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A Revista Científica da Ordem dos Médicos

A AMP Agradece!

AMP Says Thank You!

Miguel GUIMARÃES[1,2,3], Tiago VILLANUEVA✉[4,5]
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Entre 1 de janeiro e 31 de dezembro de 2022, a Acta Médica Portuguesa recebeu 1196 submissões através da sua plataforma eletrónica *Open Journal Systems*. Ao longo do ano, os nossos serviços editoriais publicaram 200 artigos distribuídos pelas 11 edições regulares, e 122 artigos em formato *ahead of print*, o que equivale a mais sete edições. No total, foram publicadas 931 páginas, um número recorde nos mais de quarenta anos de existência da revista, o que traduz o empenho e dedicação da equipa editorial.

Decidir quais os trabalhos a publicar, procurando constituir uma mais-valia efetiva para os nossos leitores e assim contribuir para a promoção de boas práticas na investigação científica, para a melhoria da prática clínica, e para a divulgação do conceito da moderna autoria científica, é um processo complexo.

Neste âmbito, a colaboração dos peritos a quem solicitámos a avaliação dos trabalhos propostos para publicação é fundamental. Fruto do trabalho conjunto desenvolvido pelo Corpo Editorial e pelos Especialistas convidados a avaliar os artigos, a Acta Médica Portuguesa subiu em 2022 para o terceiro quartil do *Journal Impact Factor* (*Journal Citation Reports*, Clarivate Analytics), na categoria "Medicine, General and Internal", algo que nunca havia acontecido desde 2010, ano em que, pela primeira vez, lhe foi atribuído Factor de Impacto.

Não o teríamos conseguido sem o vosso contributo!

Por todos estes motivos, vimos encorajar-vos a referenciarem-nos Colegas cujas competências, mérito e produção científica vos pareçam poder constituir uma mais-valia para este projeto que a cada ano cresce, de forma segura, planeada, sóbria, mas nem por isso menos significativa no que representa para a comunidade médica. Para o efeito, bastará enviarem um simples e-mail dirigido a secretariado@actamedicaportuguesa.com indicando nome, afiliação profissional e três áreas de interesse para revisão do especialista em causa.

É nossa intenção que continue a ver-nos como uma mais-valia na sua prática clínica. Do nosso lado, pretendemos também continuar a contar convosco. A todos e a cada um de vós, que de forma contínua doam generosamente o vosso tempo, deixamos o sincero reconhecimento da Ordem dos Médicos e da Acta Médica Portuguesa.

Lisboa, 13 de janeiro de 2023

Miguel Guimarães	Tiago Villanueva
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A Dor Neuropática Periférica Induzida por Quimioterapia no Doente Oncológico/ Sobrevivente de Cancro

Chemotherapy-Induced Peripheral Neuropathic Pain in Cancer Patients/Survivors

Andreia CAPELA✉[1,2], Rosário ALONSO[3], António ARAÚJO[4,5], Beatriz CRAVEIRO-LOPES[6], Rosa Maria FRAGOSO[7], Hélder MANSINHO[8], Rita MOUTINHO[9], José Alberto TEIXEIRA[10], Cláudia VIEIRA[11,12], Dalila VEIGA[13,14]

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Keywords: Antineoplastic Agents/adverse effects; Cancer Survivors; Neuralgia/etiology; Peripheral Nervous System Diseases/chemically induced

INTRODUÇÃO

A quimioterapia sistémica é uma das opções de tratamento na estratégia terapêutica de vários tipos de cancro. No entanto, os efeitos persistentes após o tratamento podem levar à redução da qualidade de vida e da funcionalidade, tanto no doente em tratamento ativo como no sobrevivente de cancro. Um destes efeitos é a dor neuropática periférica induzida por quimioterapia (dNPIQ), caracterizada por lesão ou doença dos nervos periféricos, plexos, gânglios das raízes dorsais ou raízes, associada à neurotoxicidade destes medicamentos.[1,2] Esta é uma das etiologias mais comuns de dor neuropática induzida por fármacos. Afeta milhões de doentes em todo o mundo e é caracterizada por sinais/sintomas sensoriais (dormência, ardor) que podem ser positivos (hiperexpressão de um sintoma — hiperalgesia, alodinia, hiperestesia) ou negativos (hipoexpressão de um sintoma — hipoestesia). Pode ser de longa duração e tornar-se irreversível, refletindo-se em morbilidades associadas, como a depressão ou a insónia, que comprometem a qualidade de vida e as atividades de vida diária dos sobreviventes.[1,3,4]

A incidência de dNPIQ é variável, sendo reportados diferentes valores dependendo dos métodos de diagnóstico ou agentes quimioterápicos usados. Em doentes tratados com paclitaxel e oxaliplatina pode variar entre 81% a 98%, respetivamente.[5] Dados de uma extensa meta análise envolvendo 13 683 pessoas com NPIQ estimou uma prevalência de dNPIQ superior a 40%.[6] Aproximadamente 20% a 30% dos doentes com dNPIQ podem desenvolver um quadro persistente e crónico com consequências significativas ao longo do tempo, não só na qualidade de vida, como na eficácia do tratamento oncológico.[2] Em Portugal, à data, não foi encontrada evidência publicada relativa à prevalência de dNPIQ.

Para os profissionais de saúde, a gestão da dNPIQ representa um desafio significativo por vários motivos: não é possível evitar a sua causa, nem determinar previamente quem vai desenvolver sintomas; também não estão identificados, à data, fatores preditivos de resposta aos diferentes tratamentos disponíveis, nem estão comprovadas estratégias para a sua prevenção.[7] A dNPIQ não costuma ser diagnosticada atempadamente.[3,8]

De forma a colmatar esta lacuna, um grupo de médicos especialistas em Anestesiologia e Oncologia, alguns dos quais dedicados ao tratamento da dor, propôs-se analisar esta temática de forma a sensibilizar para a identificação precoce de dNPIQ no doente oncológico, valorizando e validando as queixas dos doentes, caracterizando fatores de risco e sintomas associados no doente sob quimioterapia ou após o referido tratamento.

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CARACTERIZAÇÃO DE FATORES DE RISCO E SINTOMAS DA dNPIQ

A dNPIQ inclui um conjunto de diferentes condições patológicas que dificulta a sua definição e o diagnóstico. Os processos fisiopatológicos da dNPIQ dependem do fármaco e são multifatoriais, podem ter atingimento sensitivo, motor e autonómico, e ser de instalação aguda ou crónica.[8] Quaisquer patologias concomitantes e/ou subjacentes à neuropatia que possam ter impacto no sistema nervoso periférico podem facilitar o desenvolvimento de dNPIQ e, assim, interferir com os resultados do tratamento oncológico.[8]

Os sintomas da dNPIQ dependem da neurotoxicidade associada ao agente antineoplásico (sais de platina, taxanos, alcaloides da vinca, bortezomib, ixabepilona, eribulina, talidomida, lenalidomida, imunoterapia), estando habitualmente relacionados com a dose administrada e o efeito cumulativo da mesma.[2,4,7,9,10] A duração da exposição, da dose administrada, combinação de fármacos, fatores de risco e comorbilidades/antecedentes clínicos do doente devem ser tidos em conta, valorizando e validando as queixas dos doentes.[10]

Os principais fatores de risco identificados incluem: i) cirurgia prévia ou traumatismo no local de apresentação da dor; ii) idade avançada (≥ 75 anos); iii) neuropatia pré-existente; iv) insuficiência renal; v) diabetes *mellitus*; vi) outras doenças com polineuropatia associada (HIV, hepatite B e sífilis, hipotiroidismo, doenças autoimunes, paraproteinemias); vii) medicação/tratamentos concomitantes (fármacos citotóxicos, anti-maláricos, radioterapia); viii) *deficit* de ácido fólico; ix) *deficit* de vitamina B12; x) outras comorbilidades (ansiedade, depressão, perturbações do sono); xi) alcoolismo.

As manifestações clínicas que caracterizam a dNPIQ incluem os seguintes sintomas: i) sensação de queimadura, ardor/calor; ii) choque elétrico/dor lancinante; iii) frio doloroso; iv) hiperalgesia; v) alodinia; vi) hipoalgesia; vii) parestesia/dormência/formigueiro; viii) disestesia. A caracterização de sinais e sintomas deve ser complementada com a classificação do nível de disfunção sensitiva, motora ou autonómica.

FLUXOGRAMA DE GESTÃO DO DOENTE COM NPIQ

De forma a alertar os profissionais de saúde para esta

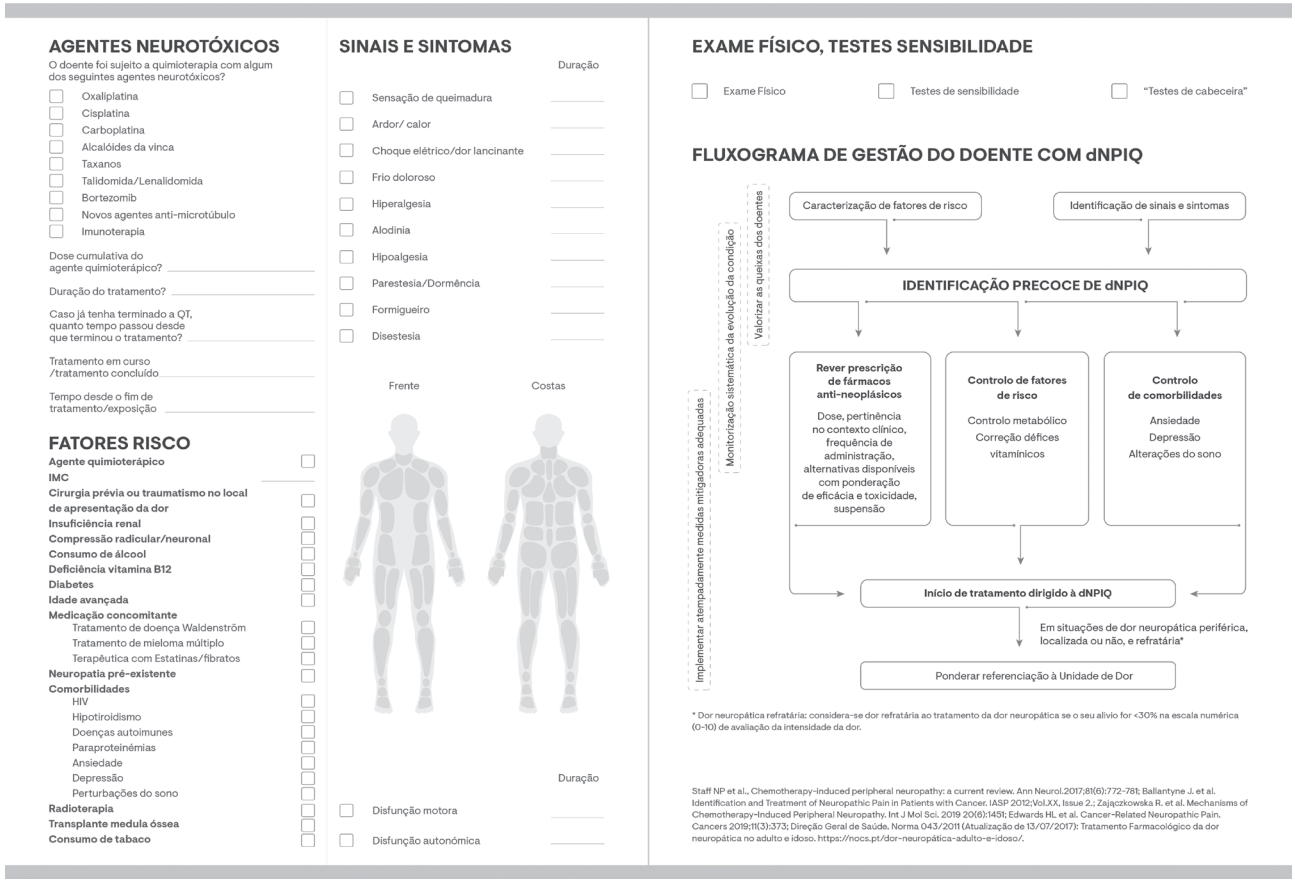

Figura 1 – Ferramenta para avaliar o doente com dNPIQ

temática, os autores propõem uma ferramenta para avaliar o doente com dNPIQ, para que, com monitorização e reavaliação sistemática da evolução, se possam implementar precocemente medidas mitigadoras adequadas (Fig. 1). A ferramenta foi desenvolvida pelos autores, um grupo de peritos com experiência na gestão de dor neuropática induzida por quimioterapia, oncologistas e anestesiologistas, tendo por base a revisão da bibliografia e reuniões regulares de consenso até ao resultado final.

Após identificação da dNPIQ, sugere-se a revisão dos fármacos antineoplásicos prescritos e administrados, tendo em conta a dose, pertinência no contexto clínico e frequência de administração. Numa intervenção multidisciplinar poderão ser equacionadas, se indicado, alternativas disponíveis em função da ponderação de parâmetros de eficácia e toxicidade podendo mesmo levar à suspensão. O controlo de fatores de risco deverá incluir o controlo metabólico, correção dos défices vitamínicos, evicção de tóxicos e correção de outros fatores causais documentados. No que diz respeito ao controlo de morbilidades associadas, propõe-se o rastreio sistemático da ansiedade, depressão e perturbações do sono.

Dada a situação dinâmica e evolutiva da dNPIQ, deve ser iniciado tratamento sintomático após o diagnóstico. Tais como nos casos de dor neuropática periférica, localizada ou não, e refratária [considera-se dor refratária ao tratamento da dor neuropática, se o seu alívio for inferior a 30% na escala numérica (0 - 10) de avaliação da intensidade da dor],[1] deve ser ponderada referenciação a uma Unidade de Dor.

Em conclusão, os autores consideram que muitos dos conhecimentos sobre gestão da dor neuropática periférica de outras etiologias podem ser aplicados na dor neuropática periférica oncológica. Quando associados ao diagnóstico e tratamento precoces poderão diminuir a incidência e melhorar os resultados dos tratamentos antineoplásicos, com expectável melhoria da qualidade de vida e eventualmente da sobrevivência global.

CONTRIBUTO DOS AUTORES

AC, DV: Conceção, escrita, revisão de conteúdos e aprovação do manuscrito.

RA, AA, BCL, RMF, HM, RM, JAT, CV: Revisão e aprovação 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

Todos os autores declaram que receberam subsídio de Grünenthal S.A. pela participação neste trabalho.

JAT declara que participou em *advisory boards* de Grünenthal, Ipsen, Merck, Pfizer e Janssen-Cilag.

HM declara que recebeu da Astra Zeneca subsídios para a elaboração/publicação de artigos e pagamentos para participar no Simpósio EGFR; recebeu da Merck pagamento para moderar uma sessão internacional; recebeu pagamentos da APFH, Vifor Pharma, Grunenthal, Sociedade Portuguesa Oncologia, LEO, Pierre Fabre, EXIGO, Novartis, ROCHE e Astra Zeneca relativos a participação em palestras, moderação de sessões internacionais, consultadoria e moderação de sessões; recebeu da Servier apoio para participação no ESMO-GI; e participou no painel de peritos de MSD, BMS, AMGEN, Pfizer e IPSEN.

RA declara que recebeu apoio financeiro de Grünenthal S.A. relativa a formações clínicas.

CV declara que recebeu apoio financeiro referente a despesas de viagem relativo a consultoria ou participação em *advisory boards* de Bristol Myers Squibb, Genentech/Roche, Grünenthal, Lilly, Merck Serono, MSD, Novartis, Pfizer.

RMF declara que prestou formação a internos de formação específica financiada por Angellini e Grunenthal, bem como formação pós-graduada financiada por INSPIC e FMUP.

FONTES DE FINANCIAMENTO

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ACTA MÉDICA PORTUGUESA
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Molecular Heterogeneity of Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency in the Portuguese Population

Heterogeneidade Molecular da Deficiência em Glicose-6-Fosfato Desidrogenase (G6PD) na População Portuguesa

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ABSTRACT

Introduction: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect in the world, affecting more than 500 million people. In Portugal, the average frequency of G6PD deficiency in males was estimated at about 0.5% and since the year 2000 several G6PD-deficient variants have been identified. The main goal of this study was to improve the knowledge on the molecular heterogeneity of G6PD deficiency in the Portuguese population.

Material and Methods: A retrospective analysis of the mutational profile of 138 unrelated Portuguese individuals (101 males; 37 females), with no known sub-Saharan ancestry, who had been diagnosed with G6PD deficiency between 1994 and 2020 at the Molecular Hematology Unit of Centro Hospitalar e Universitário de Coimbra. The molecular study was done by direct Sanger sequencing or PCR-RFLP analysis.

Results: Twenty-one different pathogenic mutations were found. Among them, 20 were missense, causing the amino acid change, and one was an in-frame deletion in exon 10. The three most frequent mutations belong to the *G6PD* c.376A>G African background haplotype, namely the G6PD variants: A- (c.202G>A; p.68Val>Met) (58.6%), Betica (c.968T>C; p.323Leu>Pro) (12.1%) and Santamaria (c.542A>T; p.181Asp>Val) (4.3%).

Conclusion: There is a wide molecular heterogeneity of G6PD deficiency in the Portuguese population.

Keywords: Anemia, Hemolytic; Glucosephosphate Dehydrogenase Deficiency/epidemiology; Mutation; Portugal

RESUMO

Introdução: A deficiência de glicose-6-fosfato desidrogenase (G6PD) é o defeito enzimático mais comum no mundo, afetando mais de 500 milhões de pessoas. Em Portugal, a frequência populacional da deficiência de G6PD no sexo masculino foi estimada em cerca de 0,5%, e desde o ano 2000 têm vindo a ser descritas diversas variantes G6PD causadoras da deficiência. O principal objetivo deste estudo foi melhorar o conhecimento sobre a heterogeneidade molecular da deficiência de G6PD na população portuguesa.

Material e Métodos: Análise retrospetiva do perfil mutacional de 138 indivíduos não-aparentados de naturalidade portuguesa (101 homens e 37 mulheres), sem ascendência subsaariana conhecida, diagnosticados com deficiência de G6PD entre 1994 e 2020 na Unidade de Hematologia Molecular do Centro Hospitalar e Universitário de Coimbra (CHUC). O estudo molecular foi feito por sequenciação direta de Sanger ou análise por PCR-RFLP.

Resultados: Identificaram-se 21 mutações patogénicas diferentes. Destas, 20 são mutações *missense*, que levam à troca de aminoácido, e uma é uma deleção *in-frame* de 18 nucleótidos no exão 10. As três mutações mais frequentes pertencem ao haplótipo subsaariano *G6PD* c.376A>G, nomeadamente as variantes G6PD: A- (c.202G>A; p.68Val>Met) (58,6%), Betica (c.968T>C; p.323Leu>Pro) (12,1%) e Santamaria (c.542A>T; p.181Asp>Val) (4,3%).

Conclusão: Existe uma elevada heterogeneidade molecular da deficiência de G6PD em Portugal.

Palavras-chave: Anemia Hemolítica; Deficiência de Glucosefosfato Desidrogenase /epidemiologia; Mutação; Portugal

INTRODUCTION

Since Glucose-6-phosphate dehydrogenase (G6PD) deficiency (OMIM#300908) is the most common enzyme defect in human populations, affecting more than 500 million people.[1] The prevalence of G6PD deficiency is highly variable with a particular high incidence in tropical Africa and Asia, Middle East, Southern Europe and Mediterranean countries, reflecting mainly the association with the worldwide distribution of malaria, but also the impact of human migration and resettlement events.[2]

The G6PD enzyme (E.C. 1.1.1.49) is responsible for the first step of the pentose phosphate pathway, in which NADPH, the reducing power required to protect red blood cell against oxidative stress, is produced.[3-5] Most of G6PD deficient individuals are asymptomatic, only experiencing episodic acute haemolytic anaemia (AHA) in the contexts of oxidative stress when exposed to infection, certain drugs or fava beans ingestion (classes II, III and to IV of G6PD variants).[5,6] Only a few rare class I variants, cause chronic non-spherocytic hemolytic anemia (CNSHA).[5,7,8]

The enzyme deficiency results from mutations in the *G6PD* gene (OMIM#305900) located in the telomeric region of chromosome Xq28.[9] Therefore, the inheritance of G6PD deficiency shows a typical X-linked pattern: hemizygous males, as well as homozygous females for *G6PD* mutations, will have the disorder; heterozygous females are just carriers even though they may have haemolytic episodes, specially at an advanced age, due to an imbalanced lyonisation (X-inactivation) favouring the mutated allele.

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The *G6PD* gene spans over 18 kb and is composed of 13 exons and 12 introns.[10] More than 200 G6PD variants are reported, and most of them are due to single nucleotide substitutions that lead to changes of aminoacids (missense mutations).[11,12] In sub-Saharan Africa, the G6PD A- variant (c.376A>G / c.202G>A), with about 12% of normal activity, is the most common and can be present with a frequency of up to 25%.[7] In the Mediterranean region, the Middle East and India, the most common mutation, c.563C>T (Mediterranean variant), characterized by less than 10% of normal enzyme activity, is present at a frequency of 2% - 20% in different populations.[7] Patients with CNSHA have the Class I variants, with mutations more frequently located in exon 10, which encode aminoacids positioned at the dimer interface, and are thus essential for protein stability.[1,5]

In Portugal, the average frequency of G6PD deficiency in males was estimated to be 0.51%[13] and 0.39%[14] in different studies, and not uniformly distributed throughout the country. The aim of the present study is to describe the molecular heterogeneity of G6PD deficiency in the Portuguese population, based on the molecular studies performed at the Molecular Hematology Unit of Centro Hospitalar e Universitário de Coimbra (CHUC) between 1994 and 2020. *G6PD* mutations found in other Portuguese individuals previously described in the literature were also included for analysis.

MATERIAL AND METHODS

Population

This retrospective study assessed the mutational profile of 138 Portuguese individuals with G6PD deficiency (101 males and 37 females; aged between 2 and 74 years), diagnosed between 1994 and 2020, based on recent data and results obtained in past periods, some of which have been published.[15,16] All individuals, unrelated and with no known sub-Saharan ancestry, were mostly from central Portugal (about 65%), but also from the southern (about 15%) and northern (about 8%) regions, and the Azores archipelago (about 2%). In about 10% of the cases, it was not possible to identify the place of birth.

The study was conducted in accordance with the Declaration of Helsinki. All data were anonymized and analyzed together, never individually. Being a retrospective study, with anonymized data, analyzing results obtained between 1994 and 2020, some of them already published, it was not considered mandatory the submission to the ethics committee approval, and it was not possible to obtain now the informed consent.

Hematological and biochemical studies

The diagnosis of G6PD deficiency was made based on the clinical history, routine hematological parameters quantified in a Sysmex XN-1500™ analyzer (Sysmex Europe GMBH, Norderstedt, Germany) and demonstration of a reduced erythrocyte G6PD activity apart from the hemolytic episode. Enzyme quantification was accomplished by quantitative spectrophotometric enzymatic assay according to recommendations of the International Committee for Standardization in Hematology (ICSH).[17] The percentage of enzymatic activity compared to normal levels was calculated using as a control, in each case, a healthy age-matched male without G6PD deficiency.

Molecular studies

Genomic DNA was extracted from EDTA peripheral blood samples, using standard methodologies. *G6PD* exons 2 to 13 were amplified by the polymerase chain reaction (PCR) using appropriate oligonucleotide primers, as previously described.[18-20] Molecular studies of the *G6PD* gene were performed by direct Sanger sequencing of all the exons and adjacent intronic regions and 3'UTR regions. The three most common mutations were analyzed by PCR-RFLP. Mutation c.376A>G was verified with *Fok*I, and the alleles with this nucleotide change (G6PD A variants), were tested for mutation c.202G>A with the restriction enzyme *Nla*III; alleles with both mutations c.376G/c.202A were classified as G6PD A-. Alleles classified as A but not as A- were then tested for mutation c.968T>C (G6PD Betica) with *Msp*I, or for mutation c.542A>T (G6PD Santamaria) with *Sfa*NI. Sanger sequencing was performed using the ABI Prism BigDye® Terminator V 1.1 Cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) and the ABI 3130 genetic analyzer (Applied Biosystems).

Statistical analysis

Hematological, biochemical and molecular data from 138 Portuguese individuals with G6PD deficiency were collected and anonymized. Frequencies of mutated alleles were calculated as the number of mutated alleles (one in hemizygous males, one in heterozygous females, and two in homozygous females) divided by the total number of mutated alleles. The levels of G6PD enzymatic activity, estimated in IU/g Hb, were compared between the two groups, hemizygous males versus heterozygous females, using the T test for equality of means. Data normality in both groups was verified using the Kolmogorov-Smirnov test. The continuous variable was described as the mean ± standard deviation (SD). Statistical analysis and graphics were performed using IBM SPSS software, version 24 (IBM, NY, USA). A *p*-value lower than 0.05 was considered statistically significant.

RESULTS

Mutational spectrum

The pathogenic *G6PD* mutations identified in a total of

138 Portuguese individuals with the enzyme deficiency, including 101 hemizygous males, 35 heterozygous females and two homozygous females, are detailed in Table 1. Twenty-one different pathogenic mutations were found in a total of 140 mutated chromosomes: 20 missense mutations, which led to an amino acid change, and an in-frame deletion of 18 nucleotides in exon 10 (G6PD Tondela), identified in an elderly female with CNSHA.[16]

The most frequent *G6PD* mutations that were identified belong to the African background haplotype c.376G (*G6PD* A allele). The most frequent variant is G6PD A- (c.202G>A; p.68Val>Met), found in 57 hemizygous males, 23 heterozygous females and 1 homozygous female (82/140 chr; 58.6%) (Table 1). The variant G6PD Betica (c.968T>C; p.323Leu>Pro) is the second most common, and was found in 16 hemizygous males and one heterozygous female (17/140 chr; 12.1%). The variant G6PD Santamaria (c.542A>T; p.181Asp>Val) was found in four hemizygous males and two heterozygous females (6/140 chr; 4.3%).

Eighteen rare variants of G6PD were also found (Table 1). The *G6PD* mutation underlying variants known as Vanua Lava (c.383T>C), Taipei (c.493A>G), Shinshu (c.527A>G), Chatham (c.1003G>A), Mira d'Aire (c.1048G>C), Tondela (c.1076-c.1093del), Anadia (c.1193A>G), Covão do Lobo (c.1205C>A), Canton (c.1376G>T), Kamiube (c.1387C>T) and Flores (c.1387C>A) were found in just one chromosome; mutation underlying variants known as Azores (c.595A>G), Mexico City (c.680G>A), Figueira da Foz (c.1366G>C) and Kaiping (c.1388G>A) were found in two chromosomes; and mutation Mediterranean (c.563C>T), Coimbra (c.592C>T) and Seattle (c.844G>C) were found in three chromosomes (Table 1).

Genotype-phenotype correlation

From the subjects with the common G6PD A- variant, we obtained information on G6PD enzyme activity for 22

Table 1 – *G6PD* mutations found in 138 individuals (101 males and 37 females), studied at the Molecular Hematology Unit of CHUC

Variant	Mutation	Consequence	n chr (%)	Exon	Class	Hemi/Het/Hom	Reference
A-	c.376A>G / c.202G>A	p.126Asn>Asp / p.68Val>Met	82 (58.6%)	5/4	III	57/23/1	14,15
Betica	c.376A>G / c.968T>C	p.126Asn>Asp / p.323Leu>Pro	17 (12.1%)	5/9	III	16/1/0	14,15
Santamaria	c.376A>G / c.542A>T	p.126Asn>Asp / p.181Asp>Val	6 (4.3%)	5/6	II	4/2/0	14,15
Vanua Lava	c.383T>C	p.128Leu>Pro	1	5	II	0/1/0	This study
Taipei	c.493A>G	p.165Asn>Asp	1	6	II	1/0/0	This study
Shinshu	c.527A>G	p.176Asp>Gly	1	6	I	1/0/0	This study
Mediterranean	c.563C>T	p.188Ser>Phe	3	6	II	1/2/0	14
Coimbra	c.592C>T	p.198Arg>Cys	3	6	II	1/2/0	15,26
Azores	c.595A>G	p.199Ile>Val	2	6	II	0/2/0	15
Mexico City	c.680G>A	p.227Arg>Gln	2	7	III	2/0/0	This study
Seattle	c.844G>C	p.282Asp>His	3	8	III	1/0/1	14,15
Chatham	c.1003G>A	p.335Ala>Thr	1	9	II	1/0/0	15
Mira d'Aire	c.1048G>C	p.350Asp>His	1	9	III	1/0/0	15
Tondela	c.1076-c.1093del	p.362-367del	1	10	I	0/1/0	16
Anadia	c.1193A>G	p.398Glu>Gly	1	10	II	0/1/0	15
Covão do Lobo	c.1205C>A	p.402Thr>Asn	1	10	I	1/0/0	15
-	c.1311C>T	p. 437Tyr=	5	11	III	5/0/0	This study
Figueira da Foz	c.1366G>C	p.456Asp>His	2	12	I	2/0/0	15
Canton	c.1376G>T	p.459Arg>Leu	1	12	II	1/0/0	15
Kamiube	c.1387C>T	p.463Arg>Cys	1	12	III	1/0/0	15
Flores	c.1387C>A	p.463Arg>Ser	1	12	II	0/1/0	14
Kaiping	c.1388G>A	p.463Arg>His	2	12	II	2/0/0	This study

n chr: number of mutated chromosomes; Hemi: hemizygotic males; Het: heterozygous females; Hom: homozygous females.
A total of 140 mutated alleles were found.
References are from published cases of Portuguese origin.

hemizygous males and 14 heterozygous females. The hemizygous males showed a mean G6PD activity of 1.46 ± 0.95 IU/g Hb and the heterozygous females a mean enzyme activity of 3.01 ± 1.94 IU/g Hb, approximately twice than that of G6PD deficient males, as expected (a statistically significant difference, p = 0.013). The mean value of G6PD activity in 62 normal individuals (all males) was 9.01 ± 1.69 IU/g Hb, ranging from 6 to 13.1 IU/g Hb (Fig. 1). Considering all the available G6PD deficient males with information on enzyme activity, most variants can be classified according to the WHO classification: class I and II, activity < 10% of normal; class III, activity 10% - 60% of normal (Table 2). Only four variants, G6PD Covão do Lobo (c.1205C>A), G6PD Figueira da Foz (c.1366G>C), G6PD Tondela (c.I1076-c.1094del) and G6PD Shinshu (c.527A>G), were associated with chronic hemolytic anemia (class I variants) (Table 1).

The c.1311C>T polymorphism

Five hemizygous individuals with G6PD deficiency (enzymatic activity at about 75% according to G6PD class III variants) had the silent mutation c.1311C>T (rs2230037) (p.437Tyr=), in combination with the IVS11+93T>C (rs2071429) polymorphism. No other pathogenic mutations were found within the coding region and adjacent regions of the *G6PD* gene of these individuals.

