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A Short Guide on How to Carry Out Validation of Scales Measuring Health Outcomes

Um Breve Guia sobre Como Validar Escalas Usadas em Contexto de Saúde

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Keywords: Reproducibility of Results; Sample Size; Surveys and Questionnaires; Validation Studies as Topic
Palavras-chave: Estudos de Validação; Inquéritos e Questionários; Reprodutibilidade dos Testes; Tamanho da Amostra

The need to measure health outcomes

Assessment and quantification happen every day and enhance the capacity of making good decisions that can impact a patient's survival, quality of life and quality of health care provided. The true score of any health assessment relies on the strength and verisimilitude of the instrument that measures it. The strongest and most reliable method to assess quantifiable measures, characteristics, or attributes is called the gold standard.[1] Yet, gold standards are not immutable. They exist up to a point in which they are replaced by faster, more cost-effective, or more reliable methods, that will then be considered the gold standards until a better method arises.[2]

The less we know about a measure, the more need there is for creating an instrument that allows its reliable assessment. The need for stronger methods is greater for constructs, i.e., abstract concepts or ideas that are not directly observable but inferred from observable behaviors, attitudes, and characteristics, for example loneliness, and even more for those who never went through the process of scale validation.[3-5]

The true score of a construct is like the horizon line. There is a need to understand what the most accurate way is of measuring its true score, but the path is hard.[2] For example, one can imagine all possible questions that can be asked to assess the construct of 'poverty'. There are several questions that we can ask to assess poverty, and one can just hope to get close to the true score, because poverty will mean different things to different people. The strategy will be to come up with the largest possible number of questions and then to create a system to decrease its number in a cost-effective way, meaning that we are attempting to create an instrument with the lowest possible number of questions, but that maximizes the explained variance of the construct. Or, in other words, an instrument that optimizes parsimony and explanatory power.[2] Explanatory power refers to the extent to which the instrument can account for the variation in the observed variables. A good instrument should identify a small number of factors that explain a large proportion of the variance in the data. This ensures that the factors identified are meaningful and relevant to the research question. Parsimony, on the other hand, refers to the simplicity of the instrument. A good instrument should be as simple as possible, while still being able to explain the observed variance. This is because a more parsimonious instrument is easier to interpret and use in practice. An instrument that optimizes parsimony and explanatory power is one that strikes a balance between being as simple as possible while still being able to explain most of the variation in the observed data. This ensures that the resulting factors are both meaningful and easy to use in subsequent analyses.

Moreover, it is also necessary to consider the multicultural dimension of assessing constructs.[6] Countries such as Iceland, Angola, United States, Japan, and others will have different views of what poverty is. Even within each country one can easily identify several different population characteristics in which the concept of poverty will vary. Therefore, it is sometimes necessary to confirm the validation of scales that were previously validated in other populations.[6]

When we do not know enough about a construct, the best methodological approach is exploratory. With this approach, researchers will attempt to propose an initial structure of variables to measure the construct.[3,7,8] On the other hand, if a construct has already been studied and there is at least one proposed structure to assess it, one can move to a confirmatory analysis, which will test if a previous structure can be applied to a different population or data.[3,7,8]

We present a step-by-step guide to researchers interested in developing original instruments to measure health outcomes or attempt validations of previously created instruments. This guide does not intend to be exhaustive, but to address the key aspects of scale validation.

How to measure health outcomes

There are several steps that should be followed in order to develop an instrument to measure one or more constructs.

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Stage 1: Construct and item selection

Step 1 – Choosing the constructs: In this step the research constructs are identified to bind the item generation process. This process can be deductive, i.e., if constructs already exist/ there is a lot of information about them, or inductive, where constructs do not previously exist/ there is limited information about them, or both.[9]

Step 2 – Brainstorming in order to select items: After choosing the constructs, the generation of items/questions begins. At first, the maximum number of items is created. Initial inspections will allow the reduction in the number of items by clearing redundancies.[9]

Stage 2: Content validity to ensure that the selected items are related to the research construct

Step 3 – The initial structure of constructs and items is assessed for relevance and representativeness by a panel of experts in the field of research.[5]

