Monro-Kellie).[10] Porém, cerca de 20% dos casos de HIE apresentam RM cerebral sem qualquer alteração. Mantendo-se a suspeita clínica de HIE, deverá proceder-se a RM vertebromedular, que permite identificar coleções de LCR extradurais espinhais (tradutoras de uma fístula de LCR) em até metade dos casos de HIE. Poderá identificar-se, em simultâneo, o local exato do ponto de fístula de LCR, através de sequências dirigidas ao estudo mielográfico (mielo-RM).[2] A realização de um estudo vertebromedular é sugerida apenas se a RM cerebral for normal, resultando de um compromisso entre a evidência científica disponível e a capacidade real dos nossos centros para desenvolverem investigações iniciais mais completas (RM cerebral e mielo-RM) em tempo útil para o doente. Dado que a RM cerebral permite o diagnóstico de HIE na maioria dos casos (80%), pode-se iniciar o tratamento de forma mais célere, não obviando a possibilidade de completar o estudo imagiológico *a posteriori*, se indicado.

Não existem estudos randomizados controlados que permitam guiar o tratamento da HIE, pelo que as recomendações que se seguem derivam de estudos observacionais e da opinião de peritos. Tem sido proposto iniciar o tratamento de HIE não complicada com medidas conservadoras: repouso no leito, reforço da hidratação oral e analgesia simples (paracetamol, anti-inflamatórios não esteroides, cafeína 200 a 300 mg 2 – 3 id PO). Alguns estudos descrevem, também, eficácia do bloqueio anestésico do grande nervo occipital, tendo sido reportada uma taxa de resolução da cefaleia de 66% numa série de casos de cefaleia pós-punção dural.[4] O bloqueio anestésico do gânglio esfenopalatino também foi reportado como eficaz no controlo da cefaleia pós-punção dural em algumas séries de casos.[11] A literatura reporta uma taxa de sucesso destas medidas conservadoras até cerca de 30%.[1,2,4,10]

É de salientar que existe frequentemente um atraso no diagnóstico e consequente tratamento desta entidade; por outro lado, alguns doentes já empregaram métodos empíricos de tratamento conservador antes da admissão hospitalar (nomeadamente, repouso no leito e analgesia simples no domicílio).[1] Na experiência do Serviço de Neurologia do CHUSJ, sugere-se aplicar o tratamento conservador durante cinco dias (contados a partir do diagnóstico ou do início dos sintomas, caso o doente tenha iniciado tratamento de forma empírica), após os quais se deve tentar o levante progressivo do doente, erguendo a cabeceira a 45º, mantendo a hidratação e analgesia. Se se verificar melhoria da cefaleia, é razoável progredir com o levante e gerir a analgesia conforme a tolerância do doente. O intervalo de tempo sugerido para aferir a eficácia do tratamento conservador é baseado na experiência dos autores (suportada por raros relatos na literatura).[2,10,12] Com estas recomendações, pretende-se um equilíbrio razoável entre permitir tempo suficiente para que estas medidas nutram algum grau de eficácia e não atrasar a escalada terapêutica em caso de ausência de resposta.

Caso não haja melhoria clínica e/ou o doente permaneça muito sintomático apesar desta estratégia, deverá ser efetuado um *blood patch* epidural. Esta técnica consiste na injeção de 15 mL de sangue autólogo (colhido por punção venosa em condições assépticas) no espaço epidural lombar, sem necessidade de identificar o local de fístula de LCR. Antes da sua realização, o doente deve expressar por escrito o seu consentimento e deverá ser obtido um hemograma com contagem plaquetária. Em caso de dor local (por distensão excessiva do espaço epidural) ou cefaleia (por irritação meníngea) intensas no início do procedimento, este deverá ser imediatamente interrompido para evitar possíveis complicações. Trata-se de um procedimento geralmente seguro, com efeitos adversos *minor* e autolimitados, como desconforto/dor lombar ou radicular, tonturas, parestesias e, em casos raros, bradicardia transitória. O doente deve permanecer em posição de Trendelenburg (30º) durante cerca de 12 a 24 horas após o procedimento, seguido de levante progressivo. Pensa-se que o rápido alívio das queixas resulta do aumento da pressão de LCR (causado pelo 'hematoma' epidural) e da eventual formação de um coágulo de fibrina a nível do defeito dural, que selaria a fístula de LCR.[1,2,4,10,13–15]

O doente deverá ser reavaliado 24 a 48 horas após o levante. Se se tiver verificado resolução da cefaleia, ou esta tenha melhorado substancialmente (cefaleia ligeira não incapacitante), deverá ser mantida vigilância dos sintomas até perfazer cinco a sete dias após a realização do *blood patch.* Deverá ser evitada a realização de esforços físicos moderados a intensos durante este período (idealmente, manter esta recomendação durante cerca de duas semanas adicionais).

Estima-se que um primeiro *blood patch* não dirigido seja eficaz em cerca de dois terços dos doentes. Caso haja recrudescência ou ausência de melhoria da cefaleia, deverá ser realizado um segundo *blood patch* epidural lombar não dirigido (no mínimo, os procedimentos deverão ser espaçados por cinco dias). Alguns estudos sugerem maior eficácia se for injetado um maior volume (> 20 mL) de sangue no espaço epidural.[1,2,10,15]

Os estudos observacionais existentes demonstraram que a maioria dos doentes obteve alívio sintomático após um ou dois *blood patches,* e que este efeito poderá ser cumulativo. Alguns autores sugerem, ainda, a realização de um terceiro *blood patch* lombar não dirigido, se houver alívio parcial da sintomatologia com os primeiros dois procedimentos. Se não houver resolução ou melhoria substancial da cefaleia após o segundo (ou terceiro) *blood*

patch epidural não dirigido, preconiza-se a realização de imagem espinhal dirigida, com o objetivo de encontrar o local de fístula de LCR. Nos casos em que ainda não tenha sido realizado estudo de mielo-RM, este deverá ser a escolha inicial; caso seja identificado uma fístula de LCR, será realizado um *blood patch* epidural dirigido (guiado por tomografia computorizada-TC/fluoroscopia). Se não for identificado um ponto de fístula de LCR por mielo-RM, a literatura sugere a realização de mielo-TC ou mielografia por subtração digital (convencional) e posterior realização de *blood patch* dirigido ao local da fístula de LCR (particularmente importante em caso de fístulas de alto débito). Em caso de ausência de resposta clínica favorável, poderá ser ponderado um segundo *blood patch* dirigido ou prosseguir para intervenção neurocirúrgica (reparação microcirúrgica da fístula de LCR, ou clipagem/encerramento de divertículo meníngeo).[1,2,4,10,13]