DISCUSSION

In this retrospective study, we described the *G6PD* gene mutations found in 138 Portuguese individuals with G6PD deficiency, including 101 hemizygous males, 35 heterozygous females and two homozygous females. Twenty-one different *G6PD* pathogenic mutations were found in a total of 140 mutated alleles. The most common was the variant G6PD A- (c.202G>A) (58.6%), followed by variants G6PD Betica (c.968T>C) (12.1%) and G6PD Santamaria (c.542A> T) (4.3%) (Table 1). Despite being found on the sub-Saharan X-chromosome haplotype c.376G (variant G6PD A), which is similar to previous studies in African populations,[21-24] these three pathogenic *G6PD* mutations were identified in Portuguese (Caucasian) individuals with no known African ancestry. However, the possibility of African origin for these mutations cannot be excluded.

Of the 18 rare variants identified, six were, to the best of the authors' knowledge, only found in the Portuguese population, having already been the subject of previous publications[14-16]: they are the G6PD variants known as Mira d'Aire (c.1048G>C), Anadia (c.1193A>G), Tondela (c.I1076-c.1094del), Covão do Lobo (c.1205C>A), Figueira da Foz (c. 1366G>C) and Flores (c.1387C>A) (Table 1). The variant G6PD Azores (c.595A>G) was also found in Papua New Guinea and named as G6PD Dagua.[25]

This study describes five rare G6PD variants previously identified in other populations around the world but

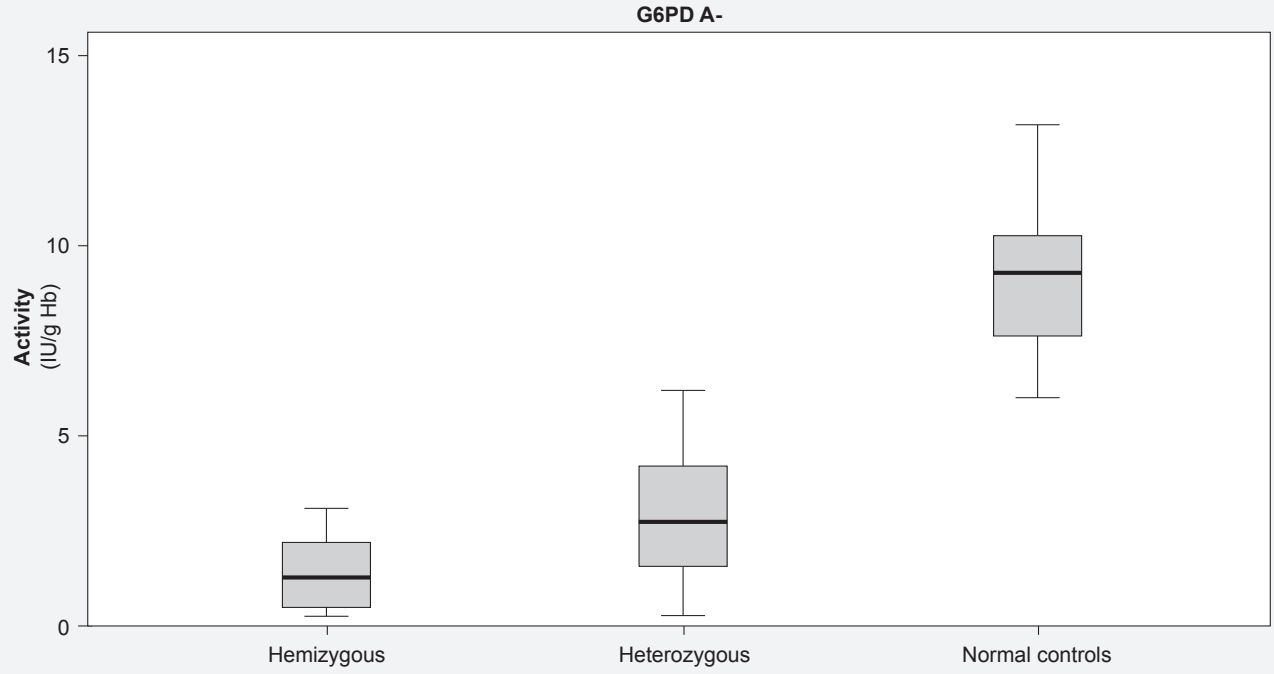

Figure 1 – Box plots showing the complete distribution of G6PD activity expressed in IU/g Hb in hemizygous individuals and heterozygous females for the G6PD A- variant and in 62 normal individuals (all males)

Table 2 – Enzymatic activity for 10 different G6PD variants found in 37 hemizygous males

Variant	Mutation	Class	Clinical symptoms	n	Enzymatic activity (IU/g Hb)	Enzymatic activity (% of n)
A-	c.376A>G / c.202G>A	III	AHA	22	1.46 ± 0.95	14.9
Betica	c.376A>G / c.968T>C	III	AHA	2	1.85 ± 1.91	18.5
Mexico City	c.680G>A	III	AHA	1	3.6	53.0
-	c.1311C>T	III	No*	2	5.65 ± 0.21	75.5
Santamaria	c.376A>G / c.542A>T	II	AHA	3	0.47 ± 0.38	6.0
Taipei	c.493A>G	II	AHA	1	0.5	6.0
Kaiping	c.1388G>A	II	AHA	2	1.25 ± 1.2	13.5
Covão do Lobo	c.1205C>A	I	CNSHA	1	0.1	0.9
Figueira da Foz	c.1366G>C	I	CNSHA	2	0.50 ± 0.28	4.5
Shinshu	c.527A>G	I	CNSHA	1	1.5	15.0

n: number of individuals with the mutation.
* Diagnostic in malaria context.
Enzyme activity values were calculated as mean ± standard deviation for two or more individuals.
Classification of mutations was performed according to WHO guidelines.

reported herein for the first time in the Portuguese population: Vanua Lava (c.383T>C), Taipei (c.493A>G), Shinshu (c.527A>G), Mexico City (c.680G>A) and Kaiping (c.1388G>A).[11] The G6PD variants Chatham (c.1003G>A), Canton (c.1376G>T) and Kamiube (c.1387C>T) were previously described in Portuguese individuals[15] and the variants Seattle (c.844G>C) and Mediterranean (c.563C>T), also found in this study, had already been previously identified in Portugal by Rodrigues *et al*.[14] The variant G6PD Coimbra, identified in three chromosomes, was previously found in a Portuguese patient,[26] and it is common in several Asian populations. Two variants previously described in the Portuguese population, G6PD Aveiro (c.806G>A)[27] and G6PD Gaohe (c.95A> G),[14] were not found in this study.

The prevalence rate of the c.1311C>T mutation observed in this study (3.6%), in combination with the IVS11+93T>C polymorphism, was similar to that found in most previous studies performed for normal or G6PD-deficient populations.[28-31] It was reported that these two polymorphisms in association with the 3′ UTR c.*+357A>G (rs1050757) polymorphism can be responsible for a *G6PD* haplotype associated with G6PD deficiency.[32] Interestingly, in our sample, all the subjects with the c.1311C>T allele also had the 3′ UTR c.*+357A>G polymorphism. However, it is commonly accepted that the putative functional role of the c.1311C>T polymorphism in the enzyme activity needs to be further clarified.

With this study, the authors intend to contribute to the knowledge of the mutational profile of G6PD deficiency in the Portuguese population, which, in addition to the anthropological and populational interest, may contribute towards a better understanding of the pathophysiology of the disease and greater diagnostic suspicion, especially in the presence of chronic hemolytic anemia. In some severe class I variants, such as the Tondela variant, identification of the mutation allows for genetic counseling and prenatal diagnosis. All the pathogenic mutations identified and described to date in patients of Portuguese origin with G6PD deficiency are presented herein. While most mutations were the subject of previous publications, others, however, are described here for the first time in the Portuguese population. The lack of reliable records of the enzymatic activity of many individuals outside the acute episode does not allow a more detailed analysis of the correlation between the different mutations and G6PD activity.

CONCLUSION

There was a wide genetic heterogeneity of G6PD deficiency in the Portuguese population. The most common variant was G6PD A- (c.202A) (58.6%), followed by the Betica (c.968C) (12.1%) and Santamaria (c.542T) (4.2%). Although these mutations are present in the sub-Saharan African background haplotype c.376G, any African ancestry in the individuals of Portuguese origin observed here with these mutations is unknown. The study also depicted a set of rare variants, previously described in several human populations, five of them reported here for the first time in the Portuguese population. It should be noted that six of these rare variants were, as far as we know, only found in the Portuguese population: they are the G6PD variants Mira d'Aire (c.1048G>C), Anadia (c.1193A>G), Tondela (c.I1076-c.1094del), Covão do Lobo (c.1205C>A), Figueira da Foz (c.1366G>C) and Flores (c.1387C>A). The putative functional role of c.1311C>T polymorphism in G6PD-deficient

phenotype needs to be clarified.

AUTHOR CONTRIBUTIONS

LM: Conception and redaction of the work, data collection.

CB: Data collection, critical review of the work.

LR: Data collection.

TM: Clinical diagnosis.

MLR: Conception and critical review of the work, clinical diagnosis.

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

LM received funding for provision of laboratorial materials and support for attending meetings and/or travel from Fundação para a Ciência e Tecnologia - FCT (Institutional Grant: UIDB/00283/2020).

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CB, LR and TM have no conflicts of interest to disclose.

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A Case Series Study on Growth Hormone Therapy in Children with Prader-Willi Syndrome in Portugal

Estudo de Série de Casos sobre Terapia com Hormona de Crescimento em Crianças com Síndrome de Prader-Willi em Portugal

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ABSTRACT

Introduction: Prader-Willi syndrome is a multisystemic genetic disorder associated with shorter adult height. Nowadays, all paediatric Prader-Willi syndrome patients are considered for growth hormone treatment. We present the experience of this treatment at a Portuguese paediatric endocrinology unit and intend to emphasise the importance of creating a follow-up national network of these patients.

Material and Methods: Longitudinal, retrospective, analytical study of Prader-Willis syndrome patients using data between 1989 and 2021. Growth hormone therapy was offered to eligible patients. The analysis included all Prader-Willis syndrome patients, with a comparison between treated and untreated patients; a longitudinal analysis of patients receiving growth hormone therapy (baseline, 12 and 36 months of follow-up) was also carried out. The statistical analysis was carried out using STATA® v13.0.

Results: Out of 38 patients with Prader-William syndrome, 61% were male. The median age at diagnosis was four months and 61% received growth hormone therapy. The patients who reached adulthood, or 18 years old, had a median near-adult height, Z-score of −2.71, and their median body mass index indicated class 2 obesity, regardless of growth hormone therapy. Patients had a lower body mass index in the growth hormone group (35 *vs* 51 kg/m^2, $p < 0.042$) near-adult height.

Conclusion: This case series represents the first national study that included patients on growth hormone therapy after the National Health Service started supporting the treatment for Prader-Willi syndrome patients and supports its use, reinforcing the positive effects on growth and body mass index. Longer follow-up studies are needed to analyse the effect of growth hormone on patient metabolic profiling, body composition and cognitive level.

Keywords: Child; Human Growth Hormone/therapeutic use; Portugal; Prader-Willi Syndrome/drug therapy

RESUMO

Introdução: A síndrome de Prader-Willi é uma doença genética multissistémica associada a baixa estatura. Atualmente, todos os doentes pediátricos com síndrome de Prader-Willi são candidatos a terapia com hormona do crescimento. Apresentamos a experiência desta terapêutica numa unidade de Endocrinologia Pediátrica portuguesa e realçamos a importância de criar uma base de dados nacional de seguimento destes doentes.

Material e Métodos: Estudo longitudinal, retrospetivo e analítico de doentes com síndrome de Prader-Willi utilizando dados entre 1989 e 2021. A terapia com hormona de crescimento foi administrada aos doentes elegíveis. Foi realizada análise de todos os doentes com síndrome de Prader-Willi, com comparação doentes tratados/não tratados; foi também realizada uma análise longitudinal dos doentes sob hormona de crescimento (início/12/36 meses de seguimento). O tratamento estatístico foi realizado com recurso ao STATA® v13.0.

Resultados: De um total de 38 doentes com síndrome de Prader-Willi, 61% eram do sexo masculino. Idade média de diagnóstico quatro meses e 61% sob hormona de crescimento. Os doentes que atingiram a idade adulta apresentaram um *Z-score* de mediana de estatura alvo de -2,71, e índice de massa corporal obesidade nível 2, independentemente da terapêutica com hormona de crescimento. Os doentes apresentaram um índice de massa corporal menor no grupo tratado com hormona de crescimento (35 *vs* 51 kg/m^2, $p < 0,042$).

Conclusão: Este estudo de série de casos de doentes com síndrome de Prader-Willi tratados com hormona de crescimento é pioneiro a nível nacional desde a comparticipação deste tratamento pelo Sistema Nacional de Saúde português e apoia esta terapêutica, reforçando os seus efeitos positivos no crescimento e índice de massa corporal. Serão necessários estudos com seguimento mais prolongado para analisar o seu efeito no perfil metabólico, composição corporal e cognição.

Palavras-chave: Criança; Hormona do Crescimento Humano/uso terapêutico; Portugal; Síndrome de Prader-Willi/tratamento farmacológico

INTRODUCTION

Prader-Willi syndrome (PWS) is a multisystemic genetic disorder that occurs in approximately 1/10 000 – 30 000 live births.[1] The prevalence of the disorder is similar in both males and females.[2] PWS is associated with a loss of expression of paternal alleles in the PWS region of chromosome 15.[3] In 70% of cases, PWS is caused by a non-inherited paternal deletion in the region 15q11-q13. Twenty-five per cent occur by maternal uniparental disomy of the chromosome (two chromosome 15 inherited from mother and none chromosome 15 inherited from father), 15.3% by genomic imprinting defects, and the last 2% of cases are caused by rare translocations.[3] In the past, the diagnosis

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was usually made only after the onset of hyperphagia and obesity – the most common features of this syndrome – but currently it is frequently diagnosed during the neonatal period with confirmation by a genetic test.[4]

The clinical signs and symptoms of PWS vary by age group. During pregnancy, it is not uncommon to detect some abnormalities such as decreased foetal activity, polyhydramnios and abnormal position of the extremities (elbows in flexion and feet in dorsal extension).[2] During the neonatal period and the first months of life, the most common features are severe hypotonia, feeding difficulties, weak crying, growth retardation, genital hypoplasia (cryptorchidism, scrotal and clitoral hypoplasia), among many other signs and symptoms.[2] Hyperphagia and subsequent obesity (unless a restrictive diet is implemented) are the main characteristics of these patients during childhood. Other common findings are decreased muscular mass, increased body fat, developmental delay, temperature instability, decreased pain sensitivity, respiratory problems such as central or obstructive apnoea, scoliosis and behavioural problems such as hiding or stealing food, as well as taking food out of the trash.[1,2] Adolescence is a period characterised by compulsive eating and an increase in weight with a high prevalence of morbid obesity and related complications such as obstructive sleep apnoea syndrome, *cor pulmonale*, diabetes *mellitus*, atherosclerosis, hypertension and hepatic steatosis.[1,2] Neurodevelopmental and psychiatric features such as cognitive impairment, skin picking, maladaptive behaviour including a high propensity to psychosis and self-injury may be seen.[1,2] All these characteristics plus the delayed onset of puberty seem to be related with a complex hypothalamic dysfunction.[1] A typical pattern of growth may be noted, with approximately half of the newborns being small for gestational age, with a later decline in growth velocity culminating in a shorter adult height.[1]

In the early 1990s, a treatment for PWS patients was recommended for those with confirmed growth-hormone (GH) deficiency.[2] Human recombinant GH was introduced with the aim of improving linear growth, body composition, and bone density in children with PWS. Treatment not only improved the lipid profile and measures of physical performance but also benefitted cognitive and motor development. Currently, children with PWS should all be considered for treatment with GH without a prior need to test for GH deficiency, provided they meet the clinical criteria for growth failure. Situations that preclude starting therapy are related to comorbidities such as severe obesity, uncontrolled diabetes *mellitus*, untreated severe obstructive sleep apnoea (OSA), active cancer, non-alcoholic hepatitis, psychosis and severe scoliosis.[2,4] With the purpose of excluding these conditions, PWS patients are required to have normal findings upon otorhinolaryngology and orthopaedic examination and a polysomnography test prior to starting therapy.

Until 2010, due to a lack of coverage from the National Health Service (NHS) in Portugal, GH treatment for PWS children would only be given to those with confirmed GH deficiency. Since then, the Portuguese NHS has fully sponsored GH treatment for all eligible PWS patients after the approval of an expert committee.

Regarding the start of GH therapy, evidence suggests that greater effects are seen in the first years of life, thus recommending the introduction of therapy as early as four to six months of age and before age of two.[5] Consensus guidelines recommend starting GH at a dose of 0.35 to 0.5 mg/m^2/day for infants and children based on their body surface area. Subsequent increments in dosage should be made up to approximately 1 mg/m^2/day, titrating dosage to achieve an optimal IGF-1 target in the upper part of the normal range for age.[5]

Once treatment has been started, a close follow-up of comorbidities should be kept, particularly if patients develop intercurrent upper respiratory tract infections or increased obstructive symptoms. Suspension of treatment should be considered if marked worsening of obesity, OSA, metabolic profile or scoliosis occurs.[6]

Given the confirmed benefits of GH therapy in children with PWS, we present a case-series study on the experience of GH treatment in PWS patients at a Portuguese paediatric endocrinology unit of a tertiary hospital. Furthermore, we intend to emphasise the importance of creating a network for the follow-up of PWS patients at the national level.

MATERIAL AND METHODS

Study design and sample

A longitudinal, retrospective, analytical study was performed at a paediatric endocrinology unit of a tertiary hospital in Lisbon. This study included 38 patients with the diagnosis of PWS. GH therapy was offered to eligible patients. Clinical data were collected by reviewing patient medical records from 1989 to 2021.

The study was divided into two sections. The first addressed clinical data at the point of PW diagnosis, comorbidities, growth patterns at birth and inclusion criteria for the start of GH therapy. Growth pattern standards at birth were obtained by using the Fenton growth charts.[7] A comparison between the subgroups of treated and untreated patients was also performed.

The second section comprised a longitudinal analysis of growth patterns and laboratory markers on lipid profiling in patients receiving GH therapy. Clinical and laboratory data were collected at the beginning of GH therapy (baseline) and then at 12 and 36 months of follow-up. Intention-to-treat was applied. Whenever significant comorbidities were seen during GH treatment, patients were

discontinued from therapy. Growth standards in this section were obtained using the World Health Organization growth reference charts.[8] The predicted child's near-adult height based on mid-parental height was calculated using Tanner's standards of growth. Laboratory reference values for lipid profiling were applied according to the NCEP/NHANES III study,[9] in which borderline values of total cholesterol levels range from 170 - 190 mg/dL, triglycerides 75 - 129 mg/dL, LDL cholesterol 110 - 129 and HDL cholesterol 40 - 45 mg/dL.

Data analysis

A descriptive analysis was initially performed and followed by a bivariate analysis comparing patients on or off GH therapy. Continuous data with a normal distribution were presented as mean ± standard deviation, and group comparisons were performed using a Student's *t*-test. Continuous data with non-normal distribution were presented as median with interquartile ranges and compared across groups using the Wilcoxon rank-sum test. Categorical variables were presented as percentages and compared across groups using a Pearson chi-square test.

We next proceeded to use descriptive longitudinal analysis to compare growth patterns and the lipid profiling work-up from the baseline up to 36 months after the beginning of GH therapy. Two-sided *p*-values < 0.05 were used for statistical significance. Statistical analysis was conducted using STATA® v13.0.

RESULTS

Baseline characteristics

Of the 38 patients with PWS, 61% were male. The median age at diagnosis was four months (IQR 1 - 18), and the most commonly described genetic anomalies were maternal uniparental disomy (50%) followed by paternal deletion of chromosome 15 (32%). The most common clinical findings in these patients were hypotonia (37/38), feeding disturbances (23/38), undescended testis (15/38) and neurodevelopmental impairment (10/38); [see Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17559/Appendix_01.pdf)]. At birth, the mean gestational age was 37 ± 3 weeks and both weight and height averages were within normal standards (Table 1). Patients' comorbidities varied widely but the most frequently assessed were OSA (13/38), cognitive impairment (13/38), aggressiveness/impulsiveness disorders (10/38) and undescended testis (8/38); [see Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17559/Appendix_01.pdf)]. From all the PWS children, 23 (61%) were deemed eligible to receive GH therapy. The average age when beginning therapy was 9.8 ± 4.9 years. The patients who reached adulthood, that is, 18 years old, within the time of the study had a median near-adult height, Z-score of −2.71 (IQR −3.34; −2.00), and their median body mass index (BMI) indicated class 2 obesity (37.6 kg/m^2) regardless of GH therapy (Table 2).

Table 1 – Clinical characteristics of PWS patients (n = 38)/PWS patients on GH therapy (n = 23)

Sex, %	
Female	39.5
Male	60.5
Gestational age, weeks	37 ± 3
Birth weight, Z-score	−1.25 ± 0.64
Birth height, Z-score	−0.64 ± 0.93
Age at diagnosis, months	4 (1;18)
Genetic abnormalities, %	
Maternal uniparental disomy	50.0
Paternal deletion of Chr. 15	32.3
Unknown	17.7
Age at beginning of therapy, years	9.8 ± 4.9
Dose of GH, mg/m^2	
Baseline	0.28 ± 0.18
12-months	0.56 ± 0.25
36-months	0.52 ± 0.24
BMI at beginning of adulthood (18 years-old), kg/m^2	37.60 (31.70; 43.20)
Near-adult height, Z-score	−2.71 (−3.34; −1.99)

Data are reported with mean +/-standard deviation, or median and interquartile range (IQR). Categorical variables were presented as percentages.

Table 2 – Bivariate analysis comparing Prader–Willi patients according to GH therapy

	Patients w/o GH therapy (n = 15)	Patients with GH therapy (n = 23)	*p*
Age at diagnosis (months)	3.5 (1; 26)	4 (1 – 18)	ns
Sex (male, %)	46.7	69.6	ns
Gestational age (weeks)	39 (35; 40)	36 (34 – 39)	0.047
Birth weight, Z-score	−1.53 (−1.93; −1.20)	−1.07 (−1.44, −0.70)	0.031
Birth length, Z-score	−1 (−2.10; −0.50)	−0.15 (−0.80; 0)	0.007
Body mass index at adult age (kg/m^2)	50.7 (38; 58)	35 (30; 41)	0.042
Difference between mid-parental height and near-adult height (cm)	19.12 ± 11.59	13.97 ± 8.27	ns

Data are reported with median + interquartile range (IQR) and mean ± standard deviation. Group comparisons in non-normal data were performed using Wilcoxon Rank sum test, while in normal data Student *t*-test was used. Categorical variables were presented as percentages and compared across groups using a Pearson chi-square test.
ns: non-significant

Bivariate analysis

At the bivariate level, although there were no significant differences between groups regarding gender, a higher trend towards male patients was noted in the GH therapy group (70% *vs* 40%). Conversely, significant findings were found in the GH therapy group, with these patients being more premature (36 weeks *versus* 39 weeks, $p < 0.047$) and having better Z-scores in weight and height at birth (although still within normal standards). We also found that patients who had reached their final height had a significantly lower BMI in the GH group (35 *vs* 51 kg/m^2, $p < 0.042$). In the group of patients who reached the final height, those who had been on GH therapy differed less from their mid-parental near-adult height (13.90 *vs* 19.10 cm), though the results were not statistically significant (Table 2). In our sample, 14 of 23 patients treated with GH reached their final height, whereas five of 15 untreated patients reached their final height.

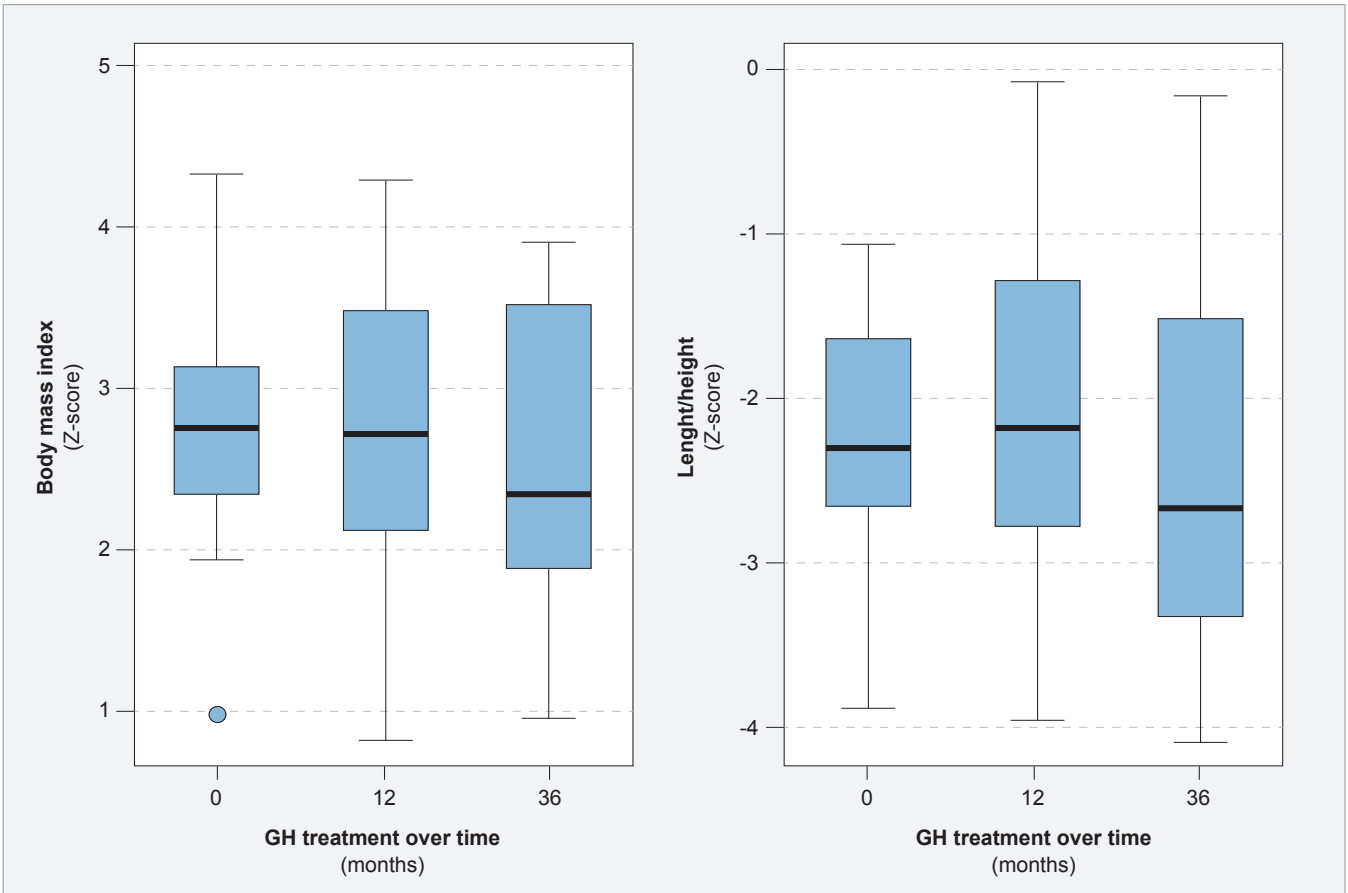

Figure 1 – Body mass index and length/height variations in PWS patients treated with GH

Longitudinal descriptive analysis: GH therapy group

In those who were treated with GH, the average age at the beginning of therapy was 9.8 ± 5 years. As per the protocol, GH was incrementally increased over time with a starting mean dosage of 0.28 ± 0.20 mg/m²/day, increasing to 0.52 ± 0.24 mg/m²/day at 36 months. Although the variables examined did not yield significant differences at the different time points of consultation, some considerations were noteworthy. In particular, BMI Z-scores seemed to follow a downward trend over time (2.76 to 2.35), whereas the trend in height leaned towards a worsening short stature (−2.30 to −2.76), as seen in Fig. 1. Regarding the lipid profile workup, changes over time in total cholesterol, LDL-cholesterol and triglycerides appeared to follow an upward trend (see Table 3), although values were still within the reference range, as seen in Figs. 2 and 3. In contrast, median HDL cholesterol values seemed to be falling over time.