Step 4 – A panel of experts will assess the initial structure of constructs and items to check if the items are measuring what they are supposed to (face validity).[4,7]

Stage 3: Pre-test and pilot study

Step 5 – A pre-test is conducted in a small sample of the target population to ensure that language is understandable,[10-15] to estimate the necessary amount of time to answer the questionnaire, to assess the graphical display, to gauge need for precoding, and to make sure that the provided answers will produce valid measurements.[5,8,10]

Step 6 – Pilot study: A pilot questionnaire is applied to an initial convenience sample of 50 to 100 participants to facilitate data collection.[6,10] After that, statistical analysis processes are implemented to explore the item's structure and the number of constructs. Usually, this is done with Principal Component Analysis.[6]

Stage 4: Gathering data

Step 7 – Prepare data collection: select the most unbiased possible sample selection method; if possible random selection or stratified random selection, considering at least 10 to 15 observations per item with a minimum of 200 to 300 observations.[10-12]

Step 8 – Repeat data collection after a wash-out period, of at least three months to assess reproducibility.[4,13]

Stage 5: Statistical analysis

Step 8 – Identify the number of factors to extract and with which to conduct different analysis to optimize conclusions: some examples are the Kaiser-criterion (eigenvalue > 1, used to determine the amount of variation in a dataset that is captured by each principal component),[3,7] parallel analyses,[7] scree plot,[7] and very simple structure.[4]

Step 9 – Exploratory factor analysis (EFA) that is used to determine the factorial structure of the scale.[2-4,9]

Step 10 – Assess reliability with Cronbach's alpha.[2,4-6]

Step 11 – Assess validity (e.g., concurrent validity, the extent to which a new measurement or test correlates with an established measurement or test that measures the same construct, discriminant validity, the extent to which a test is not related to other tests that measure different constructs, construct validity, the extent to which a measurement or test accurately measures the theoretical construct or concept it is intended to measure).[1,2]

Stage 6: Test the model in a new sample

Step 12 – Confirmatory factor analysis that is used to confirm the initial structure.[3,6]

Step 13 – Assess model: chi-square/degrees of freedom, root mean square error of approximation, root mean square of the residuals, Tucker Lewis Index, average variance extracted, composite reliability.[4,7,14]

In their paper in Acta Médica Portuguesa, Barbosa and colleagues presented an original instrument to assess anxiety during teleconsultations.[15] Because the authors followed most of the proposed guidelines, they have constructed a valid and feasible instrument to measure anxiety during teleconsultations. The use of redundancies when selecting the number of factors to extract is a good way to protect against biased results. Through the use of a covariance-based method like EFA, Barbosa and colleagues aimed to explore the underlying relationships between measured variables, thus exploring the underlying theoretical structure of the phenomena, in this case anxiety during teleconsultations. A covariance-based method is a statistical approach that uses the covariance matrix of the observed variables to estimate the factors. This method assumes that the relationship between the observed variables is explained by a smaller number of underlying factors. Moreover, in this paper, the use of extent fit measures, such as the chi-square, root mean square error of approximation (RMSEA), root mean square of the residuals (RMSR), Tucker Lewis index of factoring reliability (TLI) along with composite reliability (CR) and average variance extracted (AVE) was appropriate because they provide different types of information and allow more robust conclusions.

Improvements could be done, namely in the sample collection process, because a non-probabilistic sample was used, which means it was more exposed to selection bias, thus decreasing generalizability. Authors should consider collecting a new sample and testing their model with confirmatory factor analysis. One of the most common limitations in scale validation is the use of non-probabilistic samples, in which the selection probabilities of individuals in the sample

are not known. Because non-probabilistic sampling methods can result in different probabilities for individuals to be included in the sample, they can compromise the generalizability of the findings. This also happens in this paper. When sampling for scale validation, researchers should try to balance the need to avoid bias by collecting probabilistic samples with the resources (e.g., time, money) available to do it.