Independentemente do método de tratamento escolhido, se bem-sucedido, poderá ocorrer hipertensão intracraniana *rebound* (em até 27% dos casos). Deve-se suspeitar desta complicação do tratamento se houver modificação das características da cefaleia da HIE, passando a agravar-se com o decúbito e a melhorar com o ortostatismo. Sendo geralmente transitória, poderá haver necessidade de tratamento farmacológico (com acetazolamida, na maioria dos casos).[2,15]

Nos casos de HIE complicada (alteração do estado de consciência, disfunção do tronco cerebral, coma, trombose venosa cerebral, etc.), deve-se ponderar a redução dos tempos recomendados para avaliação da eficácia do tratamento (conservador ou *blood patch)* e realização precoce de mielo-RM (e, se não identificado o ponto de

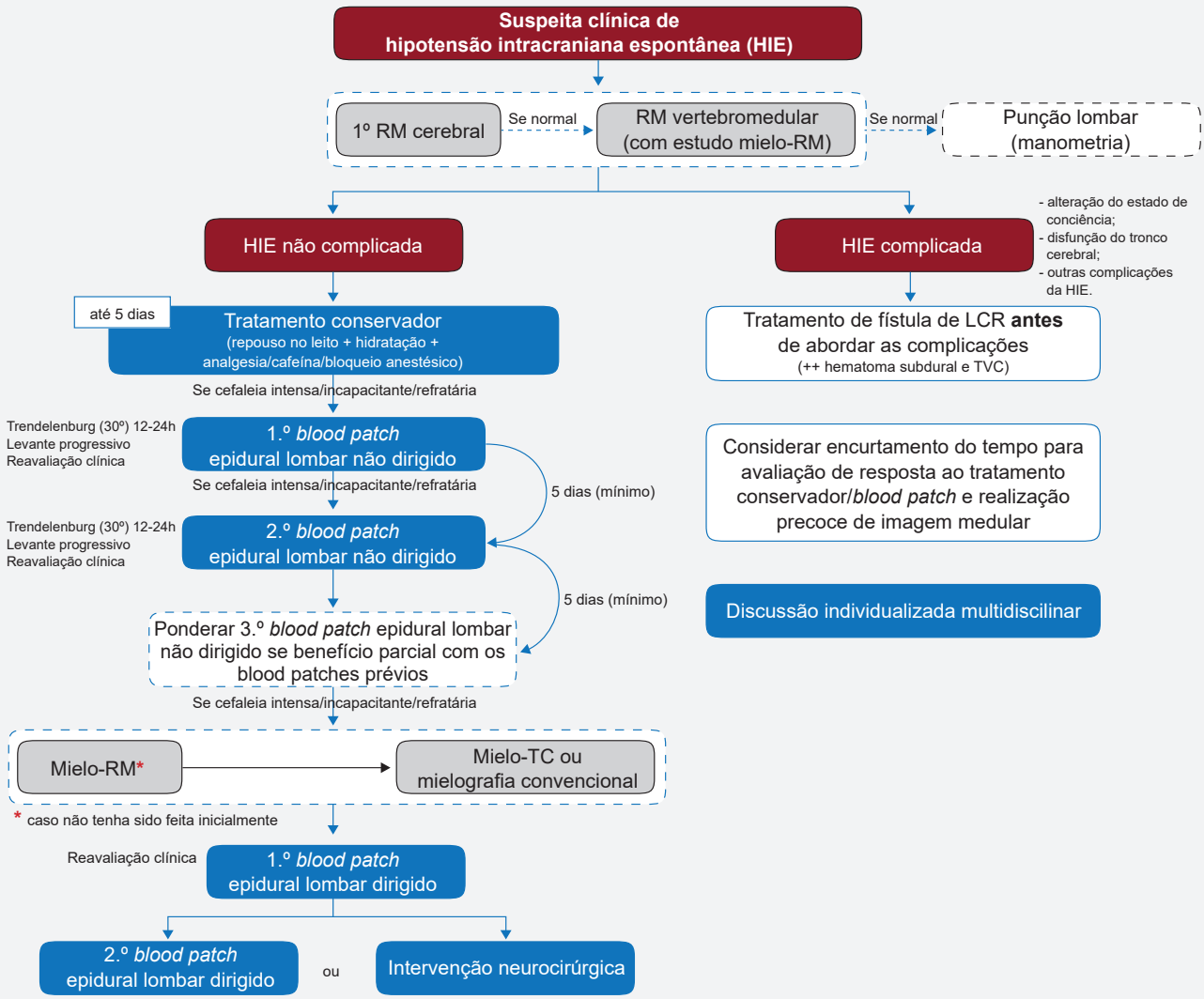

Figura 1 – Diagrama descritivo da abordagem diagnóstica e terapêutica em doentes com suspeita de hipotensão intracraniana espontânea

fístula, de mielo-TC/mielografia convencional). Sublinha-se a importância de tratar primeiro a fístula de LCR antes de abordar as complicações, nomeadamente no caso de trombose venosa cerebral e de hematoma subdural, sob risco de agravamento das mesmas. A discussão multidisciplinar individualizada assume particular preponderância na HIE complicada.[5,10,12]

A Fig. 1 apresenta uma proposta de atuação diagnóstica e terapêutica em caso de HIE.

CONCLUSÃO

O diagnóstico da HIE nem sempre é imediato. Dada a intensidade dos seus sintomas e a gravidade de algumas complicações possíveis, urge iniciar o tratamento adequado atempadamente. Este protocolo apresenta uma proposta de atuação passo-a-passo, orientando o clínico desde a confirmação do diagnóstico até ao tratamento sintomático e, se necessário, ao tratamento dirigido, guiado pelos exames complementares mais apropriados. Pretende-se, assim, facilitar a decisão clínica nos casos de HIE, através de uma conduta sistematizada e individualizada, tendo em consideração o melhor interesse do doente.