Of the 23 patients who underwent GH therapy, eight

Table 3 – Longitudinal analysis of growth characteristics and lipid workup of PWS patients that were started on GH therapy

	Baseline (n = 23)	12-month follow-up (n = 18)	36-month follow-up (n = 15)	*p*
BMI Z-score	2.76 (2.34; 3.14)	2.72 (2.13; 3.49)	2.35 (1.88; 3.51)	ns
Height Z-score	−2.30 (−2.67; −1.64)	−2.18 (−2,79; −1.29)	−2.67 (−3.33; −1.52)	ns
Total cholesterol, mg/dL	167 (144; 180)	173 (149; 195)	180 (165; 191)	ns
Triglycerides, mg/dL	64 (52; 78)	73 (43; 56)	94 (52; 107)	ns
HDL-cholesterol, mg/dL	48 (42; 57)	51 (43; 56)	47 (43; 52)	ns
LDL-cholesterol, mg/dL	102 (84; 118)	115 (85; 125)	118 (90; 121)	ns

Data are reported with median and inter-quartile range (IQR); group comparisons were performed using Wilcoxon rank sum test.
ns: non-significant

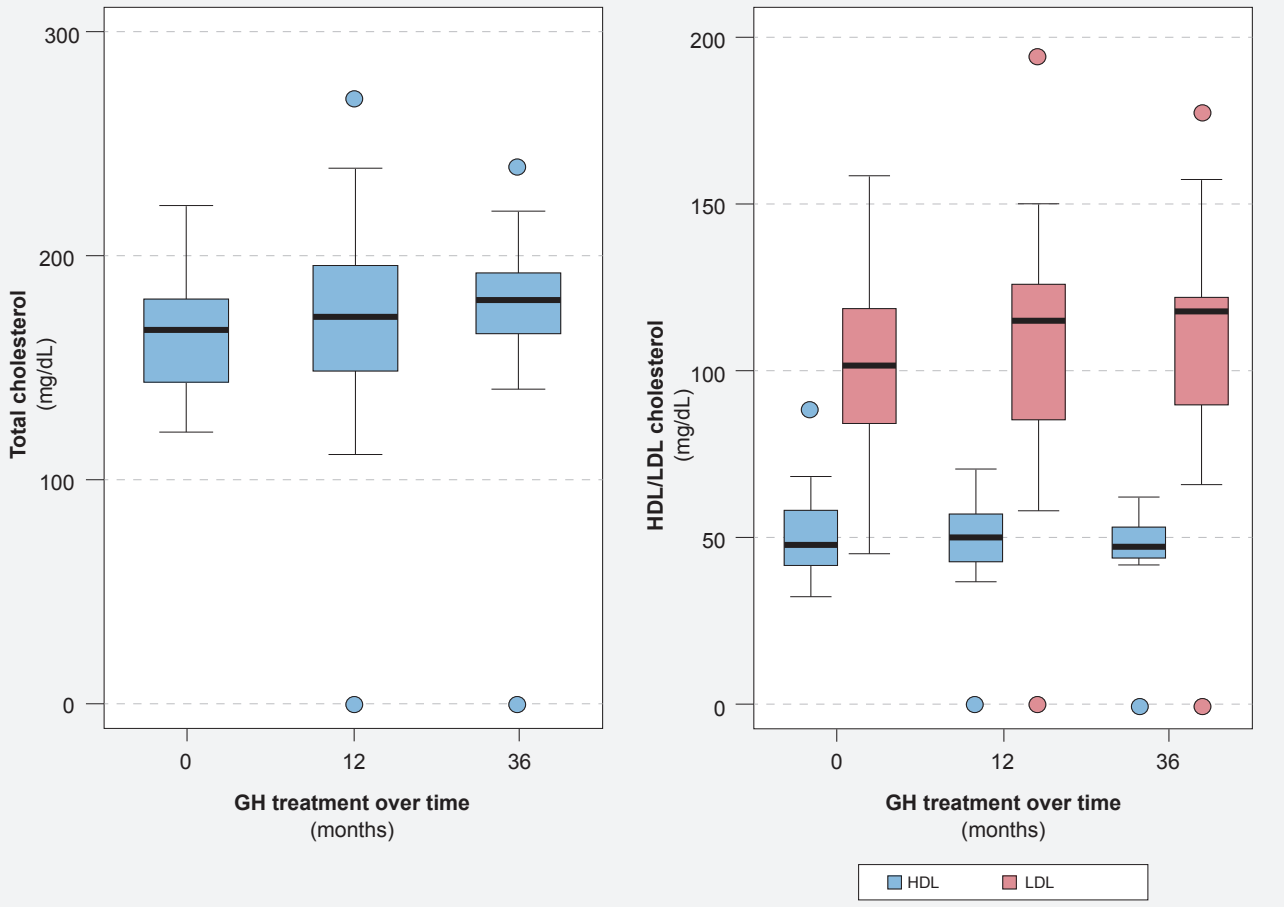

Figure 2 – Cholesterol level variations in PWS patients treated with GH

discontinued treatment due to various reasons such as sleep apnoea, development of type 2 diabetes *mellitus*, retinopathy, parental choice or having reached final height.

DISCUSSION

The findings in this study regarding PWS patients are in agreement with previous studies in the literature, namely, there was no gender predominance,[2] average age at diagnosis was similar[4] and predominant genetic abnormalities were the same.[3] An association of PWS with late prematurity may be related with complications that can occur during pregnancy such as decreased foetal activity, polyhydramnios, intrauterine growth restriction, breech presentation and abnormal position of the hands and feet (flexed elbows and feet in plantar flexion) during third-trimester ultrasonography.[2,10,11] These features may contribute to deliveries at an earlier gestational age. Nonetheless, in our case series, most deliveries occurred at gestation term, and birth weight and length agreed with reference values for the general population.

The early infancy period in PWS patients is dominated by muscular hypotonia with feeding difficulties and failure to thrive, followed in later infancy or early childhood by excessive appetite, leading to obesity.[1] As the condition is associated with changes in body composition such as decreased muscular mass, increased body fat and short stature,[12] it was unsurprising to find that all our patients had an increased BMI, indicating obesity. Those who reached final height were all also well below the reference values for the general population. Related to obesity, PWS patients are at a high risk of sleep-related disturbances, including OSA. These morbidities can manifest in up to 70% of PWS patients and may be associated with daytime sleepiness and behavioural disturbances.[13] About two-thirds of boys with PWS will display undescended testis, most likely related with hypogonadism – a universal feature of PWS. The majority of PWS patients are infertile.[14]

Neurodevelopmental delay and behavioural problems are also common findings of PWS.[2] Mental and motor retardation are almost always present and the intelligence quotient is generally 40 points below the mean values of the population.[2] PWS is also associated with a hypothalamic-hypophyseal function disorder and the patients should be investigated for central hypothyroidism and hypophyseal adrenal insufficiency at the time of diagnosis.[2] The vast majority of the clinical findings present in our patients are in agreement with the description above, particularly in regard to hypotonia, feeding disturbances, undescended testis and neurodevelopmental impairment. The most frequently assessed comorbidities were OSA, cognitive impairment, aggressiveness/impulsiveness disorders and undescended testis, which is also in line with the literature described above.

In our case series, 15 (39%) patients did not undergo treatment with GH due to a few specific situations, namely, treatment not being covered by the Portuguese National Health Service before 2010 and the presence of severe comorbidities.

Concerning body composition, we noticed a significant decrease in BMI in the GH-treated patient group, which was also described in previous studies. For instance, Aycan *et al*[2] showed an improvement of body composition, basal energy consumption, muscle strength, exercise tolerance and decreased fat mass in PWS children following therapy with GH. Additionally, although not statistically significant, the difference between mid-parental near-adult height and final height in those who reached final height by the end of our study was lower in the GH-treated group, meaning these patients were closer to their mid-parental near-adult height than the untreated patients. These findings also support the likely beneficial effect of this therapy on final stature.[12] The therapeutic dose increment was performed according to current guidelines (final dose of 1 mg/m²/day to be reached in the first weeks to months after a progressive

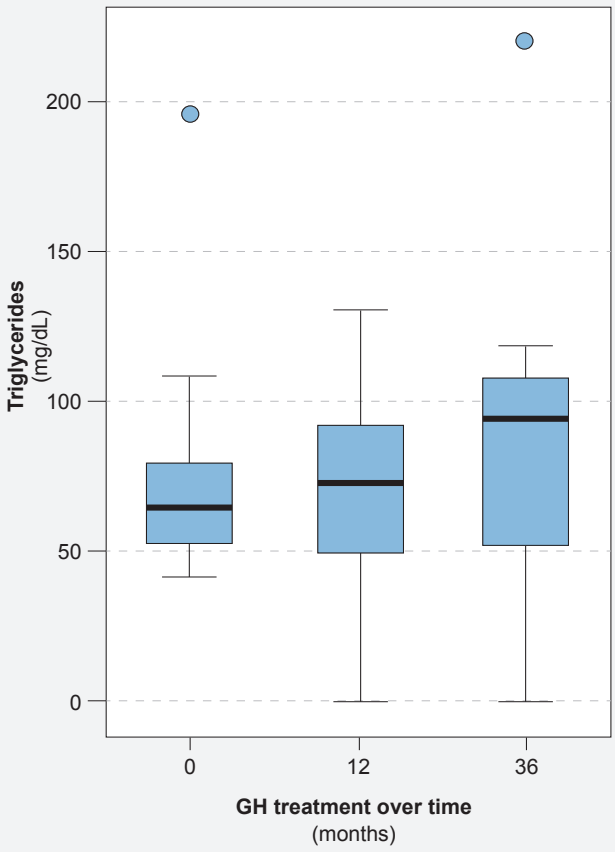

Figure 3 – Triglyceride level variations in PWS patients treated with GH

dose escalation).[3]

As expected, a downward trend in BMI was seen for GH-treated patients over the period of 36 months of treatment. However, this was not seen for stature, which seemed to worsen over the same period. This fact was contrary to what has been described in the literature.[3] A possible explanation may be that the average age at the beginning of GH therapy, which is later than the current guidelines that recommend an early introduction before two years of age, was decisive for therapeutic efficacy.[3] Moreover, the treatment follow-up time in our study (maximum 36 months) may not have been enough to show positive results for stature.

Regarding lipid profile, a slight increase in cholesterol and triglyceride levels was noticed over time, though not exceeding normal reference values. This trend was contrary to what has been described in previous studies.[2,15] A few confounders may contribute to these results, such as worsening of the compulsive eating behaviours that are characteristic of this condition,[12] and a lack of comparison with untreated patients who might have followed a different trend.

To the best of our knowledge, this case series represents the first national study that included patients on GH after the National Health Service started supporting the treatment for all eligible PWS patients. One of the strengths of this study is the detailed demographic and clinical characterisation of patients with PWS followed at one of the largest national referral centres. Despite these results demonstrating an overall benefit of GH on BMI in PWS children, other studies are needed to observe the effect of GH on patients' metabolic profiling, other aspects of body composition (body fat and muscle mass) and cognitive level.

The limitations of our study include the use of retrospective data, a higher chance of information bias, limited access to PWS patients probably due to the rarity of the disease or to undiagnosed or misdiagnosed cases, and the short time of follow-up of treated patients (maximum 36 months).

Future studies should examine prospective comparisons between treated and untreated PWS patients and include other factors such as biometric (serial impedance assessment), clinical (cognitive impairment severity) and laboratory (fasting glucose, haemoglobin A1c) parameters that were not addressed in this study.

On a final note, the present study helped advance the creation of a Portuguese nationwide database of PWS patients with the aim of expanding clinical knowledge and including the experience of other clinical centres.

CONCLUSION

This study supports GH therapy in patients with PWS, reinforcing the positive effects on growth and BMI. Other prospective studies with a longer follow-up period should be performed to evaluate other benefits of GH therapy. Based on this study, a nationwide database is being created to effectively monitor the follow-up data of patients with PWS.

AUTHOR CONTRIBUTIONS

All authors contributed to the literature research, study conception and design, data collection, analysis and interpretation, drafting of the article, version review, critical review of the article's content and approval of the final version.

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

All authors report no conflicts of interest.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Salmonellosis in Children at a Portuguese Hospital: A Retrospective Study

Salmoneloses em Crianças num Hospital Português: Um Estudo Retrospetivo

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ABSTRACT

Introduction: Salmonellosis represents a considerable health, social and economic burden in both high- and low-income countries. Recently, in Portugal, most cases of *Salmonella* infections have been reported in children under 15 years of age. The main aim of this study was to characterize, from an epidemiological, microbiological, and clinical perspective, cases of *Salmonella* isolation among children.

Material and Methods: The authors performed a descriptive study using retrospective analysis of cases of salmonellosis, in pediatric age, at a Portuguese Level II Hospital, between January 2015 and July 2020.

Results: The population included a total of 63 children, of which 81% were Portuguese. Ethnicity was identified in 13 children, most of whom were African. The median age at diagnosis was four years old (3.5 - 9 years old). Despite the small number of cases per year in our study (11), one-third were severe enough to require hospitalization. Overall, 13% of patients were treated with antibiotics. In 63% of the isolates, serotype was identified: *Salmonella enteriditis* (38%), *Salmonella typhimurium* (22%), and *Salmonella typhi* (3%). Antibiotic resistance rates were 19% for ampicillin and 6.4% for amoxicillin-clavulanic acid and cotrimoxazole. No resistance to third-generation cephalosporins was found.

Conclusion: Given the obtained results, we intend to improve knowledge on salmonellosis in Portugal and, consequently improve prevention strategies, treatment and its notification. Although the incidence of salmonellosis has been decreasing in recent years it is the second most frequent gastrointestinal infection in the European Union, contributing to significant rates of hospitalizations and use of antibiotics in Portugal.

Keywords: Child; Portugal; Salmonella enterica; Salmonella Infections; Typhoid Fever

RESUMO

Introdução: As salmoneloses representam um desafio do ponto de vista sanitário, social e económico, tanto nos países em desenvolvimento como nos desenvolvidos. Nos últimos anos, em Portugal, a maioria das infeções por *Salmonella* foi reportada em crianças com menos de 15 anos. O objetivo principal deste estudo foi caracterizar, do ponto de vista epidemiológico, microbiológico e clínico, os casos de isolamento de *Salmonella* em crianças.

Material e Métodos: Estudo descritivo com análise retrospetiva dos casos de salmonelose em idade pediátrica, no período compreendido entre janeiro de 2015 e julho de 2020, num Hospital Português de nível II.

Resultados: A população incluiu 63 doentes, dos quais 81% eram portugueses. A origem étnica foi identificada em 13 crianças, sendo a maioria africana. A idade média de diagnóstico foi quatro anos (3,5 - 9 anos). Apesar do reduzido número de casos por ano no nosso estudo (11), um terço destes foi suficientemente grave para necessitar de hospitalização e 13% dos pacientes foram tratados com antibióticos. Em 63% dos isolamentos identificou-se o serotipo: *Salmonella enteriditis* (38%), *Salmonella typhimurium* (22%) e *Salmonella typhi* (3%). As taxas de resistência aos antibióticos foram de 19% para ampicilina e 6,4% para amoxicilina-ácido clavulânico e cotrimoxazol. Não se identificaram resistências às cefalosporinas de terceira geração.

Conclusão: Com os resultados obtidos pretendemos melhorar o conhecimento sobre as salmoneloses em Portugal e consequentemente as estratégias de prevenção, tratamento e notificação. Embora a incidência de salmoneloses tenha vindo a diminuir nos últimos anos, estas são a segunda causa mais frequente de infeção gastrointestinal na União Europeia, contribuindo para uma importante taxa de hospitalizações e de uso de antibióticos em Portugal.

Palavras-chave: Criança; Febre Tifoide; Infecções por Salmonella/tratamento farmacológico; Portugal; Salmonella entérica

INTRODUCTION

Salmonella, a member of the *Enterobacteriaceae* family, includes two species - *Salmonella enterica* and *Salmonella bongori* (rarely opportunistic in humans). Based on biochemical and antigenic characteristics, *Salmonella enterica* is further divided into subspecies (I – VI) and serotypes.[1] The serotypes *Salmonella* ser. *typhi* and *paratyphi* are categorized as typhoidal *Salmonella* whereas other serotypes are grouped as Non-typhoidal *Salmonella,* and include *Salmonella* ser. *typhimurium* and *Salmonella* ser. *enteritidis*.[1] Typhoidal *Salmonella* and non-typhoidal *Salmonella* cause different clinical syndromes.

Salmonella infections represent a considerable health, social and economic burden in both high- and low-income countries, with their incidence being much higher than the cases reported.[1] In Portugal, from 2011 to 2014, 785 cases of *Salmonella* infection have been reported, 83% of which in children under 15 years of age.[2]

The main mode of transmission of non-typhoidal *Salmonella* is by ingestion of contaminated animal food products, contact with colonized animals, consumption of contaminated water and non-animal food products, and fecal-oral spread; incubation is typically six to 12 hours.[3] In high-income countries, in immunocompetent individuals, Non-typhoidal *Salmonella* usually causes bacterial acute gastroenteritis, with secondary bacteremia occurring in up to 5% of patients.[4,5] They typically experience self-limited enterocolitis with nausea, emesis, abdominal pain, fever, and watery non-bloody diarrhea (some patients may have painless

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bloody diarrhea) lasting less than 10 days.[3] However, young infants and people with immunosuppressive conditions, hemoglobinopathies (including sickle cell disease), malignant neoplasms and human immunodeficiency virus infection are at a higher risk of invasive disease, including bacteremia, meningitis, osteomyelitis, septic arthritis, pneumonia, and cholangitis.[1,6] Also, in low-income countries, there is increased recognition of non-typhoidal *Salmonella* as a major cause of severe febrile illness.[4] Bacterial fecal shedding can continue for up to 12 weeks, especially in children younger than five years and in those treated with antibiotics.[3]

Enteric fever caused by typhoidal *Salmonella* is a severe illness with an estimated 31 million cases leading to more than 215 000 deaths worldwide annually.[3] Typhoidal *Salmonella* is predominantly transmitted through contaminated water or food with human feces. In contrast to non-typhoidal *Salmonella,* that has a worldwide distribution, typhoidal *Salmonella* infection is endemic in low-income countries, where poor sanitation and lack of access to safe food and water is an unfortunate reality.[4,5]

With exclusive human reservoirs and fecal-oral transmission, the average incubation period of typhoidal *Salmonella* is seven to fourteen days. Clinical manifestations include fever, chills, slow heart rate (more common in adults), headache, malaise, anorexia, lethargy, myalgia, cough, abdominal pain and tenderness, jaundice, hepatosplenomegaly, constipation or diarrhea, “rose spots” (faint salmon-colored macules on the trunk and abdomen), dactylitis and, in severe cases, altered mental status and shock.[3,6] These symptoms typically last two to four weeks without treatment.[3] Typhoid fever can also be associated with the following complications: terminal ileal perforation, splenic abscesses, disseminated intravascular coagulation, rhabdomyolysis with acute renal failure and neurologic manifestations due to brain abscesses or Guillain-Barré syndrome.[3] Stool bacterial shedding continues for more than three months in approximately 10% of cases.[3] In 4% of the infected individuals, excretion lasts longer than one year.[3] When this occurs, it is assumed they are chronic carriers of typhoidal *Salmonella*. The predisposition to be a chronic carrier increases with age, being rare in children, and correlates with the prevalence of cholelithiasis, which might require a cholecystectomy, due to gallbladder biofilm formation.[3,6]

While in non-typhoidal *Salmonella* infections, stool culture is typically sufficient for the diagnosis of gastroenteritis, extraintestinal involvement must be confirmed by cultures from the affected organs. Blood cultures (or bone marrow cultures) are required for diagnosing typhoidal *Salmonella* infection, with repeated cultures often needed due to low sensitivity.

Non-typhoidal *Salmonella* gastroenteritis is treated with supportive measures in immunocompetent individuals.[5] However, gastroenteritis in infants younger than three to six months, immunocompromised patients, suspected or confirmed non-typhoidal *Salmonella* invasive disease, should receive antibiotic treatment.[1,5,6] Third-generation cephalosporins (ceftriaxone or cefotaxime) are indicated for extraintestinal non-typhoidal *Salmonella* disease and typhoidal *Salmonella* (five to seven days for gastroenteritis, two weeks for bacteremia, and four to six weeks for extraintestinal infections).[3] Because antibiotic resistance against *Salmonella* is increasing, local susceptibility patterns should be taken into account. Chronic typhoidal *Salmonella* carriers should be treated with four weeks of an oral fluoroquinolone after the initial treatment.[3]

The main aim of this study was to characterize, from an epidemiological, microbiological, and clinical perspective, cases of *Salmonella* isolation among children.

MATERIAL AND METHODS

This study sample encompasses the cases of isolation of *Salmonella* in fecal and/or blood cultures in the pediatric population of this hospital from 2015 to 2020. This was a descriptive, retrospective study, developed in the pediatric department of a level II hospital, in the Lisbon metropolitan area. Data on socio-demographics, epidemiological, and clinical characteristics, diagnostic tests, treatment, evolution and preventive measures were collected from the observation of the clinical records of patients.

Microbiological methods used for the diagnosis of *Salmonella* infection included culture of clinical specimens on selective culture media, colony identification and antimicrobial susceptibility testing using the automated VITEK® 2 System (bioMerieux) with interpretation according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints and further classification with serological tests. Descriptive and statistical analysis was performed with SPSS® v.23.0 (SPSS Inc, Chicago, IL, USA).

The study was approved by the hospital ethics committee. All the data collected was aggregated and thus anonymous and confidential.

RESULTS

The population included a total of 63 children, of whom 36 (57.1%) were boys (Table 1). The majority was Portuguese (n = 51; 81%). Ethnicity was assessed in 13 children, most of whom African (n = 9; 69.3%), followed by Caucasian (n = 3; 4.8%) and Indian (n = 1; 1.6%). It was only possible to determine the parents’ origin in 14 children, with Guinea-Bissau being the most frequent place of birth (n = 4; 6.4%), followed by Brazil (n = 3; 4.8%), Cape Verde and Angola (n = 2; 3.2%, each) and finally Portugal, Belgium, and India (n = 1; 1.6%, each).

Table 1 – Results obtained for the variables analyzed in the study (part 1 of 2)

Socio-demographic characteristics				
Gender	**Male**	**Female**		
Absolute number (relative frequency)	36/63 (57.1%)	27/63 (42.9%)		
Epidemiologic context				
Age of diagnosis	**Median**	**Interquartile range**	**Average**	
Years old	4	3.5 – 9	5.9	
Cases per year	**Median**	**2015**	**2017**	**2018**
Absolute number (relative frequency)	11	14 (22.2%)	14 (22.2%)	6 (9.5%)
Nursery/school	**Contact with suspected cases**	**No know contacts**	**No data**	
Absolute number (relative frequency)	3 (10.3%)	5 (17.2%)	21 (72.5%)	
Intra-family contacts	**Siblings**	**Several family members**	**Parents**	**Cousins/ Grandparents** (each)
Absolute number (relative frequency)	8 (25.8%)	6 (19.4%)	4 (12.9%)	2 (6.5%)
Contaminated food	**Milk and eggs**	**Unidentified food**	**Unknown**	
Absolute number (relative frequency)	2 (3%)	10 (16%)	51 (81%)	
Recent trips	**Guinea-Bissau / Angola** (each)	**São Tomé and Príncipe / Brazil / India / Morocco** (each)	**Unidentified destination**	
Absolute number (relative frequency)	2 (11.8%)	1 (5.9%)	9 (52.9%)	
Clinical features				
Diagnosis	**Acute gastroenteritis**	**Occult bacteremia**		
Absolute number (relative frequency)	55 (87.3%)	6 (9.5%)		
Risk factors	**None**	**HIV infection / Prematurity / Unspecified cardiac disease / Down syndrome** (each)		
Absolute number (relative frequency)	59 (93.7%)	1 (1.6%)		
Hospitalization	**Total**	**Median age of hospitalized group**	**Median age of non-hospitalized group**	
Absolute number (relative frequency)	37 (58.7%)	7 years old (interquartile range 3 – 10.5 years)	3 years old (interquartile range 1.6 – 5.5 years)	
Analytical evaluation				
Leukocytes	**Leukopenia** (< 4500/L)	**Leukocytosis** (> 15 000/L)		
Absolute number	4	7		
C-reactive protein	**< 5 mg/dL**	**5 – 15 mg/dL**	**15 – 25 mg/dL**	**> 25 mg/dL**
Absolute number	20	23	9	2
Electrolyte imbalance	**Hyponatremia** (< 135 mmol/L)	**Hypernatremia** (> 145 mmol/L)	**Hypokalemia** (< 3.5 mmol/L)	**Hyperkalemia** (< 4.5 mmol/L)
Absolute number	3	1	6	9
Complications	**Total**	**Dehydration**	**Metabolic alkalosis**	
Absolute number (relative frequency)	24 (38.1%)	22/24 (91.7%)	2/24 (8.3%)	

(Table 1 ends on next page)

Table 1 – Results obtained for the variables analyzed in the study (part 2 of 2)

Microbiological characteristics				
Samples with *Salmonella* isolation	**Stool culture**	**Blood culture**	**Stool + blood culture**	**Blood + urine culture**
Absolute number (relative frequency)	57 (90.5%)	2 (3.2%)	3 (4.8%)	1 (1.6%)
***Salmonella* enterica serotypes**	***Salmonella typhi***	***Salmonella typhimurium***	***Salmonella enteritidis***	
Absolute number (relative frequency)	2 (3%)	14 (22%)	24 (38%)	
Resistance rates by serotype (relative frequency)	***Salmonella typhi***	***Salmonella typhimurium***	**Non-typhoidal *Salmonella***	
Ampicillin		14.3%	5%	
Amoxicillin-clavulanic acid	None	5%	< 5%	
Cotrimoxazole		< 5%	< 5%	
Treatment and follow-up				
Treatment	**Symptomatic**	**Antibiotic therapy**		
Absolute number (relative frequency)	55 (87.3%)	8 (12.7%)		
Collected new stool samples	**Total**	**Negative**	**Time after diagnosis** (on average)	
Absolute number	12	12	3.5 months	

The median age at diagnosis was four years old (interquartile range 3.5 – 9 years old) and the average was 5.9 years old (Table 1). The age group under five years was the one with most cases (n = 32; 50.8%; Fig. 1).

There was a median of 11 cases per year in the study period, with a variation from 14 cases per year (22.2%) in 2015 and 2017 and only six in 2018 (9.5%). The months of May (n = 9), June (n = 8) and September (n = 7) had the highest number of cases (Fig. 2).

Regarding the epidemiological context of the 29 children attending nursery or school, only three (10.3%) had contact with suspected cases, five (17.2%) had no known contacts and it was not possible to obtain data for the remaining children (Table 1). Concerning intra-family contacts, we obtained data from 31 children, of whom eight (25.8%) had contact with sick siblings, six (19.4%) had contact with several symptomatic family members (degree of kinship not specified); four (12.9%) had contact with parents; and two (6.5%) had contact with cousins or grandparents, respectively (Table 1). Combining data obtained from contacts with suspected cases in school and within their families, 39 children (64.1%) had contact with symptomatic patients, the majority in a family context (n = 22). Regarding potentially contaminated food, we obtained data from 12 children and in two (3%) the ingestion of contaminated milk and eggs was confirmed (Table 1). Concerning recent trips, data was retrieved from 17 children: two (11.8%) had been to Guinea-Bissau, two (11.8%) to Angola and the others had traveled to São Tomé and Príncipe, Brazil, India, and Morocco (5.9% each) – Table 1.

The most frequent initial diagnosis was acute gastroenteritis (n = 55, 87.3%) followed by occult bacteremia (n = 6, 9.5%) – Table 1. The remaining children presented with another diagnosis (urinary tract infection and fever with petechial rash). Most children had no risk factors (n = 59, 93.7%) while the others had HIV infection, prematurity, unspecified cardiac disease, and Down syndrome (n = 1, 1.6% each) – Table 1. No child had hemoglobinopathy.

Hospitalization was required in 37 children (58.7%), of whom 83.8% had acute gastroenteritis with signs of dehydration. The median age between the hospitalized *versus* the non-hospitalized groups, was seven years old (interquartile range 3 – 10.5) *versus* three years old (interquartile range 1.6 – 5.5), respectively (Table 1).

Regarding the analytical evaluation, the authors highlight: leukopenia (< 4500/L) in four patients and leukocytosis (> 15 000/L) in seven; C-reactive protein < 5 mg/dL in 20 children, between 5 – 15 mg/dL in 23, 15 – 25 mg/dL in nine and > 25 mg/dL in two children (with a maximum of 30.9 mg/dL); hyponatremia (< 135 mmol/L) in three and hypernatremia (> 145 mmol/L) in one; hypokalemia (< 3.5 mmol/L) in six and hyperkalemia (> 4.5 mmol/L) in nine patients (Table 1).

There were complications in 24 children (38.1%),

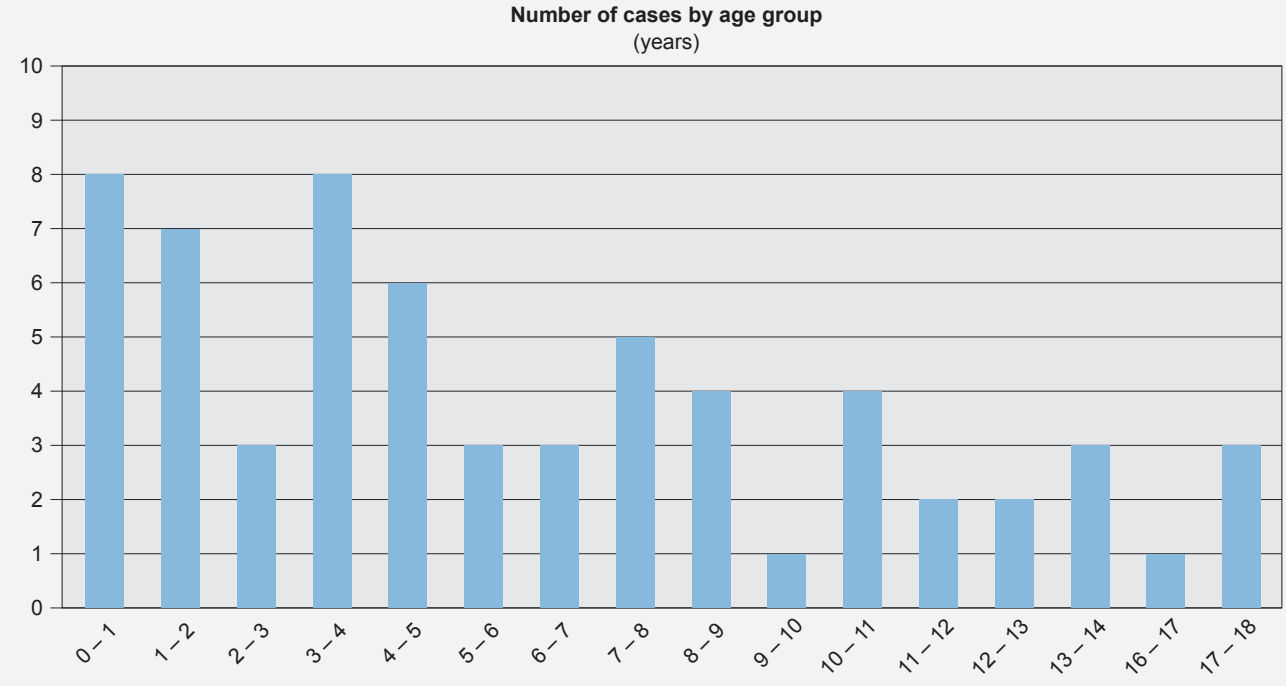

Figure 1 – Distribution of salmonellosis cases by age group, in years

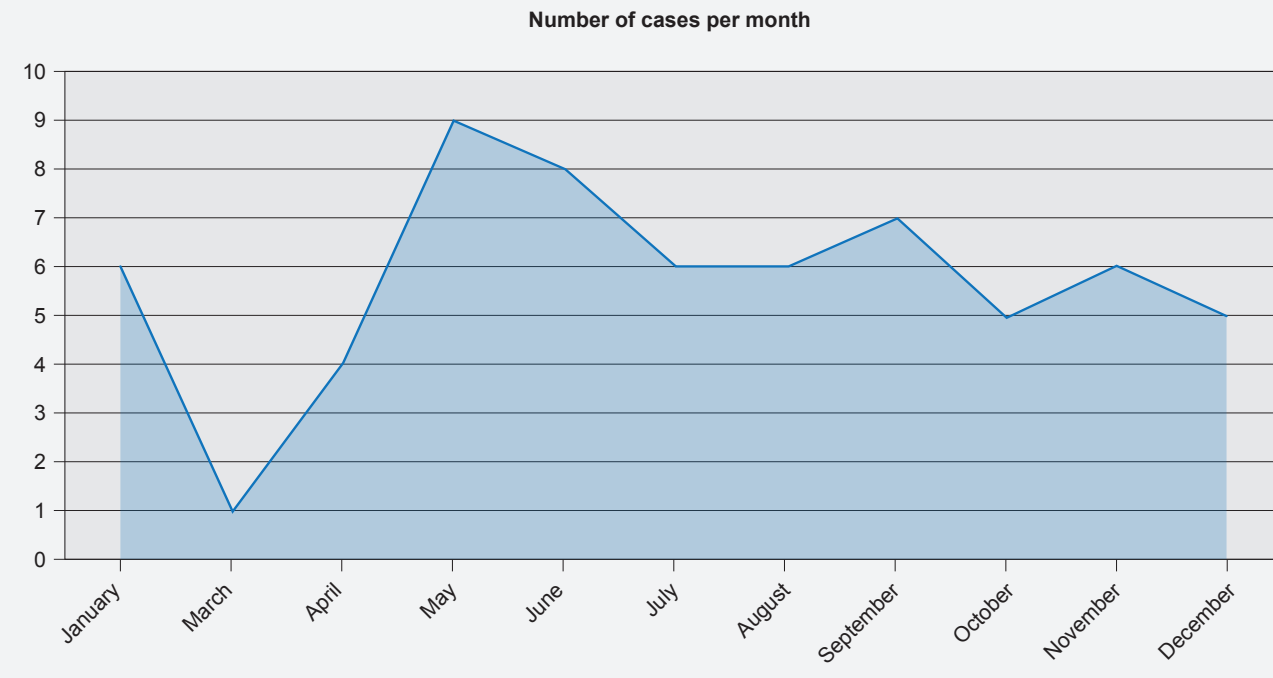

Figure 2 – Distribution of salmonellosis cases per month

with dehydration being the most frequent (n = 22; 91.7% of total complications), followed by metabolic alkalosis (n = 2; 8.3%); none of them had acute kidney injury (Table 1). Therefore, dehydration had a prevalence of 35% in the population studied.