CONCLUSION

This paper intends to be a short guide for researchers interested in building quantitative scales to measure health outcomes. The effort to build a scale is considerable, but the necessary procedures of scale validation will lead to more sound conclusions.

COMPETING INTERESTS

The author stated that there are no competing interests associated with this paper.

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Avaliação do Sistema de Triagem de Manchester em Doentes com Crise de Encerramento Agudo Primário do Ângulo Iridocorneano: Um Estudo Retrospetivo

Evaluation of the Manchester Triage System in Patients with Acute Primary Angle Closure Attack: A Retrospective Study

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RESUMO

Introdução: A crise de encerramento agudo primário do ângulo iridocorneano é uma emergência oftalmológica. O objetivo deste estudo foi descrever os casos admitidos no Serviço de Urgência do Centro Hospitalar Universitário São João, correlacionando a queixa inicial com o nível de triagem de Manchester atribuído e o tempo até observação por Oftalmologia e realização de iridotomia.

Métodos: Análise retrospetiva dos registos clínicos dos doentes com encerramento agudo primário do ângulo, admitidos no Serviço de Urgência entre janeiro de 2010 e dezembro de 2020. Foram revistos 2228 episódios com diagnóstico de glaucoma ou hipertensão ocular para identificação correta dos casos de crise de encerramento do ângulo. Foram extraídas variáveis, nomeadamente o nível de triagem de Manchester atribuído, queixa principal, pressão intraocular à admissão, especialidade responsável pelo primeiro contacto médico e tempos até observação por Oftalmologia e até iridotomia.

Resultados: Foram identificados 120 doentes, 84 (70%) do sexo feminino, com idade média de 68 ± 12 (desvio padrão) anos. A pressão intraocular média à admissão foi de 53,4 ± 12,4 mmHg. Em 9,2% dos doentes a queixa principal foi não-ocular, enquanto 9,2% apresentavam queixas não-oculares e oculares associadas. A maioria (68,1%) dos doentes com queixas não-oculares ou mistas foi triada para um não-oftalmologista. Segundo o sistema de triagem, a maioria (66,7%) dos doentes foi triada com nível amarelo (urgente), 9,2% foram triados com laranja (muito urgente) e nenhum vermelho (emergente). O primeiro especialista a observar os doentes após a triagem foi um oftalmologista em 83,3% dos casos (corretamente triados), enquanto os restantes foram inicialmente observados por outra especialidade. O tempo mediano até observação por Oftalmologia foi de 288 minutos (min. 45, máx. 871) num doente incorretamente triado e 49 minutos (min. 15, máx. 404) ($p < 0,001$) em doentes corretamente triados. O tempo mediano até realização de iridotomia laser foi de 353 minutos (min. 112, máx. 947) nos doentes incorretamente triados e 203 minutos (min. 22, máx. 1440) nos corretamente triados ($p < 0,001$).

Conclusão: A maioria dos doentes com crise de encerramento agudo primário do ângulo iridocorneano não foi triada de acordo com o grau de prioridade apropriado segundo o sistema de triagem de Manchester. Nos doentes que não foram imediatamente seguidos por Oftalmologia verificou-se um atraso significativo no diagnóstico e início do tratamento. Torna-se premente a consciencialização dos profissionais de saúde sobre esta condição clínica e a otimização do processo de triagem para minimizar a perda de visão.

Palavras-chave: Glaucoma de Ângulo Fechado/diagnóstico; Glaucoma de Ângulo Fechado/tratamento; Serviço de Urgência Hospitalar; Triagem

ABSTRACT

Introduction: Acute primary angle closure attack is an ophthalmological emergency. The aim of this study was to describe the cases diagnosed in the Emergency Department, by correlating the initial complaint with the Manchester triage level and ultimately the time needed until ophthalmological evaluation and iridotomy.

Methods: Retrospective analysis of the electronic medical records of patients with acute primary angle closure attack that attended the Ophthalmology Emergency Department of our tertiary center between January 2010 and December 2020. Overall, 2228 Emergency Department episodes coded with the diagnoses glaucoma or ocular hypertension were retrieved, followed by screening of each episode for correct identification of true acute primary angle closure attacks. Clinical data was gathered, including Manchester triage level, presenting complaint, intraocular pressure at presentation, first medical specialty that observed the patient, time until observation by Ophthalmology and time until laser iridotomy.