CONTRIBUTO DOS AUTORES

MJP, LB: Planeamento, desenvolvimento e discussão do protocolo, revisão da literatura, redação do manuscrito, revisão do manuscrito final.

JF, PP, PTB, AG: discussão do protocolo, revisão do manuscrito final.

JG: Planeamento e discussão do protocolo, revisão do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Dermatose Glútea Senil

Senile Gluteal Dermatosis

Palavras-chave: Doenças da Pele; Idoso; Nádegas/patologia
Keywords: Aged; Buttocks/pathology; Skin Diseases

Caro Editor,

A dermatose glútea senil (DGS) foi descrita pela primeira vez no Japão em 1979.[1,2] Desde então, as escassas publicações sobre esta entidade são predominantemente relatos e séries de casos de países asiáticos, onde é tida como frequente.[2] Apesar da escassez de estudos publicados no mundo ocidental, acredita-se que, apesar de subdiagnosticada,[3] seja uma entidade prevalente, o que acaba por condicionar a sua correta abordagem.

Descreve-se o caso de uma mulher de 74 anos que relata o aparecimento de lesões cutâneas assintomáticas, localizadas na região glútea, com um ano de evolução. Refere elevado nível de sedentarismo, permanecendo na posição sentada durante períodos prolongados. A doente nega alteração dos hábitos intestinais ou uso de fralda por incontinência. Foi medicada com corticoterapia e queratolíticos tópicos, sem benefício evidente. À observação, apresentava placas eritematosas liquenificadas e bem delimitadas, distribuídas simetricamente por ambas as nádegas (Fig.1). Foi realizada uma biópsia cutânea, cujo exame histopatológico revelou uma epiderme acantósica com hiperqueratose compacta, dilatação vascular na derme papilar e um discreto infiltrado linfoplasmocitário perivascular. Os achados clínicos e histopatológicos foram compatíveis com dermatose glútea senil.

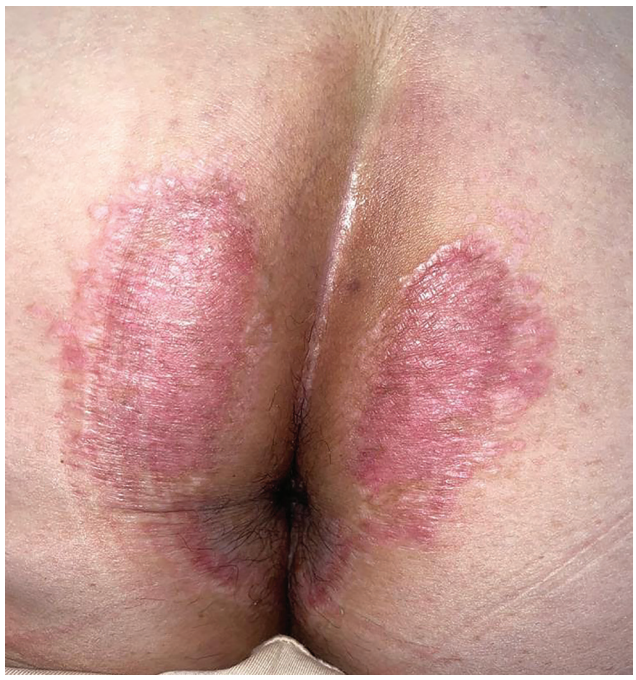

Figura 1 – Placas eritematosas brilhantes e liquenificadas, de limites bem definidos, localizadas bilateralmente nas nádegas

A irritação mecânica prolongada, associada à pressão e fricção, representa um dos principais fatores etiológicos da DGS, sendo, por isso, particularmente prevalente em indivíduos idosos, com baixo índice de massa corporal, sedentários, que permanecem sentados por longos períodos.[1-4] Foi proposto um termo alternativo – '*sitter's sign*',[3] que reforça a associação a este hábito. A redistribuição tecidular relacionada com a idade, nomeadamente com perda de tecido adiposo e muscular na região glútea, constitui outro importante fator contribuinte.[1,2,4]

A DGS manifesta-se tipicamente por placas eritematosas ou acastanhadas, hiperqueratósicas, liquenificadas, por vezes erosionadas, localizadas na fenda interglútea e em ambas as nádegas, onde coincidem frequentemente, mas não exclusivamente, com a área das tuberosidades isquiáticas.[4] Existem, no entanto, formas incompletas de DGS, em que alguns doentes apresentam lesões apenas nas nádegas, apenas na fenda interglútea ou, em alguns casos, apenas uma nádega é acometida isoladamente.[4] As lesões são geralmente assintomáticas, o que poderá contribuir para o seu subdiagnóstico.[1-4]

O diagnóstico é maioritariamente clínico, reservando-se a biópsia cutânea para a exclusão de outras patologias como o líquen simples crónico, a psoríase ou a amiloidose anosagrada.[1-3]

As medidas de alteração de estilo de vida, que incluem a evicção de períodos prolongados na posição sentada, promoção da atividade física regular e a utilização de dispositivos para alívio de pressão, nomeadamente almofadas ortopédicas com orifício central, constituem o pilar terapêutico.[1-4] O uso diário de emolientes é recomendado. Os dermocorticoides e queratolíticos tópicos são frequentemente ineficazes.

Assim, perante lesões glúteas hiperqueratósicas, liquenificadas ou erosionadas, deve considerar-se esta entidade, sobretudo em indivíduos idosos e sedentários. É importante esclarecer o doente quanto ao seu diagnóstico e tratamento adequado, evitando medidas ineficazes.

CONTRIBUTO DOS AUTORES

JB, IM: Redação do manuscrito e aprovação da versão final.

AJ: Revisão do manuscrito e aprovação da versão final.