Salmonella was isolated more frequently from stool culture (n = 57; 90.5%) but also from blood culture in two children (3.2%); in three it was isolated in both fecal and blood cultures (4.8%) and in one child it was isolated in both blood and urine cultures (1.6%) – Table 1. The identified *Salmonella* enterica serotypes were *Salmonella typhi* in two children (3%), *Salmonella typhimurium* in 14 children (22%) and *Salmonella enteritidis* in 24 children (38%) – Table 1. In 14 isolates (23%) it was only possible to determine the serogroup: group A in one, B in eight, C in three and D in two. In 23 cases (37%) it was only possible to identify the genus (*Salmonella* spp). Antimicrobial susceptibility testing was performed in 100% of the isolates and revealed 19% resistance rates to ampicillin, 6.4% to amoxicillin-clavulanate and to cotrimoxazole. The susceptibility rate to cefotaxime, from which susceptibility to ceftriaxone is inferred, was 100%. Regarding resistance by serotype, *Salmonella typhi* showed no resistance to any of the tested antibiotics. The highest rates of antibiotic resistance were identified in *Salmonella typhimurium*, namely to ampicillin in 14.3%. Still in relation to ampicillin, other non-typhoidal *Salmonella* had 5% resistance rates. Amoxicillin-clavulanic acid resistance rates were 5% for *Salmonella typhimurium* and less than 5% for other non-typhoidal *Salmonella*; lastly, for cotrimoxazole, resistance rates were less than 5% in both groups (Table 1).

Most of the children were treated only symptomatically (n = 55; 87.3%) and eight (12.7%) received antibiotic therapy due to the presence of risk factors or positive blood cultures, being ceftriaxone the most widely used (Table 1). The mean duration of antibiotic therapy was 9.5 days.

Out of the children whose medical follow-up was known (n = 18), 12 collected new stool samples, that turned out to be negative, on average, 3.5 months after the diagnosis (Table 1). All of them evolved to cure, with no chronic carriers identified. Only 27% of these *Salmonella* infections were notified.

DISCUSSION

In this study, salmonellosis was slightly more frequent in males, as observed in other Portuguese retrospective studies.[7,8]

Even though the majority of observed patients were Portuguese (81%), our hospital has a very high incidence of migrants, specially from African countries, some of them living with poor hygiene conditions, a known risk factor for this disease. We found no reference to birthplace in other Portuguese studies.

The highest incidence of salmonellosis was noted in children younger than five years old,[3,9] as observed in our study, in which this age group corresponded to about 50.8% of cases. The median age in our study was four years old, similar to the median age described in other Portuguese studies.[7,8]

There has been a significant decrease in the number of salmonellosis in recent years worldwide[2] and our results concur with this data. Comparing our results with a previous retrospective descriptive study carried out in our pediatric department, between January 1999 and August 2003 (Jacinto *et al*, unpublished, presented as a poster in "*IX Jornadas Nacionais de Infecciologia Pediátrica*", Évora, 8 – 11 October 2003) we saw an important reduction in the number of cases. Between 1999 and 2003 there were 82 cases per year, in contrast with our findings of 11 cases per year. The reduction in incidence was also observed in the retrospective study by Almeida *et al*,[7] with an annual average of 43.6 cases (between 2005 – 2009). In the Pignatelli *et al* study, the annual median was 21 cases of non-typhoidal *Salmonella* (between 1999 – 2008).[8] This reduction may be related to better hygiene conditions and better food and water control.

As noted in previous studies, this kind of infection predominates in warmer seasons, namely between May and October reaching a peak in July.[10] We achieved a higher number of cases in May, June and September as well, and the most frequent serotype in these months was *Salmonella enteritidis* (Fig. 2). As mentioned in other Portuguese studies[7,8,10] and in the Jacinto *et al* study mentioned previously, the most isolated serotype was *Salmonella enteritidis*, followed by *Salmonella typhimurium*. The INSA Epidemiological Bulletin (2014 – 2017) identified as the most frequent serotypes: *Salmonella* 4,5:i:-, followed by *Salmonella enteritidis* and *Salmonella typhimurium*, and reported an increase in *Salmonella enteritidis* serotype between 2014 and 2017.[11]

From the obtained data, 64.1% of children had contact with symptomatic patients, the majority in a familial context. Regarding the ingestion of potentially contaminated food, data was scarce, and it was only confirmed in two cases. In the Jacinto *et al* study (1999 – 2003), 27% of cases had a potential contaminated food intake of chicken and eggs while 27% had a familial or school-related context. In the Pignatelli *et al* study[8] it was assumed that eggs were a source of infection in 10% of patients and that 16% of cases occurred in the context of small outbreaks. In the Almeida *et al* study, the ingestion of a potentially contaminated food was considered in 45.3% of cases.[7]

Salmonellosis hospitalization was required in 58.7% of children, compared to 67.7% in the Jacinto *et al* study and

83.5% in the Almeida *et al* study.[7] The most frequent diagnosis was acute gastroenteritis (in 83.9%), as observed in 1999 – 2003 (in 90%). Dehydration was the most frequent complication, as seen in other studies.[7,8] These results may indicate that complications associated with salmonellosis infection are lower nowadays, corresponding to a decrease in the number of hospitalizations. These complications depend on serotype and patient, and vary from hemolytic-uremic syndrome to peritonitis, intestinal perforation, acute idiopathic pancreatitis, acalculous cholecystitis, acute liver failure, chronic diarrhea, irritable bowel syndrome, dyspepsia, manifestations of ulcerative colitis, Reiter's syndrome, or septicemia.

In the literature, a higher hospitalization rate has a predominance in lower age groups, who are more vulnerable to dehydration, and in whom it is often necessary to anticipate care in order to avoid complications.[7] Our study did not corroborate this data, as the median age from the hospitalized group was seven years, whereas from the non-hospitalized group was three years. This may be explained by the fact that the population from our study was older than usual for this disease.

Urinary tract involvement is rare, and it can occur by hematogenous spread or by ascension from the urethra to the upper urinary tract. It can occur in immunocompromised patients, patients with structural malformations of the urinary tract, nephrolithiasis, urinary catheter (or other foreign body), chronic kidney disease or very frequent sexual activity.[12] In one of the patients from our study, *Salmonella* was isolated in both blood and urine samples, but since there was no urinary tract disease, a hematogenous spread was assumed. *Salmonella* groups C and E are most frequently isolated in urine,[12] identification was not possible in this case. The other reported cases of non-typhoidal *Salmonella* bacteremia from our study were in children under two years of age, with similar distribution from groups A, B and D.

In high income countries, typhoidal *Salmonella* is usually associated with travelling to endemic areas. In this period, there were two cases of *Salmonella typhi* infection. They were siblings, both from Portugal (parents from Guinea-Bissau) and with complete Portuguese National Immunization schedules, and had not received the typhoid vaccine. They had no recent travels or suspected contacts. No pathogens were isolated in stool samples of their cohabitants (father not tested due to absence from the country).

According to literature, treatment of immunocompetent children is supportive since antibiotics do not shorten the illness course and may cause prolonged fecal bacterial shedding.[6,13] However, antibiotics (typically third-generation cephalosporins) are indicated for all individuals with typhoidal *Salmonella* and with non-typhoidal *Salmonella* extraintestinal disease.[3] In non-typhoidal *Salmonella* disease, antibiotics are also recommended for newborns; organ transplantation or AIDS; corticosteroids or others immunosuppressors; hemoglobinopathies, namely sickle cell disease; disorders of the reticuloendothelial system; asplenia; ongoing or recent chemotherapy; age under three months and over 12 years (except if apyrexia and clinical improvement).[3,13] We observed a high rate of antibiotic use (12.7%), justified by the severity of the clinical presentation, namely bacteriemia cases and presence of risk factors (HIV infection). These high rates were also observed in the Pignatelli *et al* study[8] (38% cases) and in the Almeida *et al* study[7] (11.5% cases).

Ampicillin was the most frequent antibiotic resistance in our study (19%), as in the Pignatelli *et al* study (27%).[8] In both studies, all strains were susceptible to third generation cephalosporins.[8]

When compared to the Jacinto *et al* study, it was evident that there was an important decrease of resistance rates to antibiotics for each serotype. As for ampicillin resistance rates, they decreased from 60% to 15% for *Salmonella typhimurium* and from 35% to 5% for other non-typhoidal *Salmonella.* For amoxicillin-clavulanic acid, it decreased from 50% to 5% for *Salmonella typhimurium* and 30% to less than 5% for other non-typhoidal *Salmonella*. Finally, resistance rates for cotrimoxazole decreased from around 10% to less than 5%, in both previously mentioned groups.

Salmonella resistance to antibiotics is increasing worldwide and represents a global public health concern, with increased treatment failure and risk of invasive disease.[13] As such, susceptibility patterns should be considered in patients treated with antibiotics.

It is presumed that the prevalence of salmonellosis is much higher than the one presented. One of the reasons is that, although notification in our country for all *Salmonella* infections is mandatory, many cases are not recognized during the initial assessment and therefore, are not notified. Moreover, not everyone who has a *Salmonella* infection seeks medical care, and healthcare providers may not obtain a specimen for laboratory diagnosis, or the clinical diagnostic laboratory may not be able to perform the necessary diagnostic tests.[14] In our study, from all the cases hospitalized (n = 37), 20 were not notified, probably due to early hospital discharge or late culture results. The ECDC Annual Epidemiological Report for 2017 mentions that in Portugal, the proportion of hospitalized cases was very high (72% – 85%), while salmonellosis notification rates were low.[9]

Despite the improvement in hygiene conditions, public sanitation and food safety, *Salmonella* infection persists in both high- and low-income countries. Better transmission control is possible with appropriate measures outside the medical field. Preventing contamination implies control at all stages of the food chain: specific measurements in primary

production, namely the control of animal feed and compliance with good hygiene practices in animal production and processing (to avoid cross-contamination); storage temperature control, so that growth is prevented; and particular attention to products that undergo reformulation, since it favors growth of *Salmonella*.[15] Also the treatment of municipal waters with chlorination and adequate public sanitation are basic and necessary measures to avoid cases; the elimination of the bacteria is possible through heat, at 54.4ºC for one hour or 60ºC for 15 minutes; regarding contact with animals, hand washing is imperative immediately after the collection of animal feces and/or use of gloves.[16] In the medical field, typhoid vaccine is an important way of preventing disease, despite the licensed vaccines not providing complete protection.[6] The Portuguese Society of Travel Medicine recommends vaccination of travelers over two years of age, who travel to endemic areas and whose stay lasts for more than one month, or whose travel, even if lasting less than one month, may confer an increased risk of contracting the disease.[17] There are currently no vaccines for non-typhoidal neither paratyphoid *Salmonella*.[3]

The main limitations of the study were the small sample size and the retrospective analysis. The consultation of clinical records was totally dependent on the notes made, with the omission, in some cases, of important data for epidemiological and clinical characterization of salmonellosis.

The authors consider that it would be important to carry out a prospective national study, in order to ascertain the real incidence of salmonellosis in Portugal, as well as the most frequent strains and antibiotic resistance. The notification rate, although mandatory, remains below expectations. Another area that needs further investigation is the indications for treatment of non-typhoidal *Salmonella*, namely the most effective antibiotic and optimal duration, through randomized controlled trials, in order to standardize recommendations and reduce resistance to antibiotics.

CONCLUSION

The present study obtained recent data regarding the epidemiology, microbiology (identifying serotypes and respective antibiotic resistance rates) and clinical presentation (symptomatology, risk factors, complications, hospitalization rates, treatment performed and follow-up after discharge) of pediatric salmonellosis cases in a Portuguese level II Hospital, between 2015 and 2020.

With these results we intend to improve knowledge on salmonellosis and its prevention strategies, treatment and notification in Portugal. Although the incidence of salmonellosis has been decreasing in recent years, it is the second most frequent gastrointestinal infection and an important cause of foodborne outbreaks in the European Union,[9] contributing to a high rate of hospitalizations and use of antibiotics in Portugal.

PREVIOUS PRESENTATIONS

This study was partially presented as a poster at European Society for Paediatric Infectious Diseases (ESPID) 2021, which took place online between the 24th and 29th of May.

AUTHOR CONTRIBUTIONS

IFM, SC, RVC: Design of the data collection instruments; data collection and analysis; draft of the manuscript; revision and approval of the manuscript.

SJ, PC, MJB, AF: Conceptualization of the study; revision and approval of the manuscript.

SS: Revision 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.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Perceptions of Portuguese Doctors Regarding Hastened Death Scenarios: A Cross-Sectional Study

Perceções dos Médicos Portugueses sobre Cenários de Morte Antecipada: Um Estudo Transversal

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ABSTRACT

Introduction: A growing number of countries have legalized the process of hastening death. At a time when laws decriminalizing hastened death have been passed in the Portuguese Parliament, the development of research related with decision making regarding this issue is of crucial importance. This study seeks to evaluate, in a sample of Portuguese doctors, whether the presentation of clinical vignettes changes the agreement with the practice of hastened death compared with general scenarios.

Material and Methods: A questionnaire was distributed among academic physicians from medical schools across Portugal to assess their level of agreement or disagreement with the practice of hastened death. The questionnaire included eight standard cases and eight clinical vignettes framed under conditions defined by law for the practice of hastened death. Differences were analyzed using the *t*-Student test for paired samples.

Results: There were statistically significant differences in five scenarios ($t = 3.46$; $p < 0.05$; $t = 2.47$; $p < 0.05$; $t = 4.28$; $p < 0.05$; $t = 3.38$; $p < 0.05$; $t = 3.66$; $p < 0.05$) with greater agreement concerning the clinical vignettes. The highest acceptance was found in the requests made by adults with terminal and incurable illnesses.

Conclusion: Agreement increased when the clinical vignette was presented in comparison with the respective standard for most of the cases of hastened death presented.

Keywords: Decision Making; Euthanasia/legislation & jurisprudence; Portugal; Suicide, Assisted/legislation & jurisprudence

RESUMO

Introdução: Um número crescente de países tem vindo a legalizar o processo de antecipação da morte. Numa altura em que a lei sobre a despenalização da morte antecipada foi aprovada no parlamento português, o desenvolvimento de investigação relacionada com o processo de tomada de decisão assume crucial importância. Com este estudo pretendemos avaliar se a apresentação de vinhetas clínicas altera a concordância com a prática de morte antecipada, comparando com cenários descritos de forma geral, numa amostra de médicos portugueses.

Material e Métodos: Foi distribuído um questionário por médicos docentes nas faculdades de Medicina do país, para avaliar o grau de concordância com a prática de morte antecipada. O questionário contemplou oito casos norma e oito vinhetas clínicas enquadrados em condições definidas na lei para a prática de morte antecipada. As diferenças foram analisadas através do teste *t-Student* para amostras emparelhadas.

Resultados: Verificaram-se diferenças estaticamente significativas em cinco cenários, com uma maior concordância em relação às vinhetas clínicas ($t = 3,46$; $p < 0,05$; $t = 2,47$; $p < 0,05$; $t = 4,28$; $p < 0,05$; $t = 3,38$; $p < 0,05$; $t = 3,66$; $p < 0,05$). O cenário com maior concordância foi o referente a pedidos por parte de adultos com doença incurável fatal.

Conclusão: A concordância com a vinheta clínica aumentou em comparação com o respetivo caso norma para a maioria dos casos de morte antecipada apresentados.

Palavras-chave: Eutanásia/legislação & jurisprudência; Portugal; Suicídio Assistido/legislação & jurisprudência; Tomada de Decisão

INTRODUCTION

The existence of various conceptions and ideas regarding euthanasia is old. The word euthanasia comes from the Greek terms *eu* and *thanatos*, which mean, respectively, 'good' and 'death'.[1] In general, it should be understood as "deliberately and intentionally carrying out an act with the clear intention of ending the life of a competent and informed person with an incurable disease who has voluntarily requested that his or her life be ended", corresponding to the concept of active euthanasia.[2] In contrast, the term 'medically assisted suicide' occurs when a physician prescribes to the patient the means to end his own life, but has no active role in the administration of the lethal substance, with the final action being performed by the patient himself.[3] Both actions are aimed at anticipating the moment of someone's death, and can be globally designated by the expression 'hastened death',[4] used throughout this paper to refer to voluntary euthanasia and physician assisted suicide.

Technological advances in healthcare have enabled an increase in average life expectancy, leading to a demographic shift in human mortality.[5] As an example, in Portugal data from the National Institute of Statistics indicate that in the three-year period 2016 - 2018, the estimated life expectancy at birth was 80.8 years for the total population, which shows an increase of 1.51 years, when compared to 2008 - 2010.[5] Consequently, more patients die at an advanced stage of chronic disease, most of them marked by a terminal and disabling phase, whereas the number of deaths from old age or senility has decreased.[6] Therefore, the

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discussion of hastened death has faced increasing debate in the medical field, and in countries where the practice is legal, it is an integral part of the healthcare.[7]

The involvement of healthcare professionals, particularly the physician, has become evident in the legislation, since they have an essential role in the decision making process for a request of this kind as well as for the implementation of the practice of hastened death.[7] Therefore, the physician's role, in addition to the intervention in the relief of suffering, is also related with legal and ethical issues. On one hand, it is based on the importance of respecting individual autonomy, and, on the other hand, on the respect for the patient's life.[3] Given the values at stake, which are crucial to the structuring of our society, putting hastened death under legal parameters seems to be the only solution.[3] It is, however, impossible to design a comprehensive law that meets the needs of all potential cases of hastened death.[8]

The first country to legalize euthanasia was the Netherlands in 2001, followed by Belgium the following year, and years later by Luxembourg, Colombia, Canada, and Australia (State of Victoria).[7] The practice was recently legalized in Spain.[9] Physician assisted suicide, however, has been permitted in Switzerland since 1934, and is now permitted in Germany, the Netherlands, Luxembourg, Canada, 10 US states (California, Colorado, Hawaii, Maine, Montana, New Jersey, Oregon, Vermont, Washington, and the District of Columbia), Australia (the State of Victoria).[7] In most countries, the hastened death law is available to adults suffering from an incurable terminal illness. Additionally, in Belgium, the Netherlands, Luxembourg and Spain, the law also allows this practice in adults with definitive injuries of non-terminal nature.[9–12]

A common condition in legislation around the world is the long-lasting and intolerable suffering of the patient. This leads to no other solution for the patient other than anticipating death, with a constant, conscious, free, and repeated wish to die.[13] None of the countries where hastened death is regulated refers to patients with mental disorder under the conditions established by law.[10–12] However, in those countries where a non-terminal illness can be a reason to request death, euthanasia can be carried out[14] if it is ruled out that the psychiatric illness does not affect the patient's decision-making capacity.

Public debate began in the Netherlands regarding people aged 70 and older, without associated conditions, and the idea was being able to request hastened death when they considered their life to be 'complete'.[15] The issue focuses primarily on elderly people who feel that their life no longer serves any purpose and call for the right to autonomy and determination when it comes to choosing their own time of death.[15] Nevertheless, hastened death following a 'complete life' is not eligible in any hastened death legislation.[15]

The decision to die early is also regulated by Advance Life Directives in Belgian and Dutch Law, which grants the universal right of expressing in written form their wish to anticipate death in the event of illness.[10,11] As far as the Dutch Law is concerned, these documents make hastened death possible in cases of dementia, if this has been previously written in a living will.[11]

In 2014, Belgium was the first country to legalize hastened death in children without any age limit, given consent from both the child and the parents.[10] The Netherlands also allows euthanasia in children over 12 years old with the parents' consent and after 16 years old even without the parents' consent.[11] It should also be noted that in the Netherlands, under the Groningen Protocol, it is possible to carry out abortion at the end of the gestation period or euthanasia in newborns.[16]

In Portugal, a bill to legalize hastened death has been under discussion since February 2020.[17] The law approved by the Portuguese Parliament and subsequently vetoed by the President of the Republic, allows requests for hastened death of adult patients whose suffering is intolerable, in cases of definitive injury of extreme severity or incurable and fatal illness.[17] Patients must be able to express their own conscious and informed will, and not suffer from a mental disorder or medical condition affecting their ability to make decisions.[17]

Several studies have found that agreement to hasten death can be influenced when faced with concrete scenarios.[18] Factors affecting these scenarios that tend to determine approval may be related with the patient's age, average life expectancy[19] and degree of disability.[20] Suffering also seems to play an important role, and cases of suffering associated with a physical condition show greater compliance than suffering caused by psychological factors.[20] In a study by Dany *et al*[21] using a sample of French physicians, it was shown that the general opinion in favor of euthanasia was lower when compared to its acceptance in the face of the presentation of specific cases.

Based on these assumptions, this study aims to analyze the opinions of Portuguese physicians regarding their agreement with the practice of hastened death according to scenarios described in general and specific clinical reports.

MATERIAL AND METHODS

The present study consisted of a cross-sectional analysis. The study population consisted of academic physicians from all medical schools in Portugal.

Participants

The sample consisted of 65 academic physicians in higher education, 41.5% were female and 58.5% were male with a mean age of 48.18 years (SD = 1.790).

Instruments

A questionnaire was developed in order to gauge the opinions of academic physicians in medical schools about the agreement with the practice of hastened death between general scenarios and clinical vignettes. The first section consisted of up to eight general cases, entitled standard cases (Table 1); these were defined according to the law recently passed in the Portuguese Parliament[17] and in accordance with international legislation. A hastened death scenario was also included following the Dutch government's letter on 'complete life'.

The second section presented eight detailed case descriptions in the form of clinical vignettes [Appendix 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17290/Appendix_01.pdf)], each corresponding to a standard case from the previous section. Each vignette presents a case report consulted and adapted from the literature[22–31] where the patient sought to hasten death.

We used an e-Delphi panel to collect information and found agreement among a group of experts concerning the suitability of the standard cases and clinical vignettes. This group provided a conceptual, semantic, idiomatic, and empirical analysis.[32,33] The questionnaire was sent by email to the panel, composed of seven experts, including researchers and healthcare professionals. The analysis was performed using a dichotomous classification – agree and disagree – with space for comments related with each item. Changes to the questionnaire were based on the panel's suggestions. After analysis by the research team, the new version of the questionnaire was sent to the panel, and was evaluated in as many stages as necessary to reach a consensus with at least 80% agreement among the panel members.[32,33]

The answer to each of the situations presented was given on a 5-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree).

The first section, in addition to the standard cases, included a question to assess physician perceptions about the possibility of each standard case being allowed in Portugal according to the discussed legislation.[17] This question was answered on a dichotomous scale – "would be possible," "would not be possible," and "do not know if it would be possible."

Procedures

We requested support for data collection from the various medical schools across the country to send the questionnaire to physicians. Our requests were answered online through the Google Forms platform. The link to access the questionnaire was sent by email to all participants. Data collection took place between January and February 2020.

First, information about the study was presented, as well as clarifications about confidentiality, privacy, and data protection. All performed procedures were in accordance with the 1964 Declaration of Helsinki, and its subsequent amendments or comparable ethical standards, and the General Data Protection Regulation was followed. The study was submitted to the Ethics Committee for Health of the Centro Hospitalar Universitário de São João and a favorable opinion was obtained (process number 444-2020).

Data analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS, version 26.0). Descriptive statistical analyses were performed to characterize the sample and the agreement variable. Skewness

Table 1 – Standard cases

1.	An adult in lasting and unbearable suffering, with an incurable and fatal disease, by his own conscious, free and informed decision, asks for help from health professionals to hasten death.[10–12,17]
2.	An adult in long-lasting and unbearable suffering, with an incurable disease or definitive but non-fatal injury, by his or her own conscious, free and informed decision, asks for help from health professionals to hasten death.[10–12,17]
3.	An adult over the age of 70, who considers his life complete and does not want to continue with it, by his own conscious, free and informed decision, asks for the help of health professionals to hasten death.[15]
4.	An adult with incurable disease or definitive injury and permanent inability to manifest his will, manifests his or her decision to hasten death with the help of health professionals, through an Advanced Living Will.[10,11]
5.	A child older than 12 years of age in lasting and unbearable suffering, with incurable disease or definitive injury, by conscious, free and informed decision, asks health professionals for help to hasten death, after informed consent of the caregivers.[10,11]
6.	A child under 12 years of age, in long-lasting and unbearable suffering, with incurable disease or definitive injury. The parents, expressing conscious, free and informed will, ask health professionals for help to hasten death.[10]
7.	A newborn with a severe, incurable and terminal condition that causes long-lasting and unbearable suffering and no prospect of improvement. With a high probability of dying within a short time after birth, no doubts about the diagnosis and prognosis. Both parents and doctor agree that there is no alternative solution other than hastening the end of life. The parents give informed consent.[16]
8.	A patient suffering from a psychiatric disorder refractory to all lines of treatment, in lasting and unbearable suffering, able to make a free and informed decision, asks for help from health professionals to hasten death.[10,11]

and kurtosis values were below 3 and 10, respectively, suggesting no severe deviations from the normal distribution, and therefore, the appropriateness of using parametric procedures.[34] In our data, values ranged between 0.5 and 1. To determine the differences in agreement between the standard cases and the clinical vignettes, the *t*-Student test for paired samples was performed. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The characteristics of the sample are shown in Table 2. Of the participants, 41.5% were female and 58.5% were male with a mean age of 48.18 years (SD = 1.790). Regarding length of service, most had more than 15 years (58.5%); 16.9% had between six and 10 years; 13.8% from one to five years; 9.2% from 11 to 15 years; and 1.5% with less than one year.

Table 3 presents the results of the degree of agreement regarding the applicability of hastened death in the eight standard cases. The highest level of agreement was found in the case involving adults with incurable and fatal disease (Case Norm 1), with approximately 57% of the sample in favor of the application of hastened death in this scenario. The highest disagreement regarding the practice of hastened death was found in Standard Case 3, concerning elderly people over 70 years old with a sense of completed life. Approximately 86% of the sample disagreed with hastened death in this scenario. As for Standard Case 2, including adults with irreversible but non-fatal injury, the agreement and disagreement was similar (43% respectively). As for a request for hastened death through an advanced living will (Case Norm 4), about half of the physicians disagreed and approximately 40% agreed with this scenario. In cases concerning children (Case Norm 5 and 6), more than half of the physicians (53.8% in both) disagreed with the practice of euthanasia. In Standard Case 7 concerning newborns with severe, incurable, and terminal conditions that entailed unbearable suffering and no prospect of improvement, 52.3% of the physicians agreed with hastening death. Regarding Standard Case 8 concerning patients with psychiatric disorders with decision-making capacity who require hastened death, most physicians disagreed (53.8%).

Table 2 – Characteristics of the sample

Gender	n	(%)
Female	27	(41.5)
Male	38	(58.5)
Age	**Mean**	**SD**
	48.18	1.79
Length of service (years)	**Mean**	**SD**
	4.09	0.15
	n	**(%)**
> 15 years	38	(58.5)
11 - 15 years	6	(9.2)
6 - 10 years	11	(16.9)
1 - 5 years	9	(13.8)
< 1 year	1	(1.5)

n: sample size; %: percentage; M: mean of the data; SD: standard deviation; *t*-Student: Student *t*-test for paired samples; *p*: level of significance

The results of agreement and disagreement with each of the clinical vignettes corresponding to each standard case are presented in Table 4. In Clinical Vignette 1, the majority of the sample (53.9%) agreed with hastened death. In Clinical Vignette 2, the percentage of agreement for hastened death increased slightly to 55.4%. Most physicians (80%) disagreed with the practice of hastened death in Clinical Vignette 3. In Clinical Vignette 4, 44.6% of the physicians agreed with the practice of hastened death. Approximately 45% of physicians agreed with the request for hastening death in Clinical Vignette 5. In the scenario reflecting the case of a 10-year-old child (Clinical Vignette 6), the percentage of physicians who disagreed (41.5%) was higher

Table 3 – Agreement with the applicability of hastened death in standard cases

	Mean	SD	Response percentage per case				
			I strongly disagree	I disagree	Neither agree nor disagree	I agree	I strongly agree
Standard case 1	3.54	1.592	20.0	7.7	15.4	12.3	44.6
Standard case 2	3.03	1.600	26.2	16.9	13.8	13.8	29.2
Standard case 3	1.55	1.090	72.3	13.8	4.6	4.6	4.6
Standard case 4	2.88	1.654	32.3	15.4	13.8	9.2	29.2
Standard case 5	2.54	1.552	40.0	13.8	16.9	10.8	18.5
Standard case 6	2.40	1.508	44.6	9.2	24.6	4.6	16.9
Standard case 7	3.25	1.649	29.2	3.1	15.4	18.5	33.8
Standard case 8	2.58	1.540	36.9	16.9	15.4	12.3	18.5

M: mean of the data; SD: standard deviation

Table 4 – Agreement with the applicability of hastened death in cases as clinical vignettes

	Mean	SD	Response percentage per case				
			I strongly disagree	I disagree	Neither agree nor disagree	I agree	I strongly agree
Clinical vignette 1	3.45	1.552	20.0	7.7	18.5	15.4	38.5
Clinical vignette 2	3.42	1.550	18.5	13.8	12.3	18.5	36.9
Clinical vignette 3	1.80	1.240	60.0	20.0	7.7	4.6	7.7
Clinical vignette 4	3.14	1.519	21.5	15.4	18.5	16.9	27.7
Clinical vignette 5	3.06	1.560	26.2	12.3	16.9	18.5	26.2
Clinical vignette 6	2.80	1.427	27.7	13.8	24.6	18.5	15.4
Clinical vignette 7	3.18	1.667	29.2	7.7	12.3	16.9	33.8
Clinical vignette 8	2.38	1.331	35.4	20.0	26.2	7.7	10.8

M: mean of the data; SD: standard deviation

than those who agreed (33.9%). In the case of a newborn (Clinical Vignette 7), 50.7% of physicians agreed with the practice of hastened death. As for Clinical Vignette 8 involving a patient with a mental disorder, 55.4% disagreed with hastening death practice.