Results: Among the 120 patients identified, 84 (70%) were female and the mean age was 68 ± 12 years. Mean intraocular pressure at admission was 53.4 ± 12.4 mmHg, and 9.2% of patients presented only non-ocular complaints, while 9.2% presented mixed complaints (ocular and non-ocular). Most patients (68.1%) with only non-ocular or mixed complaints were triaged to a non-ophthalmologist ($p < 0.001$). Concerning the triage system, at admission, most patients (66.7%) were labelled yellow (urgent), while 9.2% and none were labelled as orange (very urgent) or red (emergent), respectively. Most patients (83.3%) were directly sent to Ophthalmology (properly triaged), while the remaining were incorrectly assigned to a non-ophthalmologist. Median time until observation by Ophthalmology was 49 minutes in the properly triaged group (min. 15, max. 404), while it was 288 minutes (min. 45, max. 871) in those who were incorrectly triaged ($p < 0.001$). Likewise, median time until treatment with laser iridotomy was 203 minutes in the properly triaged group (min. 22, max. 1440) and 353 minutes in the incorrectly triaged group (min.112, max. 947) ($p < 0.001$).

Conclusion: Most patients with acute primary angle closure attack were not properly triaged according to the level of the Manchester triage system. There was a significant delay in the diagnosis and treatment of those patients who were first assigned to non-ophthalmologists. There is a need to raise awareness regarding the presenting signs and symptoms of an acute primary angle closure attack in order to avoid preventable vision loss.

Keywords: Emergency Service, Hospital; Glaucoma, Angle-Closure/diagnosis; Glaucoma, Angle-Closure/therapy; Triage

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INTRODUÇÃO

O glaucoma é uma doença do nervo ótico, normalmente progressiva, que conduz à perda das fibras nervosas e consequente perda de campo visual. É a principal causa de cegueira irreversível a nível mundial.[1-4] Apesar de pouco prevalente, se considerarmos todos os tipos de glaucoma, o encerramento agudo do ângulo iridocorneano (frequentemente chamado de glaucoma agudo) – uma forma de apresentação do glaucoma primário de ângulo fechado (GPAF) – constitui uma das formas potencialmente mais graves da doença. Apesar da prevalência global do GPAF ser menor que a de ângulo aberto (GPAA) (0,50% *vs* 3,5%, respetivamente), o GPAF é responsável por um maior risco de cegueira, (25% *vs* 10% ao longo da vida),[3,5] correspondendo a cerca de 50% dos casos de cegueira bilateral provocada por glaucoma.[4,5] Estimou-se que em 2020 o número total de casos de GPAF em indivíduos entre os 40 e 80 anos seria de 23,36 milhões a nível mundial e que em 2040 esse número irá aumentar para 32,04 milhões, sendo a Ásia o continente mais afetado, com um registo de 24,50 milhões de casos, e a Europa com 1,46 milhões.[1] A prevalência de GPAF é maior em esquimós da Gronelândia e Canadá e também em asiáticos, sendo menor em afrodescendentes, nos quais o GPAA é mais prevalente.[1-8]