ALJ: Revisão do manuscrito e aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Resposta a "Consulta Não Presencial no Serviço Nacional de Saúde Português Durante a Pandemia de COVID-19"

Reply to "Teleconsultation in the Portuguese National Health Service During the COVID-19 Pandemic"

Palavras-chave: Consulta Remota; COVID-19; Portugal; Serviço Nacional de Saúde; Telemedicina
Keywords: COVID-19; National Health Service; Portugal; Remote Consultation; Telemedicine

Caro Editor,

O artigo "Consulta Não Presencial no Serviço Nacional de Saúde Português Durante a Pandemia de COVID-19: Estudo da Opinião dos Médicos e Implicações para o Futuro" permitiu fazer a caracterização da utilização da teleconsulta no início da pandemia de COVID-19 e revelou que esta pode vir a ter um papel importante em Portugal.[1]

A pandemia de COVID-19 obrigou a uma re-organização dos sistemas de saúde, tendo a telemedicina desempenhado um papel fundamental.[1,2] De acordo com o artigo em análise, a consulta não presencial foi utilizada pela vasta maioria dos profissionais inquiridos e em 99% dos casos foi feita através de chamada telefónica ou teleconsulta. Esta necessidade levou a uma mudança de paradigma, visto que aproximadamente 70% dos médicos pretende continuar a utilizar esta abordagem no futuro para as consultas subsequentes.[1]

Em doentes que necessitam de um seguimento a longo prazo e em algumas doenças crónicas, como hipertensão arterial, diabetes e artrite reumatoide, as teleconsultas e a telemedicina já têm resultados demonstrados.[3] Além disso, há estudos que indicam uma elevada satisfação e adesão terapêutica dos doentes no contexto dos cuidados de saúde primários.[2]

Contudo, existem ainda barreiras que vão atrasando a sua implementação. Segundo Scott Kruse *et al*, os principais obstáculos estão relacionados com os custos associados à telemedicina a nível organizacional, com a idade e o nível de literacia dos doentes, e com as limitações técnicas e resistência à mudança por parte dos profissionais de saúde.[4] Além disso, questões éticas como, por exemplo, a relação médico-doente, a autonomia e a privacidade dos doentes deverão ser tidas em conta.

As orientações políticas e as diretrizes sobre a telemedicina são escassas em todo o mundo. Em Portugal é necessário apostar em medidas concretas que permitam pôr em prática a sua utilização. Neste contexto, em 2016 foi criado o Centro Nacional de TeleSaúde, responsável pela coordenação, regulação e promoção da telemedicina. Este grupo redigiu um plano estratégico para 2019 - 2022 com 12 medidas, onde destacamos: desenvolvimento de novas ofertas de telessaúde, com abrangência nacional, mais acessíveis e eficazes; promoção e divulgação do conceito pelos cidadãos e profissionais de saúde, de forma a aumentar a sua eficiência; capacitação dos profissionais de saúde nesta área.[5] Adicionalmente, foi emitido o Despacho n.º 3204/2023 publicado em Diário da República, onde se destaca a criação da Unidade Central de Prestação de Cuidados de TeleSaúde (UCeT) do Serviço Nacional de Saúde. Esta unidade assegura os serviços de telessaúde através dos canais do SNS 24 com um novo serviço de teleconsultas médicas, dedicado às pessoas mais idosas e/ou vulneráveis, nomeadamente beneficiários das respostas da Rede Nacional de Cuidados Continuados Integrados, da Rede Nacional de Cuidados Paliativos e da Rede de Estruturas Residenciais para Pessoas Idosas e de Lares Residenciais.[6]

Apesar do potencial das teleconsultas, é importante ter em consideração os seus benefícios *versus* as suas limitações e aspetos éticos. Acreditamos que as barreiras podem ser superadas com a implementação de medidas, como a criação de normas e a sensibilização da população. Desta forma, a telemedicina poderá tornar-se, no futuro, numa ferramenta eficaz para o seguimento de determinados utentes.

CONTRIBUTO DOS AUTORES

MAz, PMS: Pesquisa bibliográfica, organização documental, redação inicial, revisão, aprovação da versão final.

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Endometriose e a Procriação Medicamente Assistida

Endometriosis and Medically Assisted Reproduction

Palavras-chave: Endometriose; Infertilidade Feminina; Técnicas de Reprodução Assistida
Keywords: Endometriosis; Infertility, Female; Reproductive Techniques, Assisted

Caro Editor,

A endometriose afeta 10% das mulheres em idade reprodutiva, e destas, cerca de metade tem infertilidade. A apresentação variável e os sintomas inespecíficos levam ao seu diagnóstico tardio, em média seis a 12 anos após o início das queixas. Aproximadamente 10% a 25% das mulheres irão necessitar de técnicas de procriação medicamente assistida (PMA) e o diagnóstico próximo da quarta década de vida constitui um problema para a realização das mesmas através do Serviço Nacional de Saúde (SNS).[1]

Através do SNS, o uso de técnicas como a fertilização *in vitro* e a microinjeção intracitoplasmática de espermatozoides só pode ser considerado em mulheres com menos de 40 anos, e a inseminação artificial só poderá ser realizada em mulheres com menos de 42 anos.[2] Para doenças graves que comprometam as funções ováricas e/ou uterinas, se existir material genético preservado antes dos 40 anos, são ainda admitidas para PMA mulheres que não ultrapassem os 50 anos.[3]

O diagnóstico precoce, a consciencialização para a doença e o planeamento familiar adequado são essenciais para a referenciação atempada aos cuidados de saúde secundários. As mulheres que pretendam adiar o projeto da maternidade ou as que apresentem patologias como a endometriose devem ser alertadas para a possibilidade de preservação da fertilidade, uma vez que estudos retrospetivos demonstram que a idade da mulher à data da PMA e a idade à data da preservação de oócitos são fatores preponderantes para o sucesso do tratamento.[4,5]

Num país em que a natalidade reduzida é um problema, o factor monetário não pode ser a principal barreira ao acesso a técnicas de PMA e ao desenvolvimento de um projeto familiar.

Fomentar políticas de saúde que evitem a saída de médicos do SNS para o sector privado, tais como a criação de novos centros especializados e condições laborais mais atrativas, são fundamentais para reduzir os tempos de espera e promover o acesso a técnicas de PMA em tempo útil

É também necessária uma abordagem holística e multidisciplinar capaz de ultrapassar os entraves e a disparidade no acesso à PMA. Neste âmbito, os cuidados de saúde primários, em especial os Médicos de Família, devido à sua posição privilegiada no acompanhamento longitudinal das utentes, devem estar cada vez mais atentos e consciencializados para as várias dimensões da endometriose.