Table 5 shows the differences in agreement with the practice of hastened death between the standard cases and the clinical vignettes. Statistically significant differences were found between: Standard Case 2 and Clinical Vignette 2, Standard Case 3 and Clinical Vignette 3, Standard Case 4 and Clinical Vignette 4, Standard Case 5 and Clinical Vignette 5, and Standard Case 6 and Clinical Vignette 6. The results indicated that in cases 2, 4, and 5 the level of agreement increased significantly (t = 3.46; p < 0.05; t = 2.47; p < 0.05; t = 4.28; p < 0.05) when presented with the corresponding clinical vignettes (case-specific description). In cases 3 and 6, although the difference was significant (t = 3.38; p < 0.05; t = 3.66; p < 0.05) and there was an increase in the mean in the corresponding clinical vignettes, results remained below 3 (cut-off for agreement).

Table 6 shows the physician perceptions about the bills approved in the Portuguese Parliament. Approximately 60% of the physicians thought that the Standard Case 1 would be possible according to the bill approved in the Portuguese Parliament. Regarding the Standard Case 2, only 35.4% of the physicians stated that this situation would be eligible for hastened death under this law. As for standard cases 3, 4, 5, 6, 7 and 8, the highest percentage of physicians stated that it would not be possible to carry out hastened death.

Table 5 – Analysis of the difference in the applicability of hastened death between standard cases and clinical vignettes

Cases	M	SD	*t*-Student	*p*
Standard case 1	3.54	1.59	1.23	0.22
Clinical vignette 1	3.45	1.55		
Standard case 2	3.03	1.60	3.46	0.00
Clinical vignette 2	3.42	1.55		
Standard case 3	1.55	1.09	3.38	0.00
Clinical vignette 3	1.80	1.24		
Standard case 4	2.88	1.65	2.47	0.02
Clinical vignette 4	3.14	1.52		
Standard case 5	2.54	1.55	4.28	0.00
Clinical vignette 5	3.06	1.56		
Standard case 6	2.40	1.51	3.66	0.00
Clinical vignette 6	2.80	1.43		
Standard case 7	3.25	1.65	0.52	0.60
Clinical vignette 7	3.18	1.67		
Standard case 8	2.58	1.54	1.46	0.15
Clinical vignette 8	2.38	1.33		

M: mean of the data; SD: standard deviation; *t*-Student: the student *t*-test for paired samples; *p*: level of significance

Table 6 – Physicians' perceptions on eligibility to request hastened death according to the bills approved in the Portuguese Parliament

	It would be possible (%)	It would not be possible (%)	I do not know if it would be possible (%)
Standard case 1	61.5	13.8	24.6
Standard case 2	35.4	27.7	36.9
Standard case 3	4.6	83.1	12.3
Standard case 4	29.2	36.9	33.8
Standard case 5	9.2	53.8	36.9
Standard case 6	10.8	55.4	33.8
Standard case 7	26.2	27.7	46.2
Standard case 8	12.3	44.6	43.1

%: percentage

DISCUSSION

In this study, the highest level of agreement with hastened death was observed in the standard case concerning adults with long-lasting and unbearable suffering and incurable and fatal illness, where 57% of the physicians in the sample were in favor. This is in agreement with the results of a previous study carried out on a sample of Portuguese physicians.[1]

Approximately half (52.3%) of the physicians included in the sample agreed with hastening death in the standard case of a newborn who suffered from a severe and terminal condition with minimal chance of survival. Conversely, the lowest level of agreement was observed in standard cases 3 (9.2%), 5 (29.3%), 6 (21.5%), and 8 (30.5%).

Most doctors (86%) disagreed with the practice of hastened death in the standard case concerning elderly people without a diagnosed disease, which is not surprising since there is no country in the world where such practice is legislated. This reference comes from the Netherlands, and the Dutch government itself argues that cases like this cannot be included in the categories of euthanasia or assisted suicide, since no medical condition is the cause of their intolerable suffering.[15]

More than half of the physicians participating in the study opposed hastening death in cases concerning children, which seems to go along with the fact that age is a conditioning factor in the agreement with hastened death.[19] However, in the case of a newborn, about half (52.3%) of the physicians in the sample did agree with hastened death. It would be important to understand this issue and, in the future, to assess the motivations that may be behind this difference.

Similarly, the majority (54%) disagreed with the applicability of hastened death for patients with psychiatric disorders causing enduring and unbearable suffering with decision-making capacity. This is in line with previous research[20] where the opinions in favor of hastened death were lower in cases of suffering with no underlying physical dimension.

As in previous studies, the data corroborate that life expectancy seems to play an important role when it comes to physicians' acceptance of hastened death.[19] In fact, the lower acceptance of Standard Case 2 compared with terminal illness (Standard Case 1) highlights this.

In summary, the physicians in this sample favor the terminal nature of the disease and the patient's self-determination in the acceptance of hastened death in the standard cases.

The concordance between standard cases and clinical vignettes increases significantly in cases of adults with incurable diseases or definitive injuries (Clinical Vignette 2), elderly people over 70 years old with a complete sense of life (Clinical Vignette 3), request for hastened death described in a living will (Clinical Vignette 4), a child over 12 years old (Clinical Vignette 5) and a child under 12 years old (Clinical Vignette 6).

These results reinforce the idea that agreement with hastened death may not be similar when comparing the application of hastened death in the standard case with the corresponding clinical vignette. This is in accordance with a previous study[21] where the opinion in favor of hastened death increased when a specific case was presented. The study showed that clinicians may take a disparate position when faced with a different level of personal involvement. It should also be noted that the opinions in favor of euthanasia may vary with the public presentation of emblematic cases, which may contribute to the growing opinion in favor of hastened death in several countries.[18] Our results point out that in the face of a concrete clinical situation, the acceptability of hastened death increased, possibly due to a greater identification with the patient's suffering.

In cases 1, 7 and 8, there were no statistically significant differences between the standard cases and the corresponding clinical vignettes. In fact, Case 1 has the highest levels of agreement among physicians. For this reason, the terminal nature of life seems to be a determining factor in the agreement with hastened death. In this sense, it

may happen that participants who are not against hastened death motivated by personal issues, will end up agreeing with this standard case since it is the most common, and it is contemplated in the legislation of all the countries that accept this practice. It is, therefore, to be expected that there isn't an increased level of agreement in this case.

The fact that the standard case and Clinical Vignette 7 correspond to a newborn, may represent considerable specificity for the participants, so that there were no differences between the standard case and the specific case. The same is true for Case 8, in which the particularity refers to the absence of physical suffering, since it is a mental health illness. This is clear both in the standard case and in the vignette.

The levels of perception of physicians regarding the generalizability of the standard cases, considering the bills under parliamentary discussion in Portugal, seemed to suggest a considerable lack of knowledge about the proposed legislation. In fact, only in Case 1, did most physicians perceive that it was possible to carry out hastened death. In the case of definitive non-fatal injury (Standard Case 2), only 35.4% of the participants knew that this was possible. In Standard Case 3 there was an apparent certainty on the part of the participants that hastened death would not be possible (83.1%). In all other cases, none of which have been accepted in Portugal's legislative proposal, there are percentages of unawareness above 30%, reaching almost half of the participants. According to the proposed laws, hastened death would only be eligible in standard cases 1 and 2, corresponding, respectively, to adults with incurable and fatal disease and/or definitive non-terminal injury, which entail unbearable and long-lasting suffering.[17]

It should be noted that, since a convenience sample was used, the conclusions cannot be generalized to the population of Portuguese doctors. The replication of this study with a different type of sample, using doctors from all over the national health service, should be considered for future research. However, most academic physicians play the simultaneous role of doctor and tutor, and for this reason have experience in clinical practice, similar to that of other doctors.[35] Nevertheless, academic physicians play an active role in the integration of research projects and publications, which could be an advantage in this context.[35]

It would be interesting to conduct this study including nurses as well, since the law provides that they are also qualified healthcare professionals to practice or help in the act of hastening death.[17]

CONCLUSION

Agreement increased significantly when the clinical vignette was presented in comparison with the respective standard for most of the cases of hastened death presented, and therefore presenting a specific case seems like a determining factor for agreement. This shows that identification with the patient's suffering is a central condition for agreement to hasten death.

The existence of terminal illness, the patient's self-determination, and suffering are likely the central conditions for agreeing with hastened death. This should be extensively promoted, considering that physicians play a central role in the process, and that the law may be approved in Portugal.

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AUTHOR CONTRIBUTIONS

EP: Design and draft of the manuscript. Data interpretation.

SM: Contribution to the design. Processing, analysis and interpretation of data. Critical review of the manuscript.

MR: Contribution to the design. Critical review and final 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.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Portuguese Cross-Cultural Adaptations of the Pediatric International Knee Documentation Committee Score

Adaptação Transcultural do Pediatric International Knee Documentation Committee Score para Português

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ABSTRACT

Introduction: The aim of this study was to translate the Pediatric International Knee Documentation Committee Score (Pedi-IKDC) into European Portuguese language. The Pedi-IKDC was originally developed in the English language and its main construct is functional assessment of knee disorders in children and adolescents.

Material and Methods: The original English version of the questionnaire was translated to European Portuguese using the forward-backwards method. Patients aged eight to 17 with knee disorders were considered eligible for the study. An online platform was implemented to collect patient responses, including general patient information, the questionnaires Pedi-IKDC, EuroQol-5 Dimension Youth and Childhood Health Assessment Questionnaire. Three surveys were sent: at the moment of first evaluation (T0), after two (T1) and ten (T2) weeks. These surveys followed the Consensus-based Standards for the Selection of Health Measurement Instruments - COSMIN Checklist recommendations. The internal consistency, reliability, error of measurement, structural and construct validity (by means of correlation with previously validated scales), responsiveness and interpretability (floor/ceiling effects, MIC and ROC curve) were evaluated.

Results: Forty-seven patients completed T0, 42 patients completed T1 and 40 patients completed T2. The factorial analysis confirmed that the scale has one dimension. Cronbach alpha (α) was 0.94; interclass correlation coefficient was 0.92; smallest detectable change was 19.04 for individuals and 3.31 for groups; standard error of measurement was 6.87; minimum important change was 18.48; floor and ceiling effects were absent. More than 75% of the hypotheses tested for construct validity were confirmed, showing its adequacy. The variation of scores between T0 and T2 correlated with the clinical evolution of the participants ($r = 0.421$, $p < 0.05$).

Conclusion: The Portuguese version of Pedi-IKDC demonstrated good psychometric properties, being a valuable tool for clinical assessment of pediatric patients with knee disorder.

Keywords: Child; Knee; Knee Injuries; Patient Outcome Assessment; Psychometrics; Surveys and Questionnaires

RESUMO

Introdução: O objetivo deste estudo foi traduzir o questionário *Pediatric International Knee Documentation Committee* (Pedi-IKDC) para Português Europeu. O questionário Pedi-IKDC foi originalmente desenvolvido na língua inglesa e o seu construto permite a avaliação funcional de patologia do joelho, em crianças e adolescentes.

Material e Métodos: A versão original do questionário em inglês foi traduzida para português pelo método tradução e contratradução. Foram considerados elegíveis para o estudo pacientes com idade entre os oito e os 17 anos, com patologia do joelho. Foi implementada uma plataforma *online* para recolher as respostas dos pacientes, incluindo informação geral demográfica, os questionários Pedi-IKDC, *EuroQol-5 Dimension Youth* e *Childhood Health Assessment Questionnaire*. Foram enviados três inquéritos: no momento da avaliação inicial (T0), após duas (T1) e dez (T2) semanas. Estes inquéritos seguiram as recomendações da *Checklist da Consensus-based Standards for the Selection of Health Measurement Instruments* - COSMIN. Foram avaliadas a consistência interna, fiabilidade, erros de medida, validade estrutural e de construto (através da correlação com escalas previamente validadas), responsabilidade e interpretabilidade (efeitos de chão e teto, mudança mínima importante e curva ROC).

Resultados: Quarenta e sete pacientes completaram T0, 42 completaram T1 e 40 completaram T2. A análise factorial confirmou a unidimensionalidade da escala. O coeficiente de correlação entre os itens (alfa de Cronbach) foi 0,94, o coeficiente de correlação intraclasse foi 0,92, a mudança mínima detetável foi 19,04 a nível individual e 3,31 a nível de grupos de indivíduos; o erro padrão de medida foi 6,87; a mudança mínima detetável foi 18,48; não se verificaram efeitos de chão ou de teto. Mais de 75% das hipóteses testadas para a validade de construto foram aceites, demonstrando-se adequada. A variação das pontuações entre T0 e T2 correlacionou-se com a evolução clínica dos participantes ($r = 0,421$, $p < 0,05$).

Conclusão: A versão portuguesa do Pedi-IKDC demonstrou boas propriedades psicométricas, sendo uma ferramenta útil na avaliação clínica de pacientes pediátricos com patologia do joelho.

Palavras-chave: Avaliação de Resultados da Assistência ao Doente; Criança; Inquéritos e Questionários; Joelho; Lesões do Joelho; Portugal; Psicometria

INTRODUCTION

Patient-reported outcome measures (PROMs) are subjective questionnaires administered to patients to evaluate the impact of their disorders on their health status or function, not only globally, but also for specific body regions. Moreover, they allow for prospective follow-up of clinical status as well as treatment results, from the patients' perspective.[1] Knee-specific PROMs were created for function assessment, including the International Knee Documentation Committee (IKDC) subjective knee form, which evaluates symptoms, articular function, and impact on sports

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activities. Although these tools have become widespread in sports medicine studies, current evidence suggests that using adult PROMs in pediatric patients can lead to lack of validity.[2,3]

As such, and since the incidence of knee injury in the pediatric population, especially in adolescents, has seen an abrupt increase in the last few decades, partially due to the increasing level of physical and sports activities,[4-8] the availability of specific PROMs for the pediatric population that are translated and validated in different languages is of utmost importance. It is essential to use PROMs with tested psychometric properties in the pediatric population such as reliability, validity, interpretability, and responsiveness, since these metrics are useful not only as a complementary instrument in the clinical practice, but also for research purposes, so that a 'common language' can be used when reporting results.

Therefore, the Pediatric International Knee Documentation Committee Subjective Knee Form (Pedi-IKDC),[9,10] a modified version of the IKDC score, was recently developed, and was designed specifically for the pediatric population. It consists of 19 questions about knee symptoms, function and impact on physical activities. This survey has been extensively used in the literature,[11-15] and a recently published systematic review showed that Pedi-IKDC is the most studied PROM and has the best psychometric properties and, as such, should be preferred in detriment of other instruments.[12]

The Pedi-IKDC was already validated in many other languages,[15-17] with the validation studies being conducted in pediatric populations affected by a broad spectrum of knee injuries and disorders. However, to date there were no knee-specific PROMS validated for the Portuguese-speaking pediatric population.

Thus, the aim of the present study was to translate, cross-culturally adapt, and validate the Pedi-IKDC score in the Portuguese pediatric population, by means of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist.[18-20]

MATERIAL AND METHODS

Translation and cross-cultural adaptation

The questionnaire was translated into Portuguese using the forward-backwards method (Fig. 1).[21] First, the original version of the questionnaire[10] was independently translated into Portuguese by an official translator and a member of the research group, who is proficient in English (V1 and V2). The drafts were checked and compared by an independent senior expert researcher who synthesized them, creating a preliminary translated version (V1-2). This preliminary version was then translated backward into English by two independent official translators who did not know the original English version of the questionnaire (BT1 and BT2), to ensure the same meaning of the questionnaire in both languages. Finally, the research team, including the same senior author, compared the BT1 and BT2 versions with the original English version to assess unresolved comprehension issues and to approve a pre-final version of the questionnaire (VpF).

The pre-final version was pilot tested on five patients aged eight to 17 with different knee conditions, to ascertain any issue with acceptance and comprehension.

Clinical study

A longitudinal prospective cohort study was designed. It was evaluated and approved by the Ethics Committee for Research in Life and Health Sciences (CEICVS) of the University of Minho and the Ethics Committee of Braga Hospital (CEHB). Between June and September 2020, all patients aged eight to 17 affected by knee disorders, including

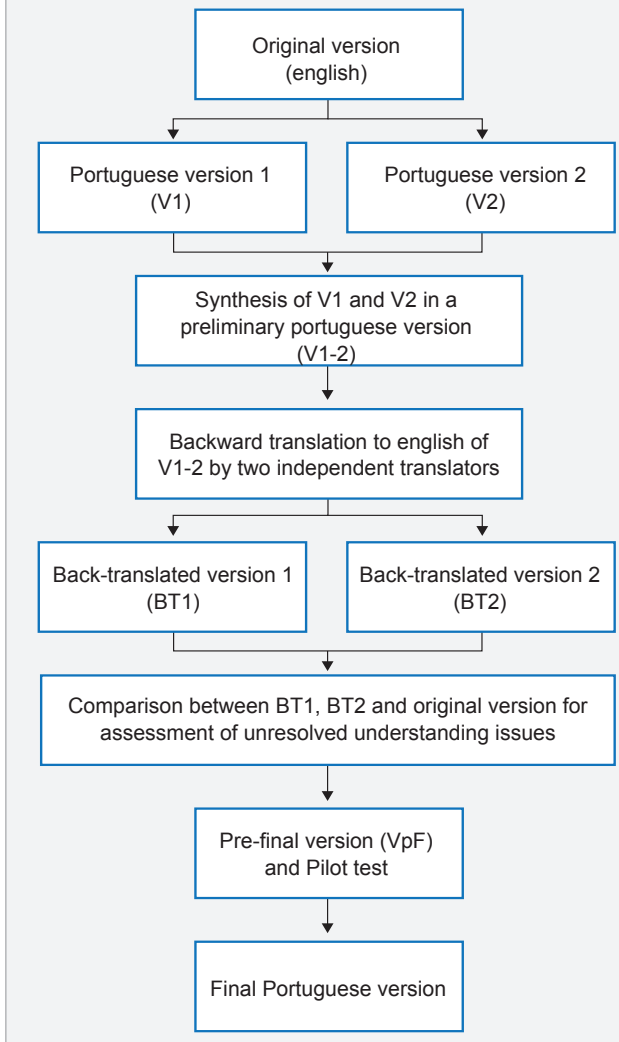

Figure 1 – Translation process by forward-backward method

trauma or deformities, who were assisted in the emergency department or referred to the orthopedics and traumatology outpatient clinic were considered eligible.

The inclusion criteria were having a knee disorder diagnosed by an orthopedic surgeon, with physical and/or functional limitation. Patients with significant comorbidities that could devalue knee symptoms and non-Portuguese speaking patients were excluded.

Complete information about the study was either given to parents on admission or later by phone contact. Those who gave consent were included in the study. Parents were advised to let the patients answer by themselves and to help them only when needed.

An open-source platform (via Google Forms®) was implemented to collect the responses. Three surveys were created (T0, T1 and T2); the translated Pedi-IKDC and the Portuguese versions of the EuroQol-5 Dimension Youth (EQ-5D-Y)(22,23) questionnaire and the Childhood Health Assessment Questionnaire (CHAQ)(24,25), which included general information (sex, age, body mass index, diagnosis).

The patients were asked to complete the surveys via e-mail initially on admission or first evaluation (T0), then two to three weeks later, under stable clinical conditions (T1), and a third time, 10 weeks later, after completion of surgical or conservative treatment (T2). An anchor-question about the patients' clinical status was included in T1 and T2 ("In relation to the previous survey, how would you consider your affected knee today?" with a multiple-choice answer: "much better", "better", "somewhat better", "same status", "somewhat worse", "worse" or "much worse").

There is evidence that electronic-based and paper-and-pencil surveys provide equivalent results[26,27] and it was also recently demonstrated that PROMs can be administered via electronic platforms in pediatric sports medicine.[28]

Questionnaires

The Pedi-IKDC score is a knee-specific questionnaire consisting of 17 Likert-based questions and four VAS-based questions on knee symptoms, sport activities, and function. The final score ranges from 0 to 100, and it is a measure of function, meaning that a higher score represents less pain, less symptoms, and a higher level of physical functioning.

The EQ-5D-Y is a questionnaire adapted for children and it measures health-related quality of life by evaluating five dimensions: mobility problems, self-care problems, problems during usual activities and the level of pain and anxiety. Each dimension is scored from 1 to 3 and it also includes a VAS-based question (0 to 100) as a quantitative health measure. Even though not specifically for knee disorders, it has shown highly valid and reliable for orthopedic problems.[29,30]

The CHAQ questionnaire was developed to evaluate the functional status of children with idiopathic juvenile arthritis, and it includes eight dimensions to evaluate their difficulty in performing usual activities and a VAS question about pain.[25]

Instruments validated in the pediatric population and translated into Portuguese are scarce. These last two questionnaires were selected to evaluate construct validity because they fulfilled the previous conditions.[24]

Statistical analysis

Data were automatically extracted on a Microsoft Excel spread sheet (Microsoft Corporation, Redmond WA). Analyses were performed in Excel or SPSS – Statistical Package for the Social Sciences v26.0 (IBM®SPPS® Statistics). Descriptive statistics were used to report demographics data as mean ± standard deviation. The significance level was considered as 5%. The normal distribution of variables was assessed by asymmetry and kurtosis values (normal if between -1 and 1) of the Komolgorov-Smirnov and Shapiro-Wilk tests and the histogram analysis.[31]

Psychometric properties

• Structural validity

Descriptive statistics were analysed for each item. The one-dimensionality of the scale was confirmed by the principal component analysis (PCA) and the eigenvalue above 1.[18,19] The Bartlett test was used to assess sphericity and the Kaiser-Meyer-Olkin (KMO) index to assess the sample consistency; a KMO above 0.6 was considered adequate.[7] Factor weights below 0.3 were considered for item deletion.

• Internal consistency

Internal consistency represents the homogeneity of the items within a score. The alpha coefficient (α) of Cronbach (range 0 – 1) as well as the correlation item-total were calculated for the responses on T0. The higher the coefficient, the more consistent is the score, and values $\alpha > 0.70$ were considered acceptable.[32]

• Reliability and measurement error

Reliability represents the precision of an outcome measure and evaluates whether it produces consistent results when repeatedly administered under stable conditions.[20] The overall scores of T0 and T1 were used to calculate the reliability. For this purpose, patients who answered "somewhat better", "same status" or "somewhat worse" on the anchor-question of T1 were considered stable and included for reliability analysis.

Test-retest reliability was assessed by means of the interclass correlation coefficient (ICC); an ICC > 0.75 was considered excellent.[33,34]

The standard error of measurement (SEM), which indicates the measurement error for every measurement,

and the smallest detectable change (SDC), which indicates the measurement error at individual level (SDC.ind) and at group level (SDC.group), were also calculated.[19,35]

• Construct validity

Construct validity is the degree to which the scores of the instrument measure the construct to be measured and three aspects were evaluated: structural validity, which concerns the internal relationships; hypotheses testing, based on the assumption that the instrument validly measures the construct to be measured (concerning the relationships to scores of other instruments or differences between relevant groups); and discriminative validity.[20]

Hypothesis testing was performed by establishing hypothesis *a priori* to correlate the Pedi-IKDC scores with previously validated instruments, i.e., EQ-5D-Y subscale scores and specific CHAQ questions, related to lower limb function. The Spearman coefficient (ρ) was used to measure correlations ($\rho < 0.3$ low, $0.3 < \rho < 0.5$ moderate, $0.5 < \rho < 0.8$ strong and $\rho > 0.8$ excellent).[36] Construct validity was considered adequate if 75% of the hypothesis were accepted.[36]

The following hypothesis were tested: 1) the final scores of Pedi-IKDC would negatively correlate with the EQ-5D-Y and CHAQ subscale scores; 2) the final scores of Pedi-IKDC would positively correlate with the VAS-Health score of EQ-5D-Y; and 3) the Spearman coefficient is > |0.4|.

Discriminative validity was determined by the low correlation between Pedi-IKDC score and the subscale "Grip" of the CHAQ questionnaire.

• Responsiveness

Responsiveness is defined as the ability to detect clinically important changes over time. It was determined with a distribution-based method from the overall scores T0 and T2 of those patients who reported a minimal clinical improvement (answers "much better", "better", "worse" and "much worse" in the anchor-question).[18]

Effect size was calculated with the formula (mean T2 score - mean T0 score/ standard deviation of T0 score); small effects were considered > 0.20, moderate effect > 0.50, and large effect > 0.80.[9] The standardized response mean (SRM) was calculated with the formula (mean T2 score − mean T0 score/standard deviation of the change in score).[18]

A priori hypothesis that the change in score between the first and last states would positively correlate with the patients' answer to the anchor-question was tested, as well as the Spearman coefficient would be greater than 0.3.[37]

• Interpretability

Interpretability is the degree to which one can assign qualitative meaning to a quantitative score. The interpretability was assessed at T0 by examining the distribution of the Pedi-IKDC score, the floor and ceiling effects and the minimal important change (MIC).[18]

Floor and ceiling effects were considered present if more than 15% of the patients scored the Pedi-IKDC with, respectively, 0 to 5 or 95 to 100. The interpretability of the Pedi-IKDC was given a positive rating if floor or ceiling effects were absent.

The MIC represents the change in score that can be considered clinically relevant. It was calculated by means of dividing the sample into two groups, based on the anchor-question: better (answers "much better"/"better") and stable ("somewhat better"/"same status"/"somewhat worse"). Then, the optimal cut-off of the receiver operating characteristic (ROC) curve was used to determine MIC.[38] The area under the curve was considered adequate if it was greater than or equal to 0.70.[39]

RESULTS

Translation and cross-cultural adaptation

The final Portuguese version of the Pedi-IKDC is shown in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18425/Appendix_01.pdf). The translation process of the questionnaire, including the pilot-test, did not raise any discrepancies or comprehension problems. In the item 11.d, the phrase "squat down like a baseball catcher" was modified to "agachar (posição de cócoras)" [i.e., "squat down (squatted position)"], since the practice of baseball is uncommon in Portugal and it could have raised comprehension issues. Also, the expression "saltar ao pé-coxinho" (i.e. the action of jumping repeatedly and landing on only one foot) was added to the item 11.h, since it is a very common expression among Portuguese children.

Demographics

In total, 47 patients completed the T0 survey, 42 patients completed the T1 survey, and 40 patients completed the T2 survey; demographic data and diagnoses of the patients are shown in Table 1.

The total scores obtained from the surveys were: 54.90 ± 23.99 for T0; 59.27 ± 25.47 for T1; and 65.32 ± 26.58 for T2. There were no statistically significant differences in the scores obtained between male and female patients or between diagnoses.

Structural validity

All 19 items were introduced in the PCA. The factorial analysis showed a total explained variance of 54.82% and the eigenvalue was stabilized after the first component, showing that the scale is one-dimensional. Bartlett test was

Table 1 – Demographic data of the patients

		Value
Sex (n, %)	Male	15 (32%)
	Female	32 (68%)
Age (years) (mean ± SD; min. - max.)		14.04 ± 2.25 (9.0 - 17.0)
BMI (kg/m^2) (mean ± SD; min. - max.)		21.60 ± 3.26 (16.4 - 32.0)
Diagnosis (n, %)	Patellar instability	21 (44.7%)
	Osgood-Schlatter	9 (19.1%)
	Meniscal injury	5 (10.6%)
	ACL failure	4 (8.5%)
	Valgus knee	3 (6.4%)
	Patellar fracture	1 (2.1%)
	Osteochondritis	1 (2.1%)
	Patellar syndrome	1 (2.1%)
	Intra-articular free body	1 (2.1%)
	Medial collateral ligament injury	1 (2.1%)
Duration of symptoms (n, %)	Less than 2 weeks	2 (4.3%)
	2 to 8 weeks	10 (21.3%)
	2 to 6 months	3 (6.4%)
	6 to 12 months	7 (14.9%)
	More than 1 year	25 (53.2%)

n: number of participants; SD: standard deviation; BMI: body mass index; ALC: anterior cruciate ligament.

significant ($p < 0.001$) and KMO index was adequate (KMO = 0.894). Every item had a factor loading greater than 0.3, so all items from the original version were maintained.

Internal consistency

Cronbach α was excellent (α = 0.941) and correlation item-total was greater than 0.3 for every item, indicating high internal consistency and correlation between items.

Reliability and measurement error

Retest was filled-in by 89.4% of the participants, after a mean of 16 days (12 to 24 days) from T0. Thirty-three (78.6%) participants were eligible for the reliability analysis. Test-retest was excellent (ICC = 0.92).

The SEM was 6.87 and the SDC at individual and group level was 19.04 and 3.31, respectively.

Construct validity

The Pedi-IKDC score was negatively correlated with EQ-5D-Y and CHAQ subscale scores and positively correlated with the VAS-Health score (Table 2), with ρ > |0.4|.

A significant ($p < 0.05$) correlation was found between the overall Pedi-IKDC score and the CHAQ domains walking (ρ = -0.656), activities of daily living (ρ = -0.547) and pain (ρ = -0.668), and the questions on running and playing activities (ρ = -0.866) and bending to reach the floor (ρ = -0.775); as well as the EQ-5D-Y domains mobility (ρ = -0.617), self-care (ρ = -0.459), usual activities (ρ = -0.690), pain (ρ = -0.608), anxiety (ρ = -0.456) and the VAS health scale (ρ = 0.589) (Table 2). The correlations found were mostly strong or, in some cases (self-care and anxiety domains of EQ-5D-Y), moderate.

Discriminative validity was confirmed by the absence of correlation between Pedi-IKDC score and the CHAQ subscale "Grip" (ρ = -0.177, $p > 0.05$).

Over 75% of the hypotheses were confirmed, so construct validity was considered adequate.

Responsiveness

The T2 questionnaire was filled-in by 85.1% of the participants, after a mean of 10 weeks (9 to 12 weeks) from T0. The Pedi-IKDC score variation between T0 and T2 showed a positive correlation (ρ > 0.3, $p < 0.05$) with the score of the anchor-question. The Pedi-IKDC showed a moderate effect size (0.671) and SRM of 1.14.

Interpretability

Floor effect was 0% for all questionnaires. Ceiling effect was 0%, 2.38% and 5.0% for T0, T1 and T2, respectively. So, both floor and ceiling effects were considered absent. The AUC of the ROC curve was adequate (AUC = 0.725) and MIC was 18.48.