O sexo feminino é o mais afetado, sendo esta diferença entre sexos mais marcada nas idades mais avançadas, tendo em consideração que as mulheres apresentam uma maior esperança de vida.[2] Este achado também se poderá dever ao facto de o sexo feminino tendencialmente apresentar câmaras anteriores mais estreitas, que diminuem de tamanho mais rapidamente entre a quarta e quinta década de vida. Por outro lado, em esquimós e asiáticos não foi possível comprovar que a maior prevalência se devesse a uma maior predisposição anatómica.[5] Além do sexo e da predisposição anatómica, o envelhecimento e a história familiar de glaucoma de ângulo fechado são outros fatores de risco conhecidos para o encerramento do ângulo.[9] Além do sexo, idade e predisposição anatómica (câmara anterior pouco profunda, reduzido diâmetro da córnea e aumento da espessura do cristalino), existem outros fatores que predispõem para uma crise de encerramento agudo do ângulo.[3-5,10] Existem determinados fármacos potencialmente predisponentes que podem condicionar anteroposição do complexo íris-cristalino, estreitamento do ângulo por midríase e/ou disrupção do ângulo com efusão uveal. Salientam-se as classes farmacológicas dos agonistas adrenérgicos alfa e beta-2, anticolinérgicos, anti-histamínicos com ação anticolinérgica, sulfonamidas e serotoninérgicos. Existe ainda uma outra classe de fármacos, os agonistas colinérgicos, responsáveis por um mecanismo diferente de encerramento do ângulo, por bloqueio pupilar decorrente de miose.[11,12] Tendo em conta o envelhecimento da população e o aumento da polimedicação em várias destas classes, nomeadamente a dos fármacos psicotrópicos, torna-se essencial considerar o risco de encerramento do ângulo em doentes idosos com predisposição anatómica de base e que estejam sob essa medicação.

O encerramento do ângulo é definido pela presença de contacto iridotrabecular em pelo menos três quadrantes, que pode ocorrer por aposição (abre com indentação gonioscópica – pressão sobre a córnea com uma lente de contacto própria para avaliação do ângulo) ou através da formação de sinéquias anteriores (não abre com indentação). Pode resultar de quatro mecanismos principais: a) bloqueio pupilar (bloqueio à passagem de humor aquoso da câmara posterior para a câmara anterior, com consequente abaulamento anterior da íris, o que encerra o ângulo), b) íris em *plateau*, c) cristalino intumescente (ou seja, componente facomórfico: o encerramento do ângulo por mecanismo facomófico decorre do bloqueio pupilar pela existência de um cristalino intumescente), ou por d) anteroposição do complexo íris-cristalino, por exemplo, como efeito secundário de fármacos ou por alterações posteriores ao cristalino (como se verifica no glaucoma maligno – *aqueous misdirection syndrome*).[3-5] Por vezes, existe uma combinação de mecanismos, pelo que pode ser difícil isolar apenas um.

O encerramento primário do ângulo pode ser dividido em três subtipos de acordo com a sua evolução temporal[4,5]:

- encerramento agudo do ângulo decorrente de aposição rápida e circunferencial da íris sobre toda a malha trabecular, impedindo abruptamente a drenagem do humor aquoso, resultando numa elevação rápida e marcada da pressão intraocular, e que requer diagnóstico célere e intervenção oftalmológica emergente;
- encerramento intermitente do ângulo, com manifestações clínicas semelhantes às do encerramento agudo, mas de intensidade menor e de resolução espontânea;
- encerramento crónico do ângulo, que decorre de forma lenta e progressiva, muitas vezes sem sintomas, podendo conduzir a glaucoma crónico de ângulo fechado.

Dependendo do mecanismo e evolução temporal, o encerramento do ângulo pode condicionar hipertensão ocular (com ou sem sintomas acompanhantes) que, se suficientemente elevada durante tempo suficiente, poderá condicionar neuropatia ótica – glaucoma.

Nos casos de crise de encerramento agudo do ângulo, o doente pode manifestar queixas agudas de carácter ocular (olho vermelho e/ou dor ocular, lacrimejo, visão turva

ou hipovisão, entre outros) e/ou não-ocular, como cefaleias, náuseas e/ou vómitos. Atentando aos sinais oculares (normalmente unilaterais), o doente frequentemente apresenta hiperémia conjuntival, edema e turvação da córnea e pupila em midríase média pouco reativa à luz (habitualmente o sinal mais facilmente identificável). Estes sinais poderão ajudar o responsável pela triagem – um médico não-oftalmologista ou outro profissional de saúde – a realizar o diagnóstico diferencial.