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O Subdiagnóstico da Hidradenite Supurativa e o Desafio da Morbilidade Crónica Associada

Underdiagnosis of Hidradenitis Suppurativa and the Challenge of Associated Chronic Morbidity

Palavras-chave: Diagnóstico Tardio; Hidradenite Supurativa/diagnóstico
Keywords: Delayed Diagnosis; Hidradenitis Suppurativa/diagnosis

Caro Editor,

A hidradenite supurativa (HS) é uma dermatose inflamatória crónica, que se associa a várias patologias, nomeadamente obesidade, síndrome metabólica, patologias cardiovasculares, psiquiátricas e autoimunes e consumo tabágico, como referido no artigo "Recomendações na Abordagem do Doente com Hidradenite Supurativa".[1]

O artigo salienta que a prevalência estimada desta doença varia entre 1% e 4% da população e que existe um atraso significativo no diagnóstico. Adicionalmente, em Portugal, estima-se que a HS seja fortemente subdiagnosticada e subtratada.[2] Neste sentido, reconhece-se a posição privilegiada dos cuidados de saúde primários (CSP) para identificar esta patologia, iniciar o tratamento precoce e referenciar os doentes a cuidados diferenciados atempadamente, impedindo desta forma a evolução para formas mais graves da doença, tratamentos de segunda linha e cirurgia.

O Médico de Família é ainda responsável pela avaliação de comorbilidades, sendo o diagnóstico de HS um incentivo ao rastreio de doenças associadas, nomeadamente na avaliação de tabagismo, obesidade, hipertensão, síndrome do ovário poliquístico, doença inflamatória intestinal e outras patologias inflamatórias. Do mesmo modo, o rastreio laboratorial da diabetes *mellitus* tipo 2, anemia e dislipidemia estão recomendados na abordagem dos doentes com HS.[3]

O enorme impacto desta doença na qualidade de vida, associado ao estigma social, disfunção sexual e baixa autoestima, relaciona-se com um aumento do risco de doenças mentais, incluindo depressão e ansiedade, sendo um motivo de incapacidade laboral e diminuição da produtividade no trabalho.[4] Assim, a avaliação do impacto psicossocial no doente e nas relações interpessoais é essencial na abordagem da doença.[5]

Os progressos recentes na compreensão da fisiopatologia da HS têm guiado novas possibilidades de tratamento incluindo a terapêutica biológica. Contudo, estas intervenções são reservadas para formas graves da doença. Nem todos os casos ligeiros desta patologia evoluem para estádios moderados a graves, podendo ser tratados de forma eficaz e holística nos CSP, de forma a evitar a sobrelotação dos cuidados hospitalares.

Atendendo ao impacto físico, mental e social da HS, são necessárias estratégias para aumentar o diagnóstico precoce desta doença crónica negligenciada e rastrear as patologias associadas. Assim, este artigo destaca-se pela sua relevância e pertinência, reforçando que o tratamento médico, aliado ao controlo da dor, da ansiedade, da depressão e de outras comorbilidades, são pilares fundamentais que melhoram a qualidade de vida e a capacidade dos doentes para gerir esta doença.

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Carta ao Editor Sobre a Utilidade do Score SAPS II numa Unidade de Cuidados Intermédios

Letter to the Editor About the Usefulness of the SAPS II Score in an Intermediate Care Unit

Palavras-chave: Medicina Intensiva; Simplified Acute Physiology Score; Unidades de Cuidados Intermédios
Keywords: Critical Care; Intermediate Care Facilities; Simplified Acute Physiology Score

A unidade de cuidados intermédios constitui uma tipologia de prestação de cuidados de saúde de âmbito hospitalar que medeia entre a Enfermaria e o Serviço de Medicina Intensiva (SMI), destinando-se a receber doentes com falência de órgão estabelecida ou em risco elevado para tal, carecendo de monitorização contínua, medidas diferenciadas de suporte e, ocasionalmente, transferência para SMI.

As ferramentas de avaliação de gravidade e prognóstico utilizadas em contexto de cuidados intensivos ainda não se encontram validadas para os cuidados intermédios. O *score* SAPS II (0 - 163 pontos) foi desenvolvido a partir dos dados provenientes de 13 152 doentes adultos, de tipologia médica e/ou cirúrgica, admitidos em 137 unidades de 12 países.[1] Encontra-se validado para estimar a probabilidade de morte durante o internamento (e no prazo de um ano, em alguns estudos) e é calculado a partir do pior resultado obtido nas primeiras 24 horas de internamento com base em 17 variáveis: 12 fisiológicas, três relacionadas com antecedentes pessoais, idade e tipologia de admissão.[2-5]

Desde novembro de 2019 que a Unidade de Cuidados Intermédios Médicos (UCIM) do Hospital de Santo António dos Capuchos (que integra o Centro Hospitalar Universitário de Lisboa Central) inclui o cálculo do *score* SAPS II nas rotinas de admissão dos seus doentes.

Durante os primeiros dois anos, a UCIM recebeu 429 doentes, 54,2% do sexo masculino, com idade média de 67,8 ± 17,7 anos, admitidos sobretudo por patologia respiratória (37,2%), cardiovascular (14,5%) e infecciosa (11,1%). As comorbilidades mais prevalentes foram a hipertensão arterial (48,2%), a insuficiência cardíaca (25,9%) e a doença vascular periférica (25,6%). O valor médio de SAPS II foi de 33 ± 13,8 pontos, correspondendo a uma taxa de mortalidade prevista de 14%. Foram transferidos para SMI 14,7% (n = 70) destes doentes, 8,8% (n = 42) faleceram durante a permanência na UCIM (na ausência de benefício na admissão em SMI) e a taxa de mortalidade a 30 dias foi de 17,5%. Verificámos uma associação entre o valor de SAPS II e a taxa de mortalidade na unidade a 30 dias, em modelo de regressão logística ajustado a idade, sexo e causa de admissão (OR 1,07 ± 0,02; $p < 0,01$ intervalo de confiança de 95%).