Table 2 – Construct validity analysis by Spearman correlation between Pedi-IKDC and domains of EQ-5D-Y and CHAQ

		Pedi IKDC Score (ρ)
EQ-5D-Y Domain score	Mobility	-0.617*
	Self-care	0.459*
	Pain	-0.608*
	Usual activities	-0.690*
	Anxiety	-0.456*
	VAS – Health	0.589*
CHAQ Domain score	Walk	-0.656*
	Bend	-0.775*
	Grip	-0.177
	ADL	-0.547*
	Activities (run and play)	-0.866*
	VAS -Pain	-0.668*

* $p \leq 0.05$; EQ-5D-Y: EuroQol-5 Dimension Youth; Pedi-IKDC: Pediatric International Knee Documentation Committee Subjective Knee Form; CHAQ: Childhood Health Assessment Questionnaire; ρ: Spearman correlation coefficient; ADL: activities of daily life; VAS: visual analogue scale.

DISCUSSION

In this study, parents or caregivers were allowed to assist participants with completion of the questionnaire and the instruments applied. Although this does create a potential bias related with outcome assessment by proxy, the authors believe that this is a typical and transversal approach in pediatric outcome assessment.

The psychometric properties studied revealed that the Portuguese version is a valuable instrument to measure knee function and symptoms in the Portuguese-speaking pediatric population.

In particular, since the content validity by means of PCA showed that the scale is one-dimensional, all items from the original version were preserved on the final version. Internal consistency demonstrated excellent results and that there are no redundant items. Moreover, we demonstrated an excellent test-retest reliability, confirming the reproducibility of the questionnaire in pediatric patients with knee musculoskeletal disorders.

Construct validity aims to assess the relationship of the instrument with an accepted outcome instrument, ideally, a gold standard, if one exists. Considering that, in the case of knee symptoms, function and activities evaluation there is no gold-standard nor any other available knee-specific scale validated for the Portuguese-speaking pediatric population, construct validity was analysed by means of 'hypotheses testing' by correlations to EQ-5D-Y and CHAQ scores. The EQ-5D-Y is a health-related quality of life questionnaire which was shown to be valid for orthopedic problems, even if not specifically for knee disorders, and its adult version has shown highly valid and reliable in knee osteoarthritis or patients undergoing arthroscopic knee surgery.[40] The CHAQ is a well-established outcome instrument, and it has been used to validate other outcome tools in the pediatric literature. Therefore, these two generic instruments were the most appropriate validated scales available for the analysis. Additionally, in order to increase the accuracy of the validation, specific items and domains related with the lower limb function were selected to perform this analysis. The tested items and domains showed a significant moderate to strong correlation with the overall Pedi-IKDC score in more than 75% of the hypotheses tested, indicating that Pedi-IKDC follows accepted hypotheses and produces results consistent with children's perceptions on their symptoms, function, limitations on their activities and expectations.

The analysis of responsiveness, as generated by completion of the Pedi-IKDC in different moments of the diagnosis and treatment, showed a moderate effect size and a moderate SRM, indicating that this instrument is responsive. When comparing these two measures (effect size and SRM) to other previous translations of the same instrument, we can verify that they variate considerably and our values are in between the previous reported outcomes (Table 3).

Finally, concerning interpretability analysis, floor and ceiling effects were absent, which is excellent, and the area under the ROC curve was adequate. These psychometric characteristics of our observed data for the Pedi-IKDC in the Portuguese pediatric population were comparable with those found in previous studies of validation in other languages.[9,10,15-17]

However, as for measurement errors, our analysis showed slightly higher values than some of the previous validation studies, even if comparable to those reported by Jacobsen *et al*[16] and Van der Velde *et al*.[15] According to our

Table 3 – Summary of the psychometric properties demonstrated by Pedi-IKDC in the currently available translations and adaptations

	n (T0, T1, T2)	Internal consistency	Reliability	Measurement error	Structural validity	Construct validity	Responsiveness	Interpretability
English (original)[9,10]	589	α = 0.91	ICC = 0.91	n.r.	Adequate	Adequate - CHAQ	Good SRM = 1.35 ES = 1.39	Floor and ceiling effects 30%
Danish[16]	99, 53, 94	α = 0.9	ICC = 0.9	SEM = 11.3 SDC.ind = 4 SDC.group = 11	n.r.	n.r.	Good SRM = 0.9 ES = 0.2	MIC = 12.0
Dutch[15]	100, 54, 71	n.r.	ICC = 0.8	SEM = 8.6 SDC.ind = 23.8	Adequate	Adequate - NRSP - Lysholm Knee Score - EQ-5D - KOOS-Child	Good SRM = 1.25 ES = 1.5	Absent floor and ceiling effects
Italian[17]	89, 81, 49	α = 0.92	ICC = 0.96	SEM = 4.4 SDC.ind = 12.3	n.r.	n.r.	SRM = 0.86 ES = 0.79	Ceiling effect 22%
Portuguese	47, 42, 40	α = 0.94	ICC = 0.92	SEM = 6.87 SDC.ind = 19.06 SDC.group = 3.31	Adequate	Adequate - CHAQ - EQ-5D-Y	Good SRM = 1.14 ES = 0.671	Absent floor and ceiling effects; MIC = 18.48

n: number of participants; T0: initial evaluation; T1: re-test evaluation; T2: evaluation after treatment; α: Cronbach alpha coefficient; ICC: interclass correlation coefficient; SEM: standard error of measurement; SDC.ind: smallest detectable change at individual level; SDC.group: smallest detectable change at group level; SRM: standardized response mean[2]; ES: effect size; MIC: minimum important change; n.r.: not reported; CHAQ: Childhood Health Assessment Questionnaire; NRS: Numeric Rating Score for pain; EQ-5D: EuroQol-5 Dimension; EQ-5D-Y: EuroQol-5 Dimension Youth; KOOS-Child: Knee Injury and Osteoarthritis Outcome Score for children.

results, in the clinical and research setting, the score variations needed to detect true clinically significant differences are not the same when analysing an individual or a group of patients: between two assessment points, a mean score variation of three points in a group of patients is clinically significant. However, when evaluating a single individual a variation of 19 Pedi-IKDC score points is needed in order to detect a clinically significant status modification. As such, in the clinical setting, the use of Pedi-IKDC is more limited when assessing one patient, when a higher score variation is needed to identify a clinically significant variation. In the research setting, however, when assessing groups of patients, the measurement error is minimal, meaning that the validated instrument is adequate for group analysis.

Even though there is no consensus on the recommended sample size for cross-cultural adaptation and validation studies of PROMs,[39,41,42] one of the determinants of the measurement error analysis is the sample size, so this limitation of individual score interpretation could be due to our relatively small sample size. However, the results of our analysis are in line with other validations of the Pedi-IKDC score. Although not all the authors systematically reported their measurement errors, SDC at the individual level varied berween 4.0 to 23.8, SDC at the group level was 11 as reported by Jacobsen *et al* and SEM varied between 4.4 and 11.3, suggesting that the measurement errors obtained are mirroring the instrument limitations and not really the small sample limitations.

Among the strengths of this study, there is the fact that the instrument was translated, adapted, and validated according to the COSMIN Checklist recommendations, allowing our methodology to be reproductible for other studies. Another aspect is that this study was conducted in a population affected by a broad spectrum of knee disorders, keeping in mind that the questionnaire was not designed as 'disease-specific' tool.

The study presents some limitations. As previously reported, the smaller sample size could have influenced our measurement errors, as well as effect size measurements. Secondly, the construct validity analysis was compromised since there are no validated instruments in the studied population available as a 'gold standard' for knee disorders. Therefore, we decided to use two general health instruments, which were already used in other translations of this questionnaire and obtained similarly adequate results.

CONCLUSION

The Pedi-IKDC was successfully translated into Portuguese and, based on the psychometric properties, it is a reliable, valid, and responsive tool to assess outcomes[1] in children and adolescents with a broad range of knee disorders. As a result, Pedi-IKDC seems to be an acceptable and valuable tool for assessment of patients aged eight to 17 with knee disorders in the clinical and research setting.

PREVIOUS PRESENTATIONS

This paper was presented as a communication at the 40th Portuguese National Congress of Orthopedic Surgery and Traumatology, which took place as a virtual conference on the 21st and 22nd of October 2021.

AUTHOR CONTRIBUTIONS

All authors declare that they had a substantial, direct intellectual contribution in the design and elaboration of the article, participated in the analysis and interpretation of data, participated in the writing of the manuscript, revision of versions and critical review of the content; approval of the final version and agree that they are responsible for the accuracy and completeness of the entire 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 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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Erasmus Syndrome: An Underrecognized Entity

Síndrome de Erasmus: Uma Entidade Pouco Reconhecida

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ABSTRACT

We present a case of a 33-year-old male who worked as a plumber and a locksmith. The patient presented with diffuse myalgia and asthenia, skin sclerosis and puffy fingers, Raynaud's phenomenon, exertional dyspnea and erectile dysfunction. The presence of specific autoantibodies enabled the diagnosis of systemic sclerosis. Chest-computed tomography revealed upper lobe consolidation. After extensive evaluation, the multidisciplinary interstitial lung disease team concluded that the patient also had advanced silicosis. After a year, there was significant clinical, radiologic, and functional deterioration of the lung disease. The patient was referred for lung transplant. Silica inhalation is the cause of silicosis but is also implicated in the development of systemic sclerosis (Erasmus syndrome). Although they share a common risk factor, it is rare to find both diseases co-existing. We present this case of a young patient where both diseases presented aggressively in order to raise awareness to this association.
Keywords: Connective Tissue Diseases; Lung Diseases, Interstitial; Silicosis; Scleroderma, Systemic

RESUMO

Apresentamos o caso de um homem de 33 anos que trabalhava como canalizador e serralheiro. Apresentava mialgias e astenia, esclerose cutânea e *puffy fingers*, fenómeno de Raynaud, dispneia de esforço e disfunção erétil. A presença de autoanticorpos específicos permitiu o diagnóstico de esclerose sistémica. A tomografia computadorizada de tórax revelou consolidações dos lobos superiores. Após extensa avaliação, o grupo multidisciplinar de doenças do interstício concluiu que o doente tinha também silicose avançada. Após um ano, houve agravamento clínico, radiológico e funcional significativo da doença pulmonar. O doente foi encaminhado para transplante pulmonar. A inalação de sílica é a causa da silicose, mas também está implicada no desenvolvimento da esclerose sistémica (síndrome de Erasmus). Embora tenham um fator de risco comum, é raro encontrar as duas doenças simultaneamente. Apresentamos o caso de um doente jovem em que ambas as doenças se apresentaram de forma agressiva para alertar sobre esta associação.
Palavras-chave: Doenças Pulmonares Intersticiais; Doenças do Tecido Conjuntivo; Escleroderma Sistémico; Silicose

INTRODUCTION

Silicosis is caused by the inhalation of free crystalline silica and is one of the most important occupational diseases worldwide. Its presentation, clinical course and severity are variable.[1] In most severe cases, there is disease progression into large fibrotic masses with upper-lobe predominance, which is known as progressive massive fibrosis.[1–3] A lesser-known association is the one between silica exposure and the development of systemic autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, antineutrophil cytoplasmic antibody-related vasculitis and systemic sclerosis (SSc).[4–6] The rare occurrence of SSc developing after silica exposure is termed Erasmus syndrome.[7]

CASE REPORT

A 33-year-old Caucasian male presented with a history of diffuse myalgia and asthenia, edema of the hands with associated pain and Raynaud phenomenon, exertional dyspnea (mMRC 1- shortness of breath when hurrying or walking up a slight hill) and new-onset erectile dysfunction. He was a light smoker (ten packs a year), worked as a plumber and a locksmith, and had a family history of rheumatoid arthritis in a grandmother and a cousin. On clinical examination, the patient was eupneic with a peripheral resting oxygen saturation of 96%; he had skin sclerosis and puffy fingers (Fig. 1). Bloodwork revealed an elevated erythrocyte sedimentation rate of 32 mm, positive ANA antibodies (fine speckled) with a titre 1:320, anti-SSA-52kDa and Scl-70 with a strong titre. Radiography of the hands showed joint space narrowing of the interphalangeal joints.

A diagnosis of SSc was made, and given the severity of the symptoms, the patient was admitted to the ward and started on intravenous immunoglobulin. During the admission, further investigation was undertaken. Videocapillaroscopy was suggestive of secondary Raynaud's, sclerodermic pattern in early stage, and the echocardiogram showed good ventricular function and no signs of pulmonary hypertension. The chest radiography done upon admission (Fig. 2) showed bilateral upper lobe opacities and left pleural effusion.

The chest computed tomography (CT) (Fig. 3) revealed areas of upper lobe consolidation, micronodular ground-glass opacities with a lower lobe predominance and a left pleural effusion.

The patient then underwent bronchoscopy which showed no endoscopic abnormalities. Bronchoalveolar

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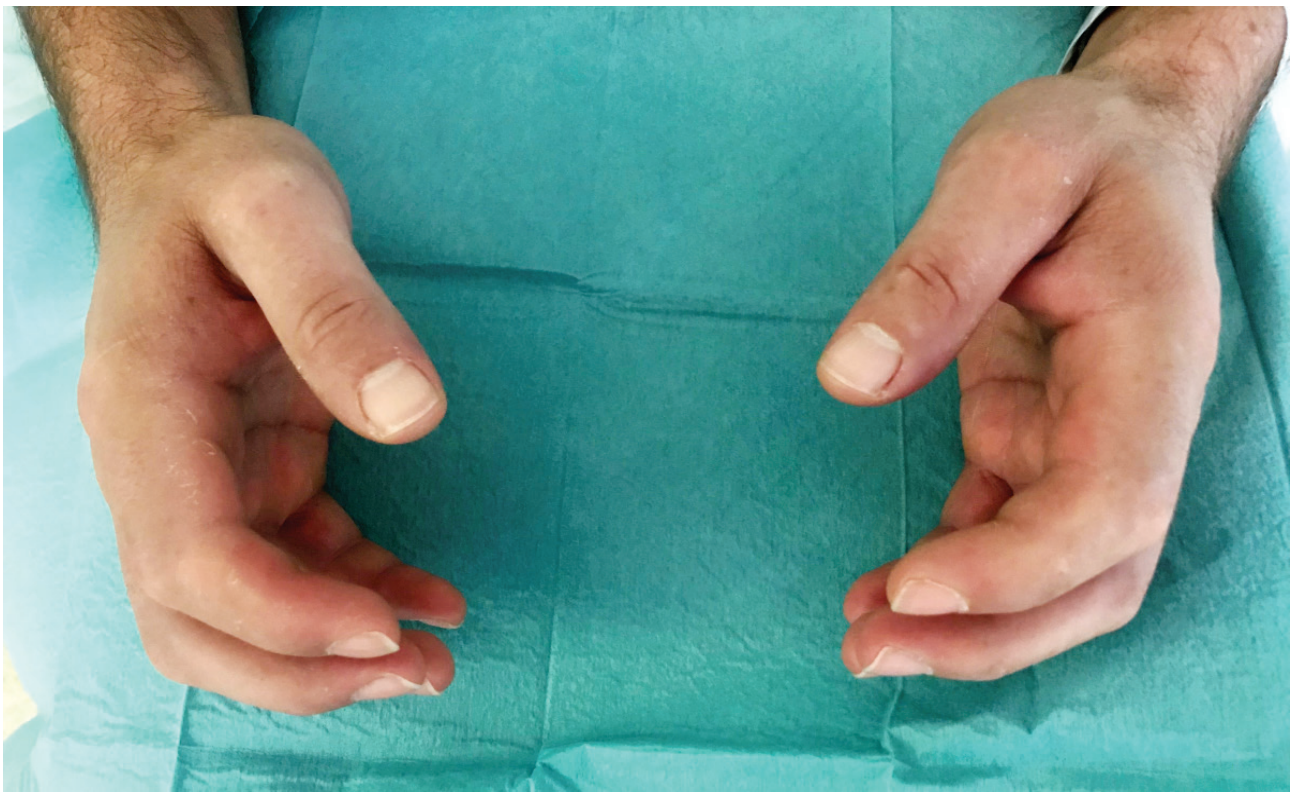

Figure 1 – Patient's hands showing skin sclerosis and puffy fingers

lavage (BAL) showed lymphocytosis (24%) with a normal CD4+/CD8+ and CD4+CD103+/CD4+ ratios and negative culture test. A Mantoux test was performed with 10 millimeters. Pulmonary function tests (PFT) revealed a moderately severe restrictive pattern and a moderate decrease in the diffusing capacity of carbon monoxide. In the six-minute walk test, the patient had a starting peripheral oxygen saturation of 96% and a minimum saturation of 94%. He walked 600 m and ended the test with extreme fatigue and moderate dyspnea.

A surgical lung biopsy was proposed, but the patient refused to undergo surgery. The case was then presented to the multidisciplinary interstitial lung disease (ILD) team. The conclusion was that, given the history of occupational exposure to silica, the radiologic findings were consistent with progressive massive fibrosis, and in the absence of alternative differentials, a solid diagnosis of silicosis could be made.

The patient had clinical improvement, and immunosuppressive therapy was adjusted to mycophenolate mofetil 1000 mg twice daily plus prednisolone 5 mg daily. He was started on sildenafil 25 mg and bosentan 125 mg for the treatment of Raynaud's phenomenon and underwent treatment for latent tuberculosis. He was discharged from the hospital after which he remained clinically stable for several months.

After about a year, the patient started to complain of worsening exertional dyspnoea and a weight loss of 11 kg in a few months. The PFTs (Table 1) showed worsening of the restrictive pattern with a decrease of the forced vital capacity (FVC) of 740 mL, which corresponds to 22%. The CT scan revealed progression of the fibrotic masses (Fig. 4). The symptoms associated with SSc remained stable.

The patient's attending physician in the Pulmonology Department advised him to undergo evaluation for lung transplantation and he was considered eligible for bilateral lung transplant, given the absence of significant calcification of the fibrotic masses and hilar lymphadenopathies. The patient is currently on the lung transplant waiting list.

DISCUSSION

SSc is an autoimmune connective tissue disease characterized by vasculopathy, progressive fibrosis with multiorgan involvement and the presence of specific autoantibodies.[8] The association between SSc and silica was first described by Erasmus in 1957 with 17 cases of SSc in South African miners and has since been called Erasmus syndrome.[7] Although little is known about the mechanisms by which silica exposure leads to the development of SSc, it has been proposed that silica leads to the activation of the

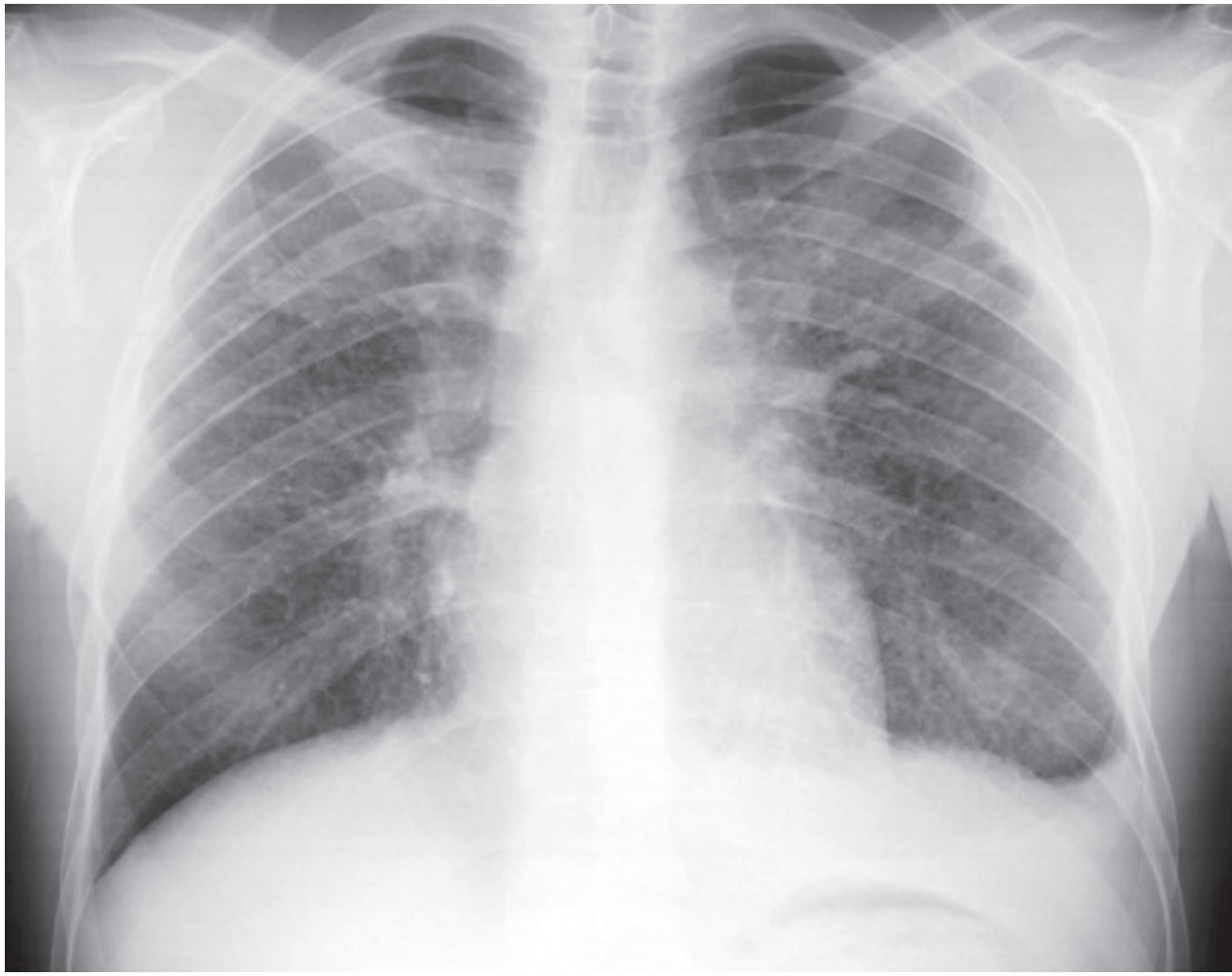

Figure 2 – Admission's chest radiography

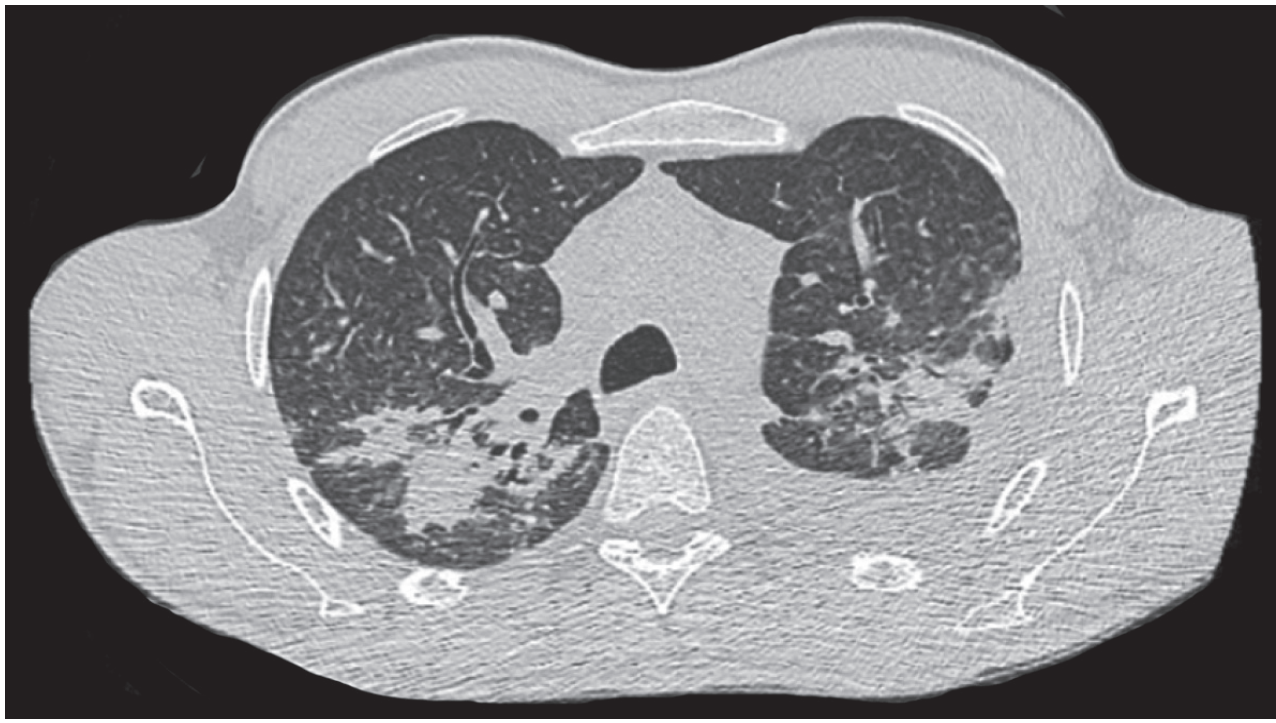

Figure 3 – Thoracic computed tomography of the chest in June 2019

Table 1 – Pulmonary function tests in June 2019 (left column) and July 2020 (right column)

	06/2019	07/2020
FVC	3.43 L (60%)	2.69 L (47%)
FEV1	2.66 L (57%)	2.01 L (43%)
FEV1/FVC	77	74
TLC	4.88 L (65%)	4.31 L (57%)
RV	1.32 L (70%)	1.32 L (70%)
DLCO	52%	45%

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: diffusing capacity for carbon monoxide

innate immune system with lung inflammation, activation of the adaptive immunity and production of autoantibodies.[4] Epidemiological studies confirmed this, and a 2009 meta-analysis concluded that exposure to silica may be associated with a 3.2-fold increase in the relative risk of SSc, while the absolute risk in the general population is less than 0.5%.[6]

In the case of this patient, with an established diagnosis of SSc and respiratory symptoms, we expected to find pulmonary complications. These typically present in the form of ILD as non-specific interstitial pneumonia or, less commonly, usual interstitial pneumonia,[9] but none of these patterns fitted the radiologic findings on the CT scan. A multidisciplinary discussion of the case led to the diagnosis of silicosis. This disease can present as acute silicosis, developing within weeks to a few years after exposure to high concentrations of silica and with rapid onset of dyspnea, cough, weight loss and fatigue. Chronic silicosis develops more than ten years after exposure with slowly progressive symptoms. Progressive massive fibrosis is the most severe form and results from the coalescence of the silicotic nodules and consolidations into large fibrotic masses in the upper lung zones.[2,3] As there is no effective treatment, efforts should be focused on its prevention, early diagnosis and swift elimination of further exposure. In end-stage disease, lung transplantation is a treatment option for selected patients.[3,10]

We add this case to the small number of published case reports of silicosis and SSc co-existing in the same patient,[11–15] with the aim of raising awareness to this association, and as a reminder that the same environmental and occupational exposures may be a risk factor for different diseases.

AUTHOR CONTRIBUTIONS

AM, IM: Draft of the manuscript.

SP, AB: Criticial review of the manuscript and redrafting.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical

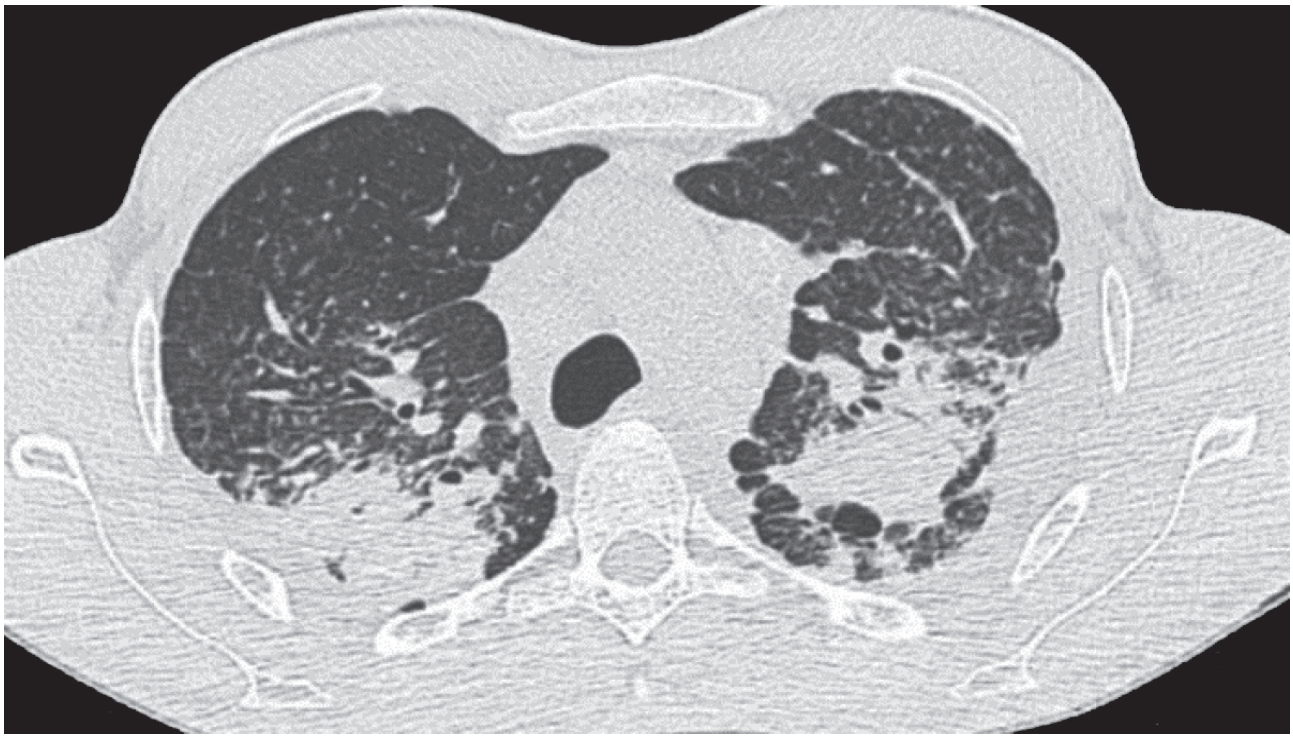

Figure 4 – Thoracic computed tomography of the chest in August 2020 showing worsening of the fibrotic masses

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

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Fever in a Patient with a Central Venous Catheter Colonized by *Pandoraea pnomenusa*

Febre numa Doente com Cateter Venoso Central Colonizado por *Pandoraea pnomenusa*

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ABSTRACT

Pandoraea species are a newly described genus of multidrug-resistant, non-fermentative Gram-negative bacilli, mainly isolated from sputum samples of cystic fibrosis patients. In immunocompromised patients or with high antibiotic selective pressure, these pathogens are generally opportunistic and invasive. Although *Pandoraea* spp. are rare, the true incidence of these infections may be underestimated due to difficulties in microbial identification by phenotypic methods. We present the case of a 51-year-old woman, with new-onset fever after a prolonged hospitalization and multiple courses of antibiotics. Mass spectrometry assays identified *Pandoraea pnomenusa* in the blood cultures taken from the central venous catheter and in the catheter tip. Fever cessation after catheter removal suggests a catheter-related bloodstream infection. To the best of our knowledge, this is the first isolation of a *Pandoraea* spp. in Portugal, which should raise awareness to the emergence of these opportunistic and multidrug-resistant microorganisms, and the importance of its prompt identification.
Keywords: Catheter-Related Infections; Central Venous Catheters/adverse effects; Fever; Pandoraea pnomenusa

RESUMO

O género *Pandoraea* é constituído por bacilos Gram-negativo não fermentadores multirresistentes, maioritariamente isolados em amostras respiratórias de doentes com fibrose quística. No entanto, em doentes imunodeprimidos e/ou sujeitos a elevada pressão antibiótica, podem ser agentes invasivos e oportunistas. Apesar de estas infeções serem raras, a incidência pode estar subestimada por dificuldades na sua identificação por métodos fenotípicos. Apresentamos um caso clínico de uma mulher de 51 anos, com febre *de novo* após um internamento complexo e múltiplos ciclos de antibioterapia. Nas hemoculturas colhidas do cateter venoso central e na ponta do cateter foi identificada, por espectrometria de massa, uma *Pandoraea pnomenusa*. A resolução da febre após retirada do cateter sugere uma bacteriemia associada a cateter. Tanto quanto é do nosso conhecimento, este é o primeiro caso reportado de *Pandoraea* spp. em Portugal, pondo em evidência a necessidade de se estar alerta para a emergência de agentes de infeção multirresistentes, bem como a necessidade da sua identificação precoce.
Palavras-chave: Cateter Venoso Central/efeitos adversos; Febre; Infecções Relacionadas a Cateter; Pandoraea pnomenusa

INTRODUCTION

The *Pandoraea* genus was first described by Coenye T *et al*[1] in 2000, after a careful genotypic and phenotypic characterization of species isolated from the environment or sputum of cystic fibrosis (CF) patients, previously misidentified as *Burkholderia cepacia, Ralstonia picketti* or *Ralstonia paucula*. The term *Pandoraea* refers to Pandora's box in Greek mythology – the origin of the evils of mankind.

These non-fermentative, Gram-negative bacilli (NFGNB), with oxidase activity, are naturally encountered in soil or water, but they can also be nosocomial pathogens associated with invasive devices, such as catheters or ventilation systems.[1–6] To date, six species have been identified in humans – *Pandoraea apista*, *Pandoraea pulmonicola, Pandoraea pnomenusa*, *Pandoraea sputorum, Pandoraea norimbergensis* and *Pandoraea fibrosis.*[1,6]

Although rare, the *Pandoraea* spp. are emerging, with most isolates originating from sputum samples of patients with CF or other lung diseases.[2–4,7,8] In addition to respiratory samples, isolation in skin lesions, urine and blood have been described in CF and non-CF patients, the latter highlighting the invasive capacity of this species.[2,4,9,10]

P. pnomenusa was the most isolated species from blood cultures (BC) in a Centers for Disease Control and Prevention study of 2001,[2] which revealed an increased potential for invasive disease. Since then, multiple invasive infections of *Pandoraea* spp. were described, mostly in non-CF patients.[5,8–11] Catheter-related bloodstream infections (CR-BSI) and colonization of catheters without bacteriemia were also reported.[3,12]

Phenotypically, *Pandoraea* spp. are very similar to *Burkholderia* and *Ralstonia genera* (with an intermediate phylogenetic position between these two), which may lead to an erroneous phenotypic identification of these agents.[1–5,8,10] In fact, the incidence of *Pandoraea* infections may be underestimated due to difficulties in its identification. However, mass spectrometry assays have proven to be able to identify NFGNB which were not correctly identified by phenotypic methods.[5,10,13,14]

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The treatment of *Pandoraea* infections can be challenging, as they have a broad resistance to antibiotics, and natural or acquired resistance mechanisms are not yet fully understood.[2–5,7,8] In the particular case of carbapenems, there is a unique discrepancy in terms of susceptibility between meropenem and imipenem. Despite the presence of meropenem-hydrolyzing β-lactamases, which causes intrinsic resistance to meropenem, susceptibility to imipenem is common.[2,4,5,8,12]

Moreover, due to its rarity, neither the European Committee on Antimicrobial Susceptibility Testing (EUCAST) nor the Clinical and Laboratory Standards Institute (CLSI) have established the antibiotic concentrations (breakpoints) at which this bacteria is considered to be susceptible to a certain antibiotic.[5,15]

CASE REPORT

We report the case of a 51-year-old woman with a past medical history of severe hearing loss of unknown etiology, type 2 diabetes *mellitus* (HbA1c levels between 7.4% and 8.5% before admission), and a recent ischemic stroke requiring hospitalization for 34 days.

Twenty days after her discharge, the patient was admitted to the intermediate care unit with the diagnosis of sepsis due to *Clostridium perfringens* colitis with bacteriemia, and initially completed 14 days of piperacillin/tazobactam and metronidazole.

Due to difficult peripheral access, a central venous catheter (CVC) was placed the following day.

The patient required a total of 78 days of hospitalization, reflecting a complex clinical course, with multiple infections and antimicrobial courses, which are summarized in Fig. 1.

On the 50th hospitalization day, while on daptomycin and ceftazidime/avibactam, the patient redeveloped subfebrile temperatures (37.4ºC) of uncertain origin. BC were drawn the following day. Due to difficulty in obtaining peripheral access, BC were taken from the CVC.

One BC set was positive 21 hours after incubation. On microscopic examination, no bacteria were visualized in Gram staining. On bacteriological cultures, MacConkey agar revealed very small, non-fermentative colonies, oxidase positive, and blood and chocolate agar small, grey and pleomorphic colonies.

On the 53rd day, due to persistence of fever (maximum of 38.6ºC) and the presence of a NFGNB on BC, empiric meropenem was initiated. The CVC was removed, and the catheter tip was cultured using a semiquantitative roll plate method (Maki's technique).

The second BC set was positive after 35 hours of incubation, and the Gram staining revealed very short and thin Gram-negative bacilli.

In both BC taken from the CVC and in the catheter tip culture, *P. pnomenusa* was identified by mass spectrometry (VITEK®MS) with 99.9% certainty. The phenotypic identification method (VITEK® 2) was only able to identify the agent as *Pandoraea* spp. with 89% certainty.

On the 54th day, it was possible to obtain two peripheral BC, which yielded negative results.

According to the PK-PD (non-species related breakpoints) of EUCAST 2021,[15] antimicrobial susceptibility was assessed by gradient tests (ETEST®) for ciprofloxacin, gentamycin, ceftazidime, ceftazidime/avibactam, piperacillin/tazobactam, imipenem and meropenem. The minimal inhibitory concentration of 2 µg/mL of imipenem suggested that the isolated *P. pnomenusa* could only be treated with this antibiotic. For this reason, meropenem was discontinued.

Fever cessation coincided with CVC removal and no further treatment was instituted. The patient remained apyretic until discharge.

DISCUSSION

We report the identification of a rare microorganism – *P. pnomenusa.* To the best of our knowledge, this is the first isolation of *Pandoraea spp*. in Portugal.

The correct identification of NFGNB is crucial as the true incidence of *Pandoraea* infections may be underestimated. Its identification should be performed with mass spectrometry assays, which have demonstrated to have greater diagnostic accuracy compared with other phenotypic methods. In our laboratory VITEK® 2 was not able to distinguish between *Pandoraea* species.

It is known that *Pandoraea* spp. are opportunistic pathogens, infecting mainly CF patients, or individuals with some degree of immunosuppression or with a high antibiotic selective pressure.[3,5,8,10,12] Our patient was hospitalized for a long period of time and received multiple antibiotic therapies, which probably favored the appearance of this organism.

Although *P. pnomenusa* was isolated in the BC taken from the CVC and in the catheter tip, the diagnosis of CR-BSI cannot be confirmed, as this agent was not identified in simultaneous peripheral BC. On the other hand, the fever had no-localized symptoms and ceased after removal of the colonized CVC, which supports this diagnosis.

To conclude, clinicians should be aware of the emergence of these multidrug-resistant microorganisms in susceptible patients, as they can be both colonizers and invasive infectious agents. Since *Pandoraea* species are a natural reservoir of carbapenem-hydrolyzing oxacilinases (antibiotic resistance genes), empirical treatment with carbapenems may be inappropriate, and even result in increased morbidity. Furthermore, the physical proximity with other species may promote plasmid-mediated horizontal

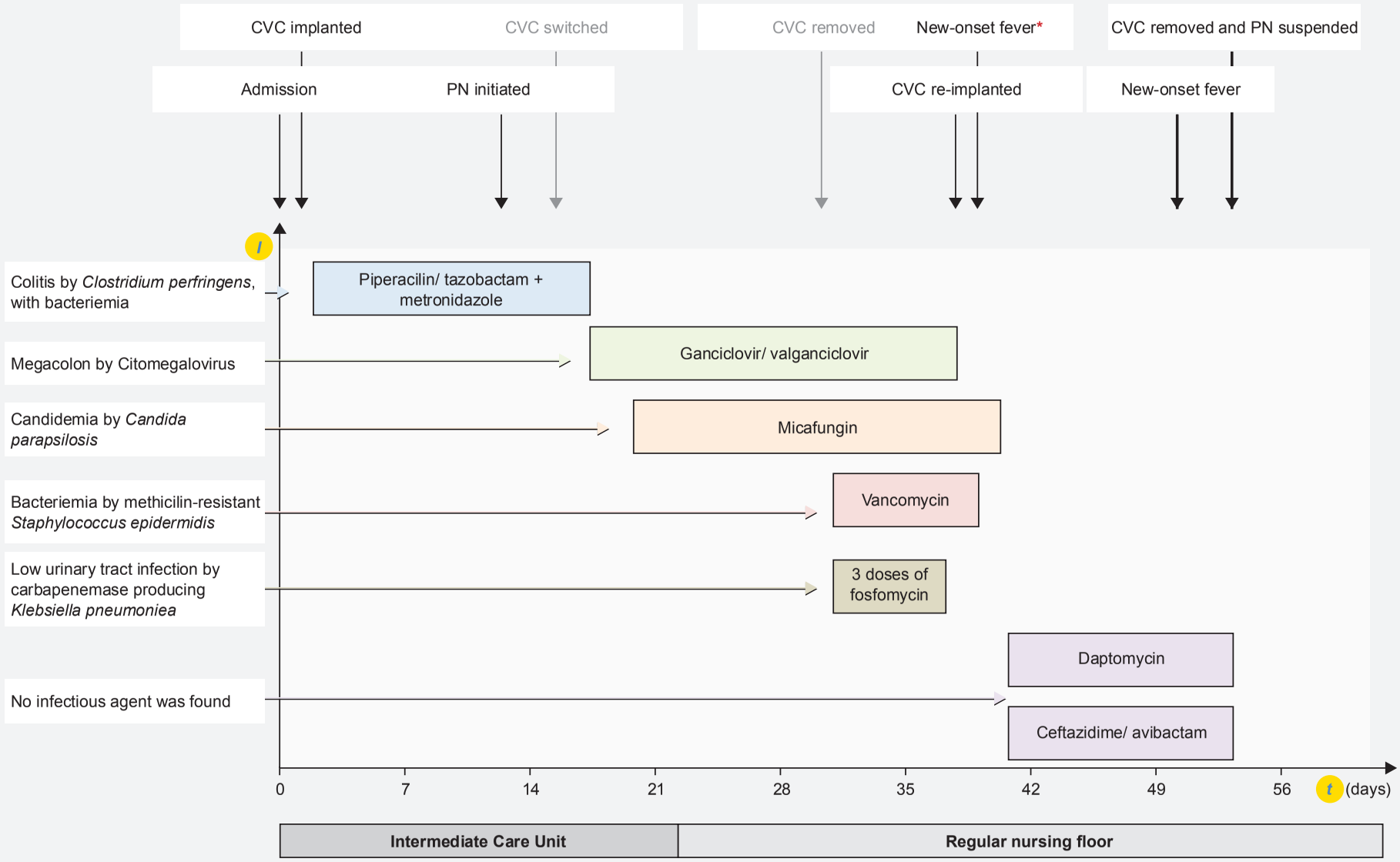

Figure 1 – Infections and antibiotics during hospital stay

t: time in days of hospital stay; *I*: infection and infectious agent; CVC: central venous catheter; PN: parenteral nutrition.

* On the 39th day, the patient initiated fever without localized symptoms. No infectious agent was found, so daptomycin and ceftazidime/avibactam were initiated empirically.

gene transfer of these resistance genes, favoring the appearance of new multi-drug resistance pathogens.[7]

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AUTHOR CONTRIBUTIONS

SRO: Literature review, data acquisition, drafting of the paper.

ICM: Literature review, data acquisition.

CR: Critical review of the paper (medical data).

MJS: Critical review of the paper (laboratory data).

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.

INFORMED CONSENT

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ACTA MÉDICA PORTUGUESA
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Fibrofoliculomas: A Pista para o Diagnóstico da Síndrome de Birt-Hogg-Dubé

Fibrofolliculomas: The Clue to the Diagnosis of Birt-Hogg-Dubé Syndrome

Catarina CORREIA✉[1], Luís SOARES-DE-ALMEIDA[1,2], Paulo FILIPE[1,2]
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Palavras-chave: Carcinoma de Células Renais; Neoplasias de Anexos e de Apêndices Cutâneos; Síndrome de Birt–Hogg–Dubé/diagnóstico
Keywords: Birt-Hogg-Dube Syndrome/diagnosis; Carcinoma, Renal Cell; Neoplasms, Adnexal and Skin Appendage

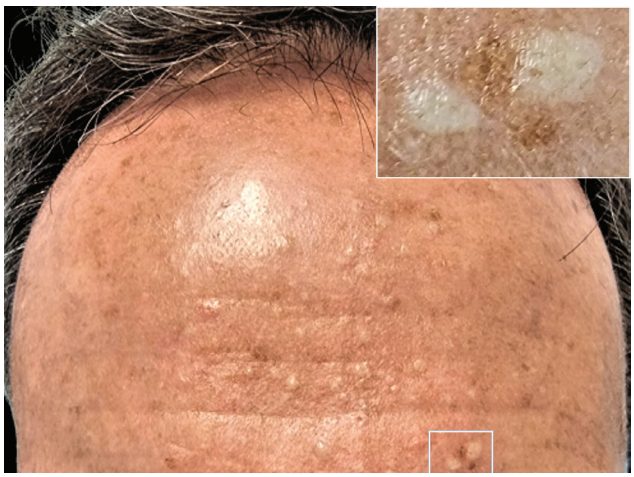

Figura 1 – Múltiplas pápulas cupuliformes esbranquiçadas com 2 - 4 mm, disseminadas na face, predominantemente na região frontal e nasal. No canto superior direito apresentam-se as duas lesões assinaladas, em maiores dimensões.

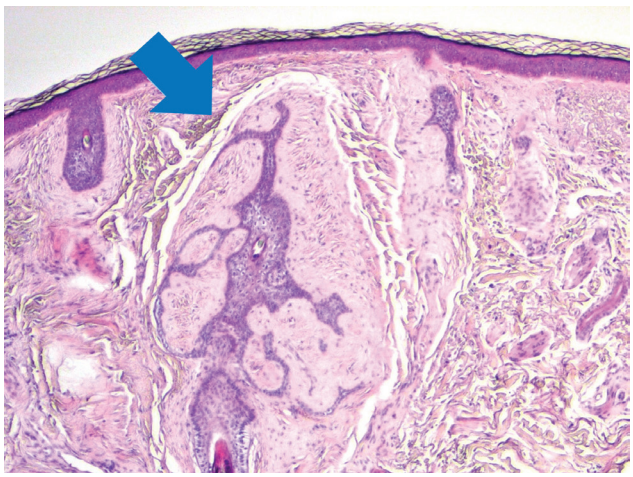

Figura 2 – No exame histopatológico observa-se, na região central, um infundíbulo folicular bem desenvolvido, rodeado por fibras de colagénio fino e eosinofílico (hematoxilina-eosina, x40)

Doente do sexo masculino de 60 anos, com antecedentes de carcinoma de células claras do rim, enfisema pulmonar e miocardiopatia hipertrófica, foi observado por múltiplas pápulas cupuliformes esbranquiçadas com 2 - 4 mm, disseminadas na face, predominantemente na região frontal e nasal, com vários anos de evolução (Fig. 1). A biópsia cutânea foi compatível com um fibrofoliculoma (Fig. 2). Por suspeita da síndrome de Birt-Hogg-Dubé foi realizado estudo genético, que revelou uma variante patogénica no gene *FLCN* [c.573_574delinsT, p. (Lys192Argfs*31)] em heterozigotia. Não se verificou evidência de quistos pulmonares ou pneumotórax na tomografia computorizada torácica. Dada a benignidade das lesões cutâneas, o doente optou por não realizar tratamento. A síndrome de Birt-Hogg-Dubé é uma genodermatose rara autossómica dominante causada por mutações no gene *FLCN*, localizado no cromossoma 17p11.2.[1,2] Caracteriza-se pela presença de manifestações cutâneas (fibrofoliculomas, tricodiscomas, fibromas perifoliculares e fibromas moles) e extra-cutâneas (quistos renais e pulmonares, pneumotórax espontâneo e carcinoma renal).[1,2] Os fibrofoliculomas são hamartomas do folículo piloso e ocorrem em 75% – 90% destes doentes, podendo ser o primeiro sinal da doença e a pista para o seu diagnóstico e tratamento precoce.[2]

CONTRIBUTO DOS AUTORES

CC: Recolha dos dados clínicos; revisão bibliográfica; elaboração do manuscrito.

LSA: Análise histológica e revisão do manuscrito.

PF: 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.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Recomendações na Abordagem do Doente com Hidradenite Supurativa

Guidelines for the Management of Patients with Hidradenitis Suppurativa

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RESUMO

A hidradenite supurativa é uma dermatose inflamatória crónica e recorrente que se caracteriza pela presença de nódulos inflamatórios e abcessos nas áreas ricas em glândulas apócrinas, que podem evoluir para fístulas supurativas e cicatrizes. Apesar de ser considerada uma das patologias dermatológicas com maior impacto na qualidade de vida dos doentes, é frequentemente subdiagnosticada. A hidradenite supurativa, sobretudo nas suas formas mais graves, associa-se a diversas comorbilidades, pelo que é fundamental adotar uma perspetiva holística e multidisciplinar na gestão destes doentes. A abordagem terapêutica é complexa e desafiante. A terapêutica médica é multifacetada e deve ser adaptada à apresentação clínica e gravidade da doença. A terapêutica cirúrgica deverá ser equacionada como adjuvante à terapêutica médica, em particular nos casos refratários e perante cicatrizes ou mutilação anatómica e/ou funcional. As presentes recomendações pretendem reunir os principais aspetos da abordagem ao doente com hidradenite supurativa e destinam-se a todos os profissionais de saúde envolvidos no seu acompanhamento.
Palavras-chave: Hidradenite Supurativa/cirurgia; Hidradenite Supurativa/diagnóstico; Hidradenite Supurativa/tratamento

ABSTRACT

Hidradenitis suppurativa is a chronic and recurrent inflammatory dermatosis characterized by the presence of inflammatory nodules and abscesses in the apocrine gland-rich areas that may progress to suppurative fistulas and scars. Despite being considered one of the dermatological conditions with the greatest impact on patient quality of life, it is often underdiagnosed. Hidradenitis suppurativa, especially in its severe forms, is associated with numerous comorbidities, so a holistic and multidisciplinary perspective is crucial for the management of these patients. The therapeutic approach is complex and challenging. The medical treatment options are diverse and must be adapted to clinical presentation and disease severity. Surgical therapy should be considered as an adjuvant to medical treatment, particularly in refractory cases and in the presence of scars or anatomical and/or functional mutilation. These recommendations reflect the main aspects of the management of the patient with hidradenitis suppurativa and are addressed to all healthcare professionals who take part in their follow-up.
Keywords: Hidradenitis Suppurativa/diagnosis; Hidradenitis Suppurativa/surgery; Hidradenitis Suppurativa/therapy

INTRODUÇÃO

A hidradenite supurativa (HS) é uma doença inflamatória crónica, recorrente e potencialmente mutilante, de envolvimento primariamente cutâneo, mas com potencial envolvimento sistémico nas suas apresentações mais graves. De etiologia ainda não completamente esclarecida, é atualmente reconhecida como uma doença auto-inflamatória para a qual concorrem fatores individuais e ambientais (incluindo disbiose, i.e. alteração do microbioma), perpetuada pela crónica ativação das imunidades inata e adaptativa.[1] A inflamação tem origem no epitélio folicular da pele rica em glândulas apócrinas, designadamente nas axilas, pregas inguinais, períneo e região perianal, glúteos, pregas mamárias e região periumbilical, entre outras.[2] Caracteriza-se pela presença de lesões primárias supurativas e recorrentes nestas localizações, designadamente nódulos inflamatórios e abcessos, que podem evoluir para lesões secundárias como fístulas supurativas, pseudocomedões e cicatrizes.[3]

A prevalência global de HS na população geral não é clara, variando de 1% a 4% nos estudos populacionais.[4] Manifesta-se habitualmente após a puberdade, com uma maior incidência e prevalência no sexo feminino e em adultos jovens (podendo ter um início mais tardio).[2]

A HS pode associar-se a várias comorbilidades. São muito frequentes o excesso de peso/obesidade e história de tabagismo.[2] As associações a acne grave e acne *conglobata*, doença pilonidal, doença cardiovascular e síndrome metabólica, doença inflamatória intestinal, psoríase, artrite e espondilatrite, pioderma gangrenoso, insuficiência renal, anemia e a doença psiquiátrica (ansiedade e síndrome depressiva) estão bem estabelecidas e denotam a inflamação sistémica e persistente documentada sobretudo nos doentes com HS moderada e grave.[5] A inflamação crónica contribui, ainda, para um risco acrescido de carcinoma espinocelular nas áreas afectadas.[6]

Embora nem todos os casos de HS sejam progressivos, com a inflamação recorrente e não devidamente tratada alguns doentes tendem a evoluir com gravidade e morbilidade crescentes.[7] A dor é um dos sintomas que mais relevância tem na percepção da doença pelos pacientes.[8] Frequentemente crónica na doença moderada a grave, é agudizada durante os surtos inflamatórios. Acrescem a imprevisibilidade das agudizações, a drenagem crónica e o odor, causando ansiedade e estigma.[8] A HS tem, assim,

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um impacto moderado a elevado na qualidade de vida dos doentes, que aumenta com a gravidade da doença. Um estudo europeu multicêntrico mostrou, inclusivamente, que a HS é a doença dermatológica com maior redução na qualidade de vida.[9] A doença repercute-se na autoimagem e interfere na capacidade de autocuidados, na vida de relação e na vida laboral, com elevados custos diretos e indiretos para o doente, para a família e para a sociedade.[8–12]

Não obstante o impacto da doença no indivíduo e na comunidade, é comum o atraso diagnóstico e, consequentemente, terapêutico. São necessários sete a 10 anos para que um doente com HS seja corretamente diagnosticado.[8,13–15] É, neste contexto, importante inverter esta realidade, apostando no diagnóstico e tratamento adequado da doença numa perspetiva multidisciplinar o mais precocemente possível. A intervenção atempada poderá permitir reduzir ou atrasar a progressão da doença, melhorar a resposta à terapêutica médica e evitar a mutilação persistente,[16] quebrar a inflamação sistémica e deste modo reduzir a prevalência das comorbilidades cardiometabólicas e psiquiátricas (entre outras).[7,17]

São vários os desafios atuais nos cuidados ao doente com HS. Alguns destes desafios parecem ser transversais às realidades dos vários países, incluindo o nosso.[8] Destacam-se:

- Reduzir o tempo necessário para o diagnóstico de HS;
- Melhorar o acesso dos doentes com HS a cuidados diferenciados, médicos e cirúrgicos;
- Reduzir a morbilidade associada à doença;
- Reduzir custos diretos e indiretos relacionados com a doença e suas comorbilidades.

O presente documento destina-se a todos os profissionais de saúde que de algum modo participam na cadeia de diagnóstico, tratamento e reabilitação funcional e/ou psicossocial da pessoa com HS e tem por objetivo melhorar a prestação de cuidados de saúde na HS.

MATERIAL E MÉTODOS

Estas recomendações foram elaboradas com base numa pesquisa bibliográfica realizada em julho de 2022 na MEDLINE às palavras-chave 'hidradenitis suppurativa', 'guidelines', 'diagnosis', 'comorbidities' e 'quality of life'. A abordagem do doente com HS foi estruturada em três partes: diagnóstico e seguimento, caracterização do doente e da doença e tratamento médico e cirúrgico.

Abordagem do doente com hidradenite supurativa

1. Diagnóstico e linhas gerais de seguimento da pessoa com hidradenite supurativa

- O diagnóstico de HS deve ser considerado em toda a pessoa, em idade pediátrica ou adulta, com pelo menos dois episódios num período de seis meses, ou persistência crónica no mesmo período, de lesões dolorosas e supurativas nas áreas típicas, acima descritas (Fig. 1).[4] As apresentações atípicas e sindrómicas existem, contudo, e devem ser consideradas.
- O diagnóstico de HS é geralmente clínico, podendo ser necessária a biopsia cutânea ou exames laboratoriais e/ou de imagem em alguns casos.[4]
- Toda a pessoa com suspeita clínica de HS deve ser

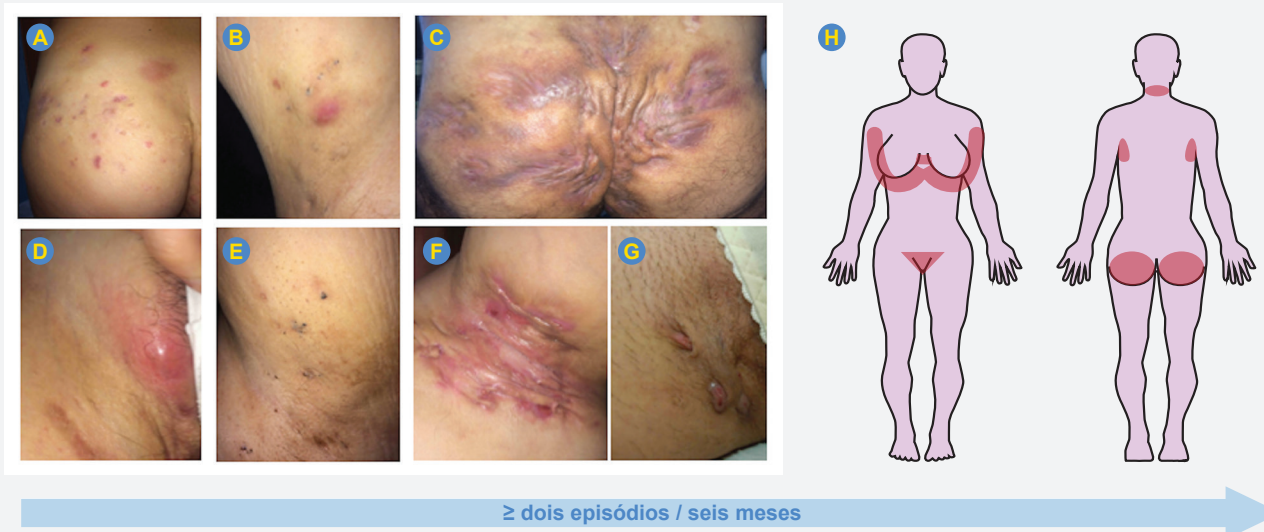

Figura 1 – Manifestações clínicas de HS. O diagnóstico de HS deve ser considerado em toda a pessoa com pelo menos dois episódios num período de seis meses de lesões dolorosas e supurativas nas áreas típicas (A). No doente com HS podem observar-se papulopústulas foliculares (B), nódulos (B, C), cicatrizes (D), abcessos (E), pseudocomedões (C, F) ou fístulas (G, H).

referenciada à Dermatologia ou a especialista em hidradenite supurativa para confirmação diagnóstica e orientação terapêutica.

- O seguimento clínico da pessoa com HS moderada a grave deve ser efetuado por um dermatologista com experiência no diagnóstico, avaliação, monitorização e tratamento da HS.[2,18] Os casos ligeiros e estáveis poderão ser orientados, após avaliação por dermatologista, para seguimento/coseguimento em cuidados de saúde primários.
- A avaliação inicial da pessoa com HS deve incluir, com registo no processo clínico[2,18–20]:
  - classificação e avaliação da gravidade, extensão e atividade da doença;
  - avaliação da qualidade de vida e da dor;
  - avaliação de fatores de risco para HS;
  - avaliação de comorbilidades.
- Na avaliação subsequente da pessoa com HS, devem reavaliar-se, com registo no processo clínico[2,18,19]:
  - extensão, atividade da doença e resposta terapêutica após cada ciclo terapêutico ou sempre que considerado adequado nas terapêuticas crónicas;
  - qualidade de vida e dor após cada ciclo terapêutico ou sempre que considerado adequado nas terapêuticas crónicas;
  - fatores de risco e de agravamento modificáveis pelo menos uma vez por ano;
  - comorbilidades pelo menos uma vez por ano.
- A periodicidade das avaliações subsequentes deve ser definida pela gravidade clínica da HS e plano terapêutico.[2,18–20] Doentes estáveis e controlados poderão ser observados a cada seis a 12 meses na doença ligeira e a cada três a seis meses na doença moderada a grave, enquanto doentes com doença não controlada ou em agudização deverão ser observados com maior periodicidade.
- A abordagem da pessoa com HS deve ser integrada num contexto multidisciplinar, com intervenção de outras especialidades sempre que a situação clínica o justifique.[2,21,22]
- Na avaliação dos fatores de risco e de agravamento modificáveis[19–21,23]:
  - se for identificado excesso de peso ou obesidade, deve ser oferecida a possibilidade de encaminhamento para consulta de nutrição e dietética e/ou a consulta multidisciplinar de obesidade;
  - se forem identificados hábitos de tabagismo ativo, deve oferecer-se referenciação a consulta de cessação tabágica;
  - medidas gerais para redução de fricção ou epilação (remoção de pelo) definitiva podem ser consideradas.
- No referente às comorbilidades, a pessoa com HS deve ser referenciada a consulta de[19–21,23,24]:
  - Cirurgia Geral ou Cirurgia Plástica e Reconstrutiva perante doença pilonidal ativa;
  - Gastrenterologia se houver sinais ou sintomas sugestivos de doença inflamatória intestinal[25];
  - Proctologia se houver envolvimento perianal[25];
  - Endocrinologia em caso de hiperandrogenismo;
  - Reumatologia ou Medicina Interna (doenças auto-imunes) em caso de artrite ou espondilartrite;
  - Medicina Geral e Familiar ou Psiquiatria se se verificar suspeita de comorbilidade psiquiátrica em relação com a HS;
  - especialista em risco cardiovascular (Medicina Geral e Familiar, Medicina Interna, Cardiologia, Endocrinologia) se for identificada dislipidémia, hipertensão arterial, diabetes *mellitus*, síndrome metabólica ou doença cardiovascular;
  - outra especialidade, caso a caso, sempre que se justifique.
- Deve ser referenciado a consulta de dor o doente com dor refratária à terapêutica médica e/ou cirúrgica da HS e aos analgésicos não opioides e opioides fracos.[26]
- No doente com lesões com drenagem ativa ou ulceração, deverá ser considerado apoio de enfermagem para realização de penso e/ou apoio na sua customização.[2,18,24]
- Deve ser referenciado para cirurgia o doente com indicação para terapêutica cirúrgica (*vide* abaixo).