Não foi obtido consentimento dos participantes para a inclusão nesta análise. Os dados apresentados estão agregados e anonimizados, não tendo sido colhida informação que permitisse identificação individual pelo que não foi necessário aprovação por comissão de ética.

O trabalho desenvolvido sugere que o *score* SAPS II é uma ferramenta útil na identificação dos doentes com maior risco de mortalidade a curto e médio prazo, podendo contribuir para uma referenciação atempada ao SMI. Contudo, permanece sujeito a interpretação cuidadosa em doentes com monodisfunção de órgão – visto que a sua validade ainda não está demonstrada neste contexto – e não substitui a avaliação clínica individualizada.

CONTRIBUTO DOS AUTORES

Os autores declaram que o presente trabalho foi concebido, desde o desenho do estudo à aprovação do manuscrito final, em estreita colaboração por todos os que o assinam, cumprindo os critérios de autoria conforme se encontram definidos pela Acta Médica Portuguesa no seu regulamento.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

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Prevenção da Mutilação Genital Feminina no Âmbito da Medicina do Viajante

Prevention of Female Genital Mutilation in Travel Medicine

Palavras-chave: Circuncisão Feminina/legislação e jurisprudência; Direitos Humanos; Medicina do Viajante; Portugal; Saúde Pública
Keywords: Circumcision, Female/legislation and jurisprudence; Human Rights; Portugal; Public Health; Travel Medicine

Caro Editor,

Lemos com interesse o manuscrito recentemente publicado de Paixão *et al.*[1]

Efetivamente, a mutilação genital feminina (MGF) é uma violação de direitos humanos e é de louvar a iniciativa de Portugal ao integrar o projeto "Práticas Saudáveis: Fim à Mutilação Genital Feminina". Devido aos seus laços históricos com países da África subsariana, Portugal é um país de risco para a MGF e os profissionais de saúde devem estar atentos aos seus sinais.[2] De igual modo, foi com agrado que vimos mencionado o artigo 144.º-A do código penal português, que penaliza os atos preparatórios para a prática de MGF, como a programação da viagem para o país onde se irá realizar.[3]

Os profissionais de saúde que acompanham o viajante em consulta pré-viagem podem desempenhar um papel fundamental na prevenção da MGF. Médicos de Família, médicos de Saúde Pública que ofereçam consulta do viajante, bem como médicos e enfermeiros da vacinação internacional estão numa posição privilegiada para identificar casos de viagens programadas que incluam a prática de MGF e, no caso de se tratar de um menor, ativar os serviços de proteção legal. Estes poderão inclusive bloquear o passaporte da criança, impedindo a viagem.[4] Este papel de sinalização é ainda de maior importância se servirem populações com viagens frequentes para visitar amigos e família em locais onde se pratica MGF. Os concelhos do distrito de Lisboa, tais como Amadora, Sintra, Loures e Odivelas, onde se encontram a maioria das sobreviventes da MGF identificadas em Portugal, são particularmente relevantes.[1]

Contudo, um estudo francês (sendo França outro país com fortes ligações a países onde se pratica MGF) mostrou que menos de 50% dos profissionais de Medicina do Viajante possuíam conhecimento adequado sobre MGF.[5] Os autores desconhecem estudos semelhantes aplicados em Portugal, mas um estudo aplicado a profissionais de saúde de reprodutiva na Maternidade Alfredo da Costa mostrou resultados semelhantes.[6] Assim, é importante promover a formação destes profissionais para identificar fatores de risco de uma viagem na qual uma menina/mulher poderá ser sujeita à MGF, e informar sobre as ferramentas legais disponíveis e como as ativar em caso de suspeita.

Concluindo, a mutilação genital feminina é um problema de Saúde Pública em Portugal e a Medicina do Viajante, nomeadamente em contexto de pré-viagem, pode constituir uma oportunidade única de prevenção. Contudo, depende do conhecimento e formação dos profissionais, pelo que se deve investir na sua formação.

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Morbimortalidade Associada à Infeção por COVID-19 nos Idosos em Portugal: Comparação entre o período de Outono/Inverno de 2020 – 2021 e de 2021 – 2022

Morbimortality Associated with COVID-19 Infection in the Elderly in Portugal: A Comparison between the Autumn/Winter Period of 2020 – 2021 and 2021 – 2022 Comparison

Palavras-chave: COVID-19; Idosos; Índice de Gravidade de Doença; Pandemia; Portugal; SARS-CoV-2
Keywords: Aged; COVID-19; Pandemics; Portugal; SARS-CoV-2; Severity of Illness Index

As temperaturas mais baixas tendem a favorecer a disseminação de vírus respiratórios, como o SARS-CoV-2,[1] afetando com maior gravidade os mais idosos. Durante dois anos e meio de pandemia, três quartos dos óbitos por COVID-19 ocorreram nas estações do outono e inverno, sendo 66% dessa mortalidade respeitante a pessoas com 80 ou mais anos.

No começo do outono de 2020, verificou-se um rápido crescimento da incidência neste grupo etário, que enfrentava a estirpe original do vírus e medidas mais restritivas do que no período homólogo de 2021 (Fig. 1A). Já no inverno 2021 – 2022, com o aparecimento da variante Ómicron (mais transmissível e menos virulenta do que as anteriores)[2] e com o avanço do processo de desconfinamento, o pico de incidência atingido foi apenas 19% superior ao do inverno anterior (Fig. 1B). Perante isto, e mesmo quando já se verificava uma diminuição da proteção da vacina contra a infeção, o reforço da vacinação neste grupo em períodos anteriores às descidas de temperatura manteve um papel essencial no controlo do número de casos de COVID-19.[3]

Em termos de hospitalizações (todas as faixas etárias) em unidades de cuidados intensivos (UCI), o impacto é díspar: no início do outono de 2020, a tendência foi