2. Caracterização do doente e da doença

- Para a classificação da doença não existem presentemente classificações fenotípicas consensuais.
- A avaliação da gravidade, extensão e atividade da doença deve valer-se do uso de instrumentos de avaliação, salientando-se, pela sua praticidade, a classificação de Hurley (embora seja estática), o HSPGA (*Hidradenitis Suppurativa Physician Global Assessment*) e o iHS4 (*International Hidradenitis Suppurativa Severity Score System*).[18,27]
- Na determinação da atividade inflamatória e avaliação da resposta terapêutica, o método de avaliação e respetivo instrumento pode ser clínico ou clínico-ecográfico, sendo que o HiSCR (*hidradenitis suppurativa clinical response*) é o único que está validado na avaliação de resposta das lesões inflamatórias à terapêutica médica.[28]
- Quanto aos *patient-reported outcomes*, na determinação quantitativa da qualidade de vida deve ser

utilizada uma escala internacional validada para a população portuguesa, como o DLQI (*Dermatology Life Quality Index*) em adultos ou o CDLQI (*Children's DLQI*) na idade pediátrica.[29] A dor deve ser mensurada utilizando escalas de avaliação da intensidade da dor (consultar Circular Normativa DGS).[30]

- Os exames complementares de diagnóstico são requisitados ou efetuados caso a caso.
- O exame microbiológico não é útil por rotina, podendo ser considerado pontualmente na avaliação de fístulas persistentemente drenantes e associando-se a sinais inflamatórios ou mesmo celulite perilesional.[21,24]
- A avaliação laboratorial deve ser realizada nos doentes com doença moderada a grave com grande atividade inflamatória e nos doentes candidatos a terapêutica biológica; a realização de exames laboratoriais nos demais doentes pode ser considerada caso a caso, na avaliação dos parâmetros inflamatórios e eventuais comorbilidades ou complicações da doença.[19,21]
- A avaliação ecográfica deve ser considerada quando a caracterização clínica do tipo de lesões não é certa, na determinação da atividade inflamatória, na documentação da progressão clínica das lesões e, portanto, da doença, na documentação da resposta à terapêutica e no mapeamento dos doentes candidatos a cirurgia.[31,32]
- A ressonância magnética deve ser realizada nos doentes com doença perianal ou perineal, bem como na doença glútea extensa.[21,25]
  - Nos doentes com afeção perianal ou perineal e, em particular, na presença de fístulas nestas localizações, deve ser investigada e excluída doença de Crohn, com necessária avaliação por ressonância magnética e eventual ecoendoscopia / colonoscopia e referenciação a Proctologia/ Gastrenterologia.[19,25]
- A biópsia cutânea com exame histopatológico deve ser considerada na suspeita de transformação maligna ou no diagnóstico diferencial de HS (por exemplo, com foliculite, furunculose, doença de Crohn, pioderma gangrenoso, entre outras).[2,23,24]

3. Tratamento da hidradenite supurativa

a. Terapêutica médica (Fig. 2)

- Na HS ligeira a moderada, localizada e com poucas lesões e superficiais, pode considerar-se o uso da clindamicina 1% tópica duas vezes por dia pelo período máximo consecutivo de três meses; na recorrência de doença, pode repetir-se o ciclo desde que mostrada eficácia clínica no tratamento anterior[18,21,33,34]; a clindamicina 1% tópica pode também ser usada em combinação fixa com peróxido de benzoílo.[22]
- O creme de resorcinol a 15% em aplicação duas vezes por dia é um tópico de segunda linha na doença ligeira e localizada.[33–35]
- Os antissépticos tópicos podem ser usados como adjuvantes da terapêutica tópica e sistémica.[18,33]
- Na HS ligeira a grave com múltiplas lesões e episódios frequentes de agudização pode considerar-se o uso de tetraciclinas orais duas vezes por dia (com preferência pela doxiciclina 100 mg duas vezes por dia pelo seu perfil de maior segurança) por um período máximo de 12 semanas[36]; na recorrência de doença, pode repetir-se o ciclo desde que mostrada eficácia clínica no tratamento anterior.[18,21–23,33,34]
- A clindamicina 300 mg duas vezes por dia associada à rifampicina 300 mg duas vezes por dia durante 10 a 12 semanas pode ser considerada na doença moderada a grave e ativa ou, como segunda linha, na doença ligeira; na recorrência de doença, pode repetir-se o ciclo desde que mostrada eficácia clínica no tratamento anterior.[18,21–23,33,34]
  - A utilização deste esquema tem sido debatida na literatura por razões várias, destacando-se o argumento farmacocinético: a rifampicina reduz substancialmente as concentrações plasmáticas de clindamicina ao fim de alguns dias de tratamento, pela indução do CYP3A4.[37] Outros esquemas alternativos têm sido sugeridos (clindamicina em monoterapia, ofloxacina com clindamicina, entre outros.[33,37,38]
- O esquema triplo de rifampicina (10 mg/kg/dia), moxifloxacina (400 mg por dia) e metronidazol (500 mg três vezes por dia) até 12 semanas, com descontinuação do metronidazol à semana seis, pode ser considerado na HS ligeira a moderada ou em qualquer hidradenite como ponte para cirurgia ou após

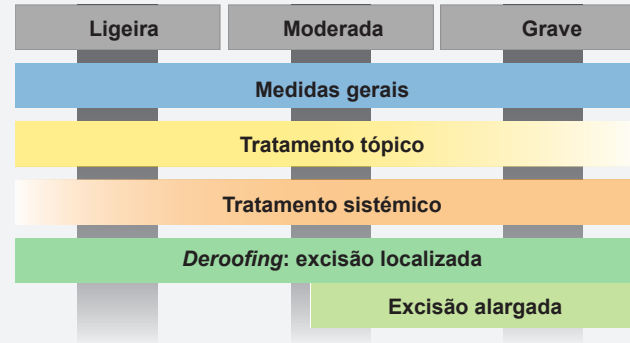

Figura 2 – Abordagem terapêutica geral do doente com HS

ciclo de ertapenem.[21,22,33,34]

- Em casos selecionados, graves e/ou refratários, pode-se considerar seis semanas de ertapenem 1 g por dia endovenoso, com possível consolidação com o esquema triplo de rifampicina/moxifloxacina/metronidazol. Este esquema pode ser usado, ainda, como terapêutica de resgate ou como ponte para cirurgia de HS.[21,22,33]
- A dapsona em dose diária de até 200 mg durante pelo menos três meses é opção de terceira linha na HS ligeira a moderada, em doentes sem défice de glucose-6-fosfato desidrogenase.[18,22,23,33,39]
- A antibioterapia sistémica pode ser usada como adjuvante na gestão dos episódios de agudização.[21]
- O adalimumab 40 mg semanal ou 80 mg a cada duas semanas, subcutâneo e após esquema de indução, é atualmente a terapêutica biológica de primeira escolha, e a única formalmente aprovada na HS moderada a grave após falência de tratamento convencional.[18,21–23,33,34]
  - A terapêutica biológica não deve ser protelada, devendo ser idealmente instituída em fases mais precoces das formas inflamatórias da doença, uma vez que a resposta à terapêutica é diminuída aquando da progressão para fístulas e cicatrizes.[16]
- O infliximab 5 - 10 mg/kg a cada quatro a oito semanas pode ser usado como terapêutica biológica de segunda linha, *off-label*, na hidradenite moderada a grave.[18,21–23,33,34,40]
- Na falência da terapêutica biológica de primeira e segunda linhas podem ser considerados outros agentes biológicos *off-label*, como o secucinumab e outros anti-IL17, fármacos anti-IL-23, o anakinra ou o ustecinumab.[21,22,33,34,40]
- Considerar suspender a terapêutica biológica se for observada uma melhoria para valores inferiores a 25% na contagem do número de abcessos e nódulos inflamatórios às 12 semanas; caso a melhoria se registe em valores entre 25% a 50%, mas sem atingir HiSCR às 12 semanas, aquela terapêutica pode ser prolongada com nova reavaliação ao fim de três meses de tratamento.[21]
- A corticoterapia sistémica de baixa dose pode ser usada no controlo inflamatório da HS recalcitrante; pode ainda ser usada, em esquema curto, como ponte terapêutica no início de terapêutica convencional ou biológica na HS grave ou no controlo dos episódios de agudização.[21,22,33,34]
  - A ciclosporina poderá ser alternativa na doença recalcitrante.[18,22,33,34]
- A corticoterapia intralesional pode ser útil no tratamento localizado de lesões inflamatórias agudas ou de lesões refractárias, em monoterapia ou combinada com as demais terapêuticas.[21–23,33,34]
- A acitretina 10 - 25 mg por dia é tratamento de terceira linha na HS ligeira a moderada do tipo não inflamatório/folicular (pode ser causa de agudização nas doses altas).[21–23,33,34]
  - O uso de isotretinoína é actualmente controverso, com tendência para a sua não recomendação no tratamento da HS pelo risco de agravamento.[23,41]
- As terapêuticas antiandrogénicas podem ser consideradas na abordagem da mulher com HS ligeira (monoterapia ou adjuvante) e moderada a grave (adjuvante) quando se verifica agravamento peri-menstrual da doença, ou na presença de doença endócrino-metabólica conhecida.[33,34]
- O tratamento de doentes em idade pediátrica, grávidas ou mulheres a amamentar deverá ser adaptado, tendo em conta as restrições ou ajustes de dose ou posologia para os fármacos acima citados.[42,43]

b. Terapêutica cirúrgica

- Segundo os critérios MIBHS[44] (*Mandatory Indications for Surgery in Hidradenitis Suppurativa*), são candidatos a terapêutica cirúrgica os doentes com fístulas (sobretudo fístulas complexas ou fístulas refractárias a terapêutica médica), cicatrizes tipo acordeão ou outras (particularmente se impacto funcional), bridas contrácteis cicatriciais, mutilação anatómica ou funcional, suspeita de neoplasia, inflamação refratária a terapêutica médica.
- Os doentes com necessidade de tratamento cirúrgico deverão ser encaminhados para tratamento na Dermatologia Cirúrgica, na Cirurgia Plástica e Reconstrutiva ou na Proctologia/Cirurgia Geral segundo critérios de gravidade/extensão/localização anatómica:
  - Dermatologia Cirúrgica: excisões localizadas não complexas, *deroofing*, laserterapia, lesões abordáveis por STEEP (*skin-tissue-sparing excision with electrosurgical peeling*);
  - Cirurgia Plástica e Reconstrutiva: excisões localizadas complexas, excisões alargadas com encerramento primário ou reconstrução por retalho ou enxerto ou cicatrização por segunda intenção;
  - Proctologia/Cirurgia Geral: fístulas perianais (simples, para-rectais, transfinctéricas).
- A referenciação a outras especialidades médicas ou cirúrgicas é decidida caso a caso.
- A excisão localizada, o *deroofing* e o STEEP podem ser usados no tratamento cirúrgico de lesões solitárias.[21,24,33]

- A excisão alargada é a abordagem cirúrgica de eleição na HS grave e/ou complicada de deformação anatómica, constrição funcional ou com transformação maligna.[21,24,33]
- No período pré-operatório do doente com HS moderada a grave ativa candidato a excisão alargada podem ser considerados esquemas anti-inflamatórios que incluem antibioterapia oral ou endovenosa e/ou terapêutica biológica e/ou corticoterapia sistémica.[24,33,34]
- A terapêutica biológica não deve, em geral, ser suspensa aquando da cirurgia da HS e deve ser mantida no pós-operatório.[21,45]

CONCLUSÃO

Numa doença de apresentação heterogénea, não é demais realçar a importância de adaptar o tratamento ao doente e à sua doença. A futura definição de fenótipos e de endotipos poderá sublinhar esta tendência na personalização do tratamento. Adicionalmente, a HS é uma doença dinâmica, o que determina, por um lado, o propósito de reavaliar com frequência a sua gravidade e resposta à terapêutica e, por outro, a necessidade de alterar ou adaptar o tratamento sempre que apropriado. Relembre-se que as agudizações são comuns, mesmo no doente estável, e devem ser tratadas.

A combinação de terapêuticas médicas deve ser considerada nos casos graves e/ou de maior complexidade, e pode também ser útil na gestão das agudizações. Finalmente, as modalidades cirúrgicas são úteis como adjuvantes à terapêutica médica, mas também nos casos refratários ou no doente com cicatrizes ou mutilação anatómica e/ou funcional. Idealmente, ao caminharmos para um diagnóstico mais precoce da HS, poderemos ter cada vez mais doentes eficazmente tratados com terapêutica médica, reduzindo a morbilidade associada à doença e a necessidade de cirurgia avançada.

Na última década, o crescente investimento da comunidade científica no estudo da HS foi determinante para o progresso da compreensão fisiopatológica e elaboração das primeiras orientações terapêuticas. Este mesmo interesse determinará, certamente, a disponibilização futura de fármacos com indicação para o tratamento da HS, e consequente necessidade de atualização das presentes orientações.

CONTRIBUTO DOS AUTORES

Todos os autores contribuíram igualmente para o 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

JC recebeu bolsas ou apoio financeiro de AbbVie e LEO, bem como honorários de consultoria de Novartis, AbbVie e LEO. Recebeu também pagamento ou honorários por palestras, apresentações, gabinetes de palestrantes, redação de manuscritos ou eventos educacionais de Novartis e LEO, e apoio para participação em reuniões e/ou viagens de AbbVie.

IAM declara não ter conflitos de interesse relacionados com o presente trabalho.

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Clinical Outcomes of COVID-19 Patients with Rheumatic and Musculoskeletal Diseases: A Single Centre Cohort Study

Resultados Clínicos em Doentes COVID-19 com Doenças Reumáticas e Musculoesqueléticas: Estudo de Coorte num Centro

Keywords: COVID-19; Hospitalization; Musculoskeletal Diseases; Rheumatic Diseases; SARS-CoV-2
Palavras-chave: COVID-19; Doenças Musculoesqueléticas; Doenças Reumáticas; Hospitalização; SARS-CoV-2

Dear Editor,

The acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease 2019 (COVID-19) pandemic is a self-limiting viral disease with a good prognosis in the majority of the population.[1] Severe disease is more likely to occur in patients with risk factors such as advanced age, male gender and/or underlying conditions.[2] A number of large population-based or healthcare-based studies have found an increased risk of hospitalization or death in patients with rheumatic and musculoskeletal diseases (RMDs).[3] However, and according to the European Alliance of Associations for Rheumatology (EULAR), patients with RMDs do not usually face worse outcomes and increased mortality than the general population.[4] The aim of our study was to understand the clinical outcomes of patients with COVID-19 and RMDs. We performed a retrospective study that included adult patients' with a diagnosis of both COVID-19 and inflammatory or noninflammatory RMDs observed in a secondary hospital, between the 2nd of March 2020 and the 31st of December 2021. A COVID-19 diagnosis was identified through the 10th International Classification of Diseases and RMDs were identified after review of the electronic health records. A COVID-19 diagnosis was based on the polymerase chain reaction test. Data collected included demographic and clinical data. Descriptive, univariate analysis and multivariate logistic regression analysis were conducted using SPSS® version 25.

Among 2169 patients with a COVID-19 diagnosis, 213 (9.8%) had RMDs. Most of the patients included were women (59.2%) with a median age of 79.0 ± 17.50 years. Patient demographic and clinical characteristics are listed in Table 1. One hundred and sixty (75.1%) patients with RMDs required hospitalization with 149 (70%) requiring oxygen support, six (2.8%) non-invasive ventilation and nine (4.2%) mechanical ventilation. A total of 53 (24.9%) patients died. As for the management of COVID-19, corticosteroids were administered to 105 patients (49.3%) and nonspecific antivirals (remdesivir) to four patients (1.9%). In line with other studies, we found an association between patients with COVID-19 requiring hospitalization and arterial hypertension (p = 0.01)[2] and age (p = 0.013).[5] Gout (p = 0.01) and vaccination status (p = 0.05) were also associated with a worse prognosis. In the multivariate analysis, only older patients [OR 1.07 (95% CI 1.04, 1.10)], gout [OR 1.16

Table 1 - Patient demographic and clinical characteristics

	RMDs
Age, years (median ± IQR)	79.0 ± 17.50
Sex (F/M), n	126/87
Rheumatic disease by subgroup, n (%)	
Non-inflammatory diseases	124 (58.2)
Inflammatory systemic diseases	89 (41.8)
Non-inflammatory diseases, n (%)	
Osteoarthritis	94 (44.1)
Osteoporosis	30 (14.1)
Inflammatory systemic diseases, n (%)	
Gout	36 (16.9)
Rheumatoid arthritis	27 (12.7)
Polymyalgia rheumatica	8 (3.8)
Spondyloarthritis	4 (1.9)
Systemic sclerosis	3 (1.4)
Vasculitis	3 (1.4)
Myositis	2 (0.9)
Systemic lupus erythematosus	2 (0.9)
Undifferentiated connective tissue disease	2 (0.9)
Sjögren's syndrome	1 (0.5)
Psoriatic arthritis	1 (0.5)
Disease duration, years (median ± IQR)	8.0 ± 12.0
Disease activity, n (%)	
Remission/Low	20 (9.4)
Moderate	18 (8.5)
High	1 (0.5)
Not applicable	174 (81.7)
Immunomodulatory or immunosuppressive treatments, n (%)	
None	174 (81.7)
Glucocorticoids	44 (20.7)
csDMARDs	30 (14.1)
TNF inhibitors	1 (0.5)
Rituximab	2 (0.9)
Other b/tsDMARDs	2 (0.9)
Smoking status (%)	
Current smoker	4.7
Ex-smoker	1.4
Comorbidities, n (%)	
Arterial hypertension	146 (68.5)
Dyslipidemia	102 (47.9)
Diabetes mellitus	58 (27.2)
Obesity	52 (24.4)
Atrial fibrillation	41 (19.2)
Obstructive lung disease	14 (6.6)
Interstitial lung disease	5 (2.3)
Vaccination status (%)	
Yes	64.8
No	35.2

IQR: interquartile range; RMDs: rheumatic and musculoskeletal diseases; M: male; F: female; n: number; cs: conventional synthetic; DMARDs: disease-modifying anti-rheumatic drugs; TNFi: tumour necrosis factor inhibitors; ts: targeted synthetic; b: biological

(95% CI 1.01, 1.34)] and no vaccination [OR 2.63 (95% CI 1.23, 5.62)] were associated with an increased risk of hospitalization. The rates of hospitalization, oxygen support and mortality found in our study were higher compared to other European countries.[4]

In our study, male patients and those receiving certain immunosuppressive treatments were not at significant risk for hospitalization. Larger studies are needed to identify groups with greater vulnerability as well as several other knowledge gaps, such as the effects of rheumatic diseases on vaccine effectiveness or the utility of additional doses.

AUTHOR CONTRIBUTIONS

CM: Study design, data collection and analysis, writing of the manuscript.

AB: Study design, 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.

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Letter to the Editor Concerning the Article "Family Satisfaction in Intensive Care during the COVID-19 Pandemic Using the FS-ICU24 Questionnaire"

Carta ao Editor Referente ao Artigo "Satisfação das Famílias nos Cuidados Intensivos durante a Pandemia de COVID-19 Utilizando o Questionário FS-ICU24"

Keywords: Communication; COVID-19; Intensive Care Units; Patient Satisfaction; Portugal; Quality of Health Care; Surveys and Questionnaires
Palavras-chave: Comunicação; COVID-19; Inquéritos e Questionários; Portugal; Qualidade dos Cuidados de Saúde; Satisfação do Doente; Unidades de Cuidados Intensivos

Dear Editor,

We read with particular interest the recently published work by Camões *et al*.[1]

We were impressed with the results of this article, which represents one more step in the change of the paradigm of treatment in Intensive Care Medicine. It is very important that the family and patients are simultaneously at the core of the decision-making processes, with transparency and without conspiracies of silence. This work may lead to a better communication pattern with families, with improvements in the satisfaction of families. Unfortunately, the families of patients who died during the study were excluded. In our Palliative Medicine practice, in the context of Primary Health Care, communication with patients and family has a key role in management of clinical status.

A recent work of Correia *et al* showed that frail people who undergo palliative interventions in Intensive Care units receive invasive supportive therapy more often and face more non-resuscitation decisions.[2] There may be several reasons for those results. We agree that training in Palliative Care should be extended to all specialties and that would bring benefits in both the quality and quantity of life of the patient, by minimizing suffering to both the patient and the family, specially in those situations where families are not allowed to be present during the hospitalization period.[3]

It would also be interesting to include, in a future analysis, the number of patients with Advance Directives, which are so under-disseminated in Portugal. This is of known importance in order to meet patient's desires, minimize family conflicts in a situation of fragility and vulnerability, and to aid healthcare professionals in the decision-making process, thus improving the quality of healthcare offered to every patient.[4] Intensive care may be an opportunity to apply Advance Directives. The recent public debate regarding the euthanasia law could improve patient awareness and knowledge of advance directives.

We conclude that palliative care offers support in clinical decision-making to both the patient and the family, and could also improve family satisfaction as well. The palliative care professionals should be seen as a support network and with whom joint work should be done.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

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ST and BB stated that no competing interests exist.

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The Importance of Carefully Evaluating Breast Masses During Pregnancy

A Importância de uma Avaliação Detalhada de Nódulos da Mama na Gravidez

Keywords: Adenoma/diagnosis; Breast Neoplasms/diagnosis; Lactation; Pregnancy; Pregnancy Complications
Palavras-chave: Adenoma/diagnóstico; Complicações da Gravidez; Gravidez; Lactação; Neoplasias da Mama/diagnóstico

Dear Editor,

Breast masses are common in women of childbearing age. Of note, the incidence of malignant tumors in pregnancy is rising, probably due to increasing maternal age. International data estimates that up to 4% of breast cancers are diagnosed during this period.[1]

The differential diagnosis of breast masses presenting during pregnancy includes fibroadenomas, galactoceles, cysts, lactating adenomas, and breast cancer.[2]

This case illustrates the diagnostic challenge that these masses present, given the reduced sensitivity of both clinical examination and radiological findings, due to the high density of breast tissue. Pregnancy-related changes in the breast are induced, mainly, by elevated estrogen levels, which in turn stimulate the proliferation of blood vessels and glandular tissue, while simultaneously reducing stromal tissue.[2,3]

The authors report the case of a 27-year-old woman, G1P0, presenting at 29 weeks of gestation with a fast-growing nodule in the left breast. Her medical history included obesity and chronic hypertension. During pregnancy, she received treatment with nifedipine, acetylsalicylic acid, iodine and iron. She did not smoke and had no family history of cancer.

Upon physical examination, a firm, mobile, painless, 3 cm-mass was palpable in the upper quadrants of the left breast. No inflammatory signs or nipple discharge were present. The ultrasound revealed an oval, well-delineated, 32 mm-mass of solid nature, containing multiple small liquid areas (Fig. 1). No other breast or axillary lesions were found. An ultrasound-guided biopsy was performed, and the histopathology examination revealed a lactating adenoma. The patient received no further treatment and the nodule disappeared spontaneously six weeks after delivery, when lactation was interrupted according to her preference.

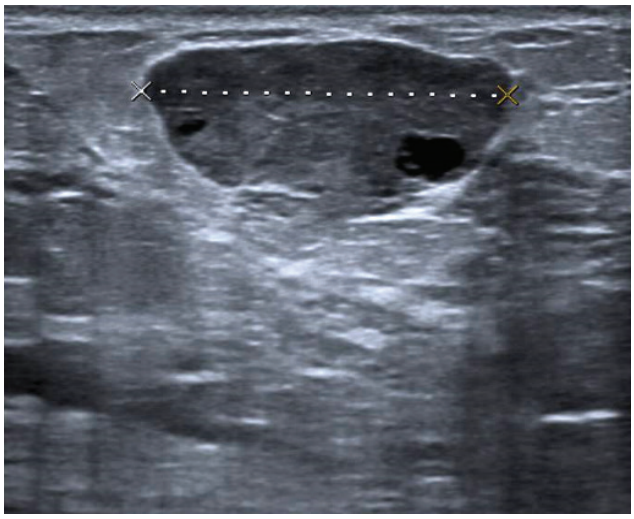

Figure 1 – Ultrasonographic appearance of the nodule, demonstrating an oval well-circumscribed lesion with cystic areas inside

Lactating adenomas are benign stromal tumors of the breast that usually appear during the third trimester of pregnancy or postpartum, with most lesions resolving after cessation of breastfeeding.[4]

Clinically, masses are solid, mobile and nontender, varying widely in size. Ultrasound features suggestive of a lactating adenoma include an oval hypo/isoechoic lesion with posterior enhancement, with sharp margins and which may contain cystic areas, especially when infarcted. A core biopsy should be performed to exclude malignancy, due to the ultrasonographic resemblance with other breast entities.[4]

Although the prognosis of lactating adenomas is very good, this case emphasizes the importance of thoroughly investigating breast nodules during pregnancy, given that the rates of breast cancer in pregnancy are rising and, in these situations, early diagnosis is essential to ensure a better prognosis and should not be delayed until the postpartum period.

AUTHOR CONTRIBUTIONS

AFM: Conception and writing of the manuscript.
RVC, MS: Conception of the work.
OA: Data acquisition and analysis.
MN: Data acquisition, critical review and approval of the manuscript.

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PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Immunotherapy in the Treatment of Metastatic Urothelial Carcinoma at a Tertiary Referral Center in Portugal

Experiência com Imunoterapia no Carcinoma Urotelial Metastizado num Centro de Referência Português

Keywords: Carcinoma, Transitional Cell; Immunotherapy; Urinary Bladder Neoplasms/drug therapy
Palavras-chave: Carcinoma de Células de Transição; Imunoterapia; Neoplasias da Bexiga Urinária/tratamento farmacológico

Urothelial cancer is the seventh most common cancer in Portugal. Despite local therapy, one-third of patients experience recurrence and develop metastatic disease[1] and an additional 5% of patients have distant metastases at diagnosis.[2] For those, platinum-based combination chemotherapy is the standard of care, even though a significant proportion of patients are ineligible for chemotherapy due to comorbid conditions.[3] Moreover, platinum regimens usually show short-term responses.[3] Immunotherapy has challenged the paradigm of metastatic disease after first line platinum-based combination chemotherapy, with longer overall survival and a higher objective response rate. The aim of this study was to evaluate the clinical outcomes of real-world patients with metastatic urothelial cancer treated with immunotherapy at a Portuguese tertiary center.

The authors retrospectively selected 20 patients from an approved anonymized database of a tertiary referral center, with informed consent for treatment and data analysis. Patients presented with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy and received treatment with immunotherapy (pembrolizumab or atezolizumab).

Descriptive analyses were performed using standard summary statistics and survival was assessed using Kaplan–Meier survival analysis with 95% confidence intervals (CI). Patients, disease, and treatment characteristics are summarized in Table 1. Median overall survival (OS) was 11.8 months (95% CI, 8.1 to 15.5) in patients treated with both drugs. Median progression-free survival was 7.8 months (95% CI, 6.0 to 9.6). The objective response rate (ORR) was 20% (three partial responses and one complete response on follow-up computed tomography (CT) scan). Treatment-related adverse events of any grade were reported in 45% of the patients with the most common being fatigue and pruritus. Grade 3 events were reported in 10% of patients, with no grade 4 or 5 events.

Despite limitations of sample size and retrospective design, efficacy in the real-world population is in line with the results of seminal trials. The median OS was comparable to the 10.3 months in the KEYNOTE-045[4] trial. The ORR was also comparable to the KEYNOTE-045[4] trial (21%) and higher than in the IMvigor210[5] trial (16%).

In our study, the included patients were older and had worse performance status, reinforcing the safety of immunotherapy and a low incidence of severe adverse events in

Table 1 – Demographic, disease, and treatment characteristics

Demographics and disease characteristics	Patients (n = 20)
Age - years	
Median	72.5
Range	48 - 84
Sex	
Male	15 (75%)
Female	5 (25%)
ECOG performance status	
0	9 (45%)
1	11 (55%)
Histological type	
Pure urothelial	16 (80%)
Mixed	4 (20%)
Primary tumor location	
Bladder	15 (75%)
Renal pelvis/Ureter	5 (25%)
Initial staging	
Non-metastatic	18 (90%)
Metastatic	2 (10%)
Metastasis location at progression	
Non-visceral	10 (50%)
Visceral	10 (50%)
Treatment	**Patients (n = 20)**
Initial surgical treatment	
Cystectomy	15 (65%)
TURBT	2 (10%)
Nephroureterectomy	5 (25%)
Context of most recent systemic therapy	
Neoadjuvant platinum	2 (10%)
Platinum for metastatic disease	18 (90%)
Immunotherapy	
Pembrolizumab	16 (80%)
Atezolizumab	4 (20%)
Immunotherapy duration - months	
Median	8
Range	2 - 51
Treatment discontinuation	
Progression/Death	16 (80%)
Adverse events	-
Time between drug indication and administration - days	
Median	49.5
Range	14 - 126

ECOG PS: Eastern Cooperative Oncology Groupe performance status; PD-L1 expression was tested using the Dako PD-L1 assay; TURBT: transurethral resection of bladder tumor

the elderly and less selected patients. In our experience, there was a substantial time gap between the decision to start immunotherapy and approval/administration. Three patients died waiting for treatment. Therefore, there is an imperative need for a faster drug approval by the national medicines agency and the creation of early drug access in high-volume referral centers.

AUTHOR CONTRIBUTIONS

VQ: Study design, data acquisition, analysis and interpretation, writing of the manuscript.

LM: Study design, data analysis and interpretation, critical review of the manuscript.

RJ, JL: Data acquisition, analysis and interpretation, critical review of the manuscript.

AF: Study design, data interpretation, critical review of the manuscript.

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COMPETING INTERESTS

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