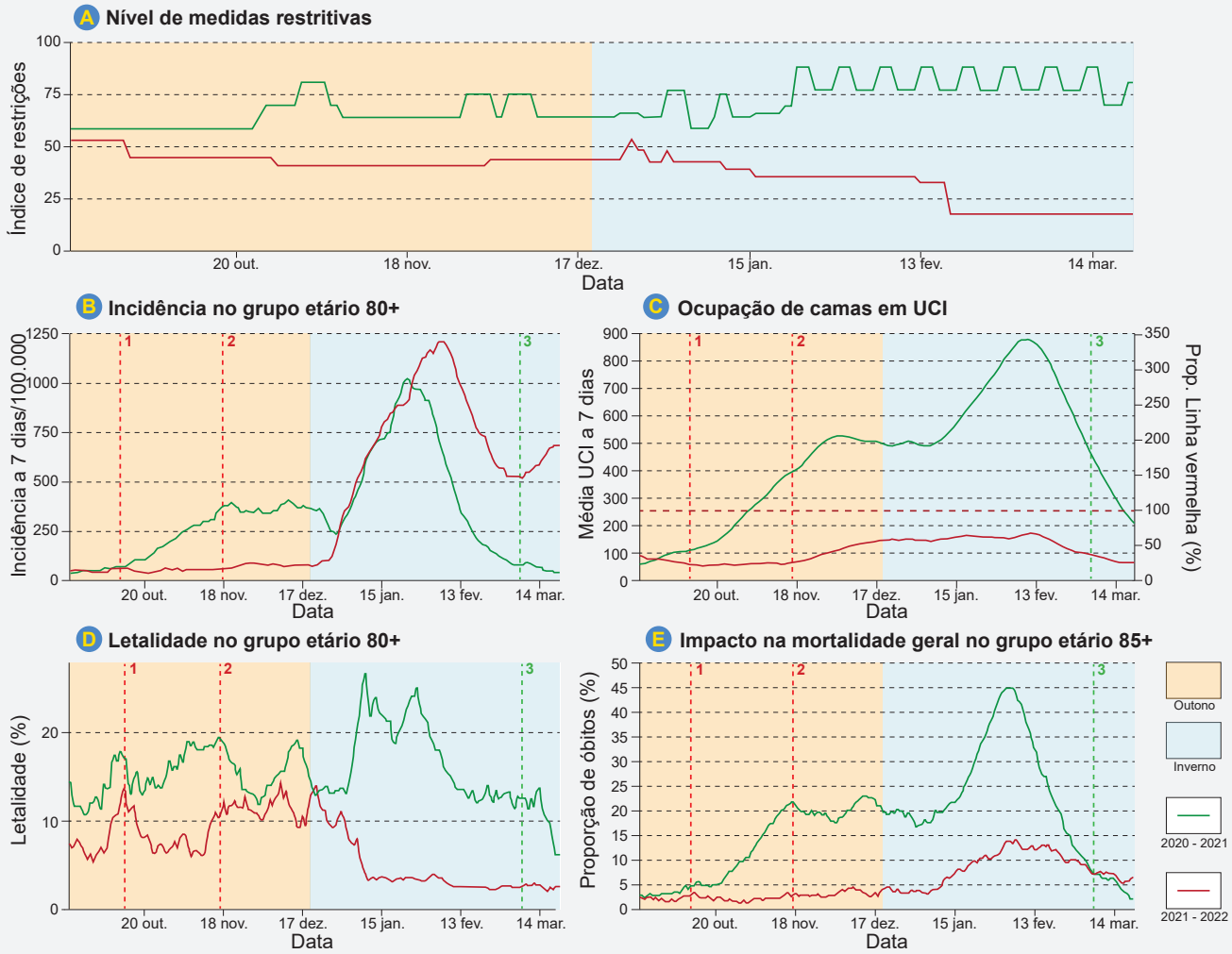

Figura 1 – Evolução da COVID-19 em Portugal (comparação outono/inverno 2020 – 2021 e 2021 – 2022). A Fig. 1A foi elaborada com os dados relativos ao índice de restrições do *Our World in Data* (https://ourworldindata.org/covid-stringency-index). As Fig.s 1B a 1E foram feitas recorrendo aos dados oficiais da Direção-Geral da Saúde relativos à pandemia COVID-19 em Portugal. No cálculo da letalidade foi assumido um intervalo temporal de 10 dias entre casos e óbitos.
1: Data do começo da terceira dose nos 80+ (11 de outubro de 2021)
2: Data onde se atinge uma cobertura da terceira dose nos 80+ de 75% (16 de novembro de 2021)
3: Data onde se atinge uma cobertura da segunda dose nos 80+ de 10% (7 de março de 2020)

fortemente crescente (crescimento superior a 100% em 30 dias), ultrapassando rapidamente o limite definido pelas linhas vermelhas de 255 camas em UCI;[4] no outono/inverno 2021 – 2022, esse limiar nunca foi atingido (Fig. 1C).

Além disso, quanto à letalidade nos mais idosos, as tendências foram similares até ao começo do inverno e, a partir daí, observaram-se tendências opostas: crescente em 2020 – 2021 (especialmente no início de 2021, mais de 20% dos casos do grupo dos 80+ morria por COVID-19) e decrescente em 2021 – 2022 (Fig. 1D). De igual modo, o impacto na mortalidade geral é muito expressivo em 2020 – 2021, onde a COVID-19 chegou a representar 24% da mortalidade nacional nos 85+ no outono e 45% no inverno, ao passo que em 2021 – 2022 não ultrapassou os 5% e 15%, respetivamente (Fig. 1E). Estes contrastes poderão estar condicionados pelas diferenças de temperatura e vacinação, mas também pela introdução de novas variantes.[1,2,3]

Embora haja uma grande incerteza, assumindo que o aparecimento de uma nova variante poderia continuar a introduzir um efeito de imprevisibilidade da situação epidemiológica, a administração da dose de reforço nos mais idosos antes das épocas de maior vulnerabilidade poderia permitir repor a proteção contra a COVID-19 e contribuir para a redução da sua severidade, minimizando assim a necessidade de medidas mais restritivas no inverno.

CONTRIBUTO DOS AUTORES

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Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

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VEXAS Syndrome: A Call for Diagnostic Awareness Based on a Case Series of Seven Patients

Síndrome VEXAS: Alerta para o Diagnóstico Baseado numa Série de Sete Casos em Portugal

Keywords: Inflammation/genetics; Myelodysplastic Syndromes/genetics; Ubiquitin-Activating Enzymes/genetics; VEXAS syndrome
Palavras-chave: Enzimas Ativadoras de Ubiquitina/genética; Inflamação/genética; Síndrome VEXAS; Síndromes Mielodisplásicas/genética

Dear Editor,

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently described disease caused by somatic myeloid mutations in *UBA1*,[1] a gene with critical importance in ubiquitylation (the addition of ubiquitin residues to a protein in order to mark it for degradation by the proteosome). Patients, mostly male and middle-aged or older, present with multisystemic inflammatory clinical manifestations (recurrent fever, neutrophilic cutaneous and pulmonary infiltrates, chondritis, vasculitis, eye and ear, nose, and throat involvement). Hematologic findings are common: macrocytic anaemia, myelodysplasia, plasma cell dyscrasia,[2] vacuolization of myeloid and erythroid precursors in the bone marrow (BM) and thrombosis.[1] The true prevalence rate of VEXAS remains unknown, but mounting evidence suggests that it may be much more common than initially anticipated. The aim of this case series is to raise awareness to the importance of earlier diagnosis and treatment of this entity. All patients authorized the publication of their anonymous case reports. Approval by the Ethics Committee was not necessary since these clinical reports were not part of a study/trial.

We reviewed the clinical and laboratory features of seven patients with VEXAS syndrome (Table 1), with confirmed somatic mosaicism (i.e., the presence of two genetically distinct cell populations within an individual, resulting from postzygotic mutations cell populations with a different genotype, as a result of a post-zygotic mutational event) for variants in exon 3 of the *UBA1* gene (by Sanger sequencing), followed at our tertiary university hospital centre. All seven patients were male, with a median age of 74 years (range 68 - 84) at diagnosis, 72 at disease onset and with five years of symptomatic onset (range 0.5 - 6.0). One patient died due to infectious complications (p.Met41Leu variant). Corticosteroid dependence led to treatment escalation with tocilizumab (n = 3), with rapid and sustained clinical improvement that also allowed for corticosteroid dose reduction.

Table 1 – Demographic and clinical characteristics of patients with VEXAS

Current age (y)	Time since symptoms onset (y)	Inflammatory manifestations	Hematologic findings	Thrombotic findings	*UBA1* Variant*	Treatment	Outcome
68	2	Polyarthritis, recurrent exanthema	Macrocytosis without anaemia or cytopenia; MG IgG/Kappa/Lambda and IgG/Lambda	No symptoms	c.121A>C (p.Met41Leu)	CCT	Stable disease
74	6	Leucocytoclastic vasculitis, chondritis, episcleritis	MDS-MLD (IPSS-R 2.5) Macrocytic anaemia MGUS IgG/Kappa	DVT	c.121A>C (p.Met41Leu)	EPO	Remitting-remission of chronic CCT; On demand transfusions.
78	5	Neutrophilic dermatosis, panuveitis	MDS-SLD (IPSS-R 3) Macrocytic anaemia MG IgM/Kappa	No symptoms	c.121A>C (p.Met41Leu)	EPO CCT MTX	Died from infection
85	5	Migratory polyarthritis, oral aphthae, chondritis	Macrocytic anaemia (without BM study)	No symptoms	c.121A>C (p.Met41Leu)	CCT TCZ	Stable disease
74	0.5	Recurrent fever, chondritis, pulmonary infiltrates	Macrocytic anaemia (without BM study)	Recurring thrombophlebitis	c.121A>G (p.Met41Val)	CCT TCZ	Stable disease
78	6	Non-infectious retropharyngeal phlegmon, constitutional syndrome	MDS EB Type 2 (IPSS-R 6/7), t (9;22) (Vacuoles in myeloid precursors) Macrocytic anaemia MG IgG/Kappa	DVT	c.121A>G (p.Met41Val)	EPO CCT Imatinib	Stable disease; No transfusions needed.
74	3	Recurrent fever, orchitis, Sweet-like dermatosis, labyrinthitis, chondritis	MDS-MLD (IPSS-R 2.5) (Vacuoles in myeloid and erythroid precursors) Macrocytic anaemia	No symptoms	c.122C>T (p.Met41Thr)	CCT TCZ	Stable disease

BM: bone marrow; CCT: corticotherapy; DVT: deep venous thrombosis; EB: excess of blasts; EPO: erythropoietin; IPSS-R: Revised International Prognostic Scoring System; MDS: myelodysplastic syndrome; MG: monoclonal gammopathy; MGUS: monoclonal gammopathy of undetermined significance; MLD: multilineage dysplasia; MTX: methotrexate; SLD: single lineage dysplasia; TCZ: tocilizumab; (**UBA1* reference sequence: NM_003334.4).

VEXAS syndrome presents with debilitating and progressive inflammatory symptoms. Our patients' features are concordant with the most recent literature.[1,3,4] As an X-linked disease, it occurs predominantly in male patients, but has also been diagnosed in women,[5] with lower somatic variant frequencies. New techniques such as quantitative digital polymerase chain reaction may allow for diagnosis in cases of low-level mosaicism (< 20% of cells) which can be undetectable by conventional Sanger sequencing. Myeloid precursors with *UBA1* variants have a high risk of progression to myelodysplastic syndrome (MDS). It is still unclear if this is due to a survival advantage of mutated cells with subsequent clonal expansion or to a highly inflammatory altered microenvironment.[4] There are still no national or international guidelines for screening and treating patients with VEXAS. Patients are frequently steroid-dependent, and we have good results with tocilizumab add-on therapy.

Due to its complexity and heterogeneity, diagnostic awareness is of utmost importance, as patients may seek physicians working in different medical specialties before a diagnosis is established. Physicians should consider a diagnosis of VEXAS in patients aged 40 years or older presenting with inflammatory and/or thrombotic manifestations, particularly when found to have macrocytic anaemia/myelodysplasia.

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AUTHOR CONTRIBUTIONS

FRP, AL: Data collection and analysis. Drafting, critical review and approval of the manuscript.

DGO, MEO, RF: Critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

DGO has received payments from Novartis for attending meetings and/or travel.

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