Pelo facto de ser uma condição ameaçadora da visão, em que cada minuto pode conduzir à perda irreversível de fibras nervosas do nervo ótico, o encerramento agudo do ângulo deve ser considerado uma emergência oftalmológica (triagem de Manchester cor vermelha), cuja suspeita clínica deverá determinar uma abordagem premente (incluindo administração de hipotensores oculares tópicos e sistémicos e posterior iridotomia laser para equalização da pressão intraocular nas câmaras posterior e anterior e resolução do mecanismo de bloqueio pupilar). As queixas oculares poderão alertar e ajudar a direcionar o doente antecipadamente para uma avaliação oftalmológica. Contudo, alguns sintomas inespecíficos (cefaleia, náuseas e/ou vómitos), podem ser considerados mais relevantes pelo utente e/ou responsável pela triagem, verificando-se, por vezes, um atraso na atuação oftalmológica.[13]

Pretendeu-se com o presente estudo caracterizar a população que recorreu ao Serviço de Urgência (SU) do nosso centro terciário com crise de encerramento agudo primário do ângulo iridocorneano, dando especial atenção à relação entre a forma como decorreu a triagem e o tempo até à atuação oftalmológica.

MATERIAL E MÉTODOS

Foi realizado um estudo retrospetivo observacional transversal de todos os doentes com encerramento agudo primário do ângulo que recorreram ao SU do Centro Hospitalar e Universitário de São João (CHUSJ), o segundo maior centro terciário do país, no período compreendido entre janeiro de 2010 e dezembro de 2020. Para evitar a exclusão de casos por codificação incorreta ou pouco específica, foram pesquisados todos os episódios com diagnóstico de glaucoma ou hipertensão ocular (*International Classification of Diseases* - ICD9 365.xx ou ICD10 H40.xx) no sistema informático ALERT®. Neste sistema, usado para todos os doentes que recorrem ao SU do nosso centro, é obrigatório definir um diagnóstico previamente à alta médica. Numa fase inicial obtiveram-se 2228 registos. Foram incluídos todos os casos de encerramento agudo primário do ângulo iridocorneano, incluíndo os mecanismos de bloqueio pupilar, iris em *plateau*, glaucoma facomórfico e encerramento por provável efeito secundário de fármacos, quando estes tivessem associação com a crise de encerramento agudo do ângulo previamente descrita na literatura. A seleção dos episódios foi baseada na presença dos seguintes critérios de inclusão:

1. A presença de pelo menos um dos seguintes sintomas: perceção de visão turva, halos luminosos, perda de visão, dor ocular ou periocular, olho vermelho, náuseas, vómitos e/ou cefaleias;
2. Pressão intra-ocular superior a 21 mmHg;
3. A presença de pelo menos um dos seguintes sinais: edema da córnea, câmara anterior baixa e/ou pupila em midríase média não reativa;
4. Encerramento do ângulo observado na gonioscopia (quando a transparência da córnea assim o permitisse).

Foram extraídas variáveis demográficas e clínicas, que incluíram medicação potencialmente predisponente para encerramento do ângulo [via Registo Nacional de Saúde (RSE)/ Registo Nacional do Utente (RNU), quando disponível], nível de triagem de Manchester (azul – não urgente; verde – pouco urgente; amarelo – urgente; laranja – muito urgente; vermelho – emergente), queixa principal (ocular – hipovisão, visão turva, olho vermelho, dor; não ocular – cefaleia, vómitos, náuseas), pressão intraocular (PIO) à admissão, especialidade responsável pelo primeiro contacto médico, tempo até observação por Oftalmologia e tempo até iridotomia.

Foi obtido o consentimento por parte da Comissão de Ética do Centro Hospitalar para acesso aos registos no sistema ALERT® e consulta do processo hospitalar na plataforma SClínico®. Foi dispensado consentimento informado dada a natureza retrospetiva e o facto de não se utilizarem quaisquer dados identificadores de utentes.

A análise estatística foi realizada através do *software* IBM SPSS Statistics®, versão 27 para Mac IOS®. O teste de Kolmogorov–Smirnov e/ou a avaliação qualitativa de histogramas foram utilizados para averiguar a distribuição normal de cada variável contínua. As variáveis contínuas foram descritas através da média (± desvio padrão) ou mediana (mínimo, máximo), consoante apresentavam distribuição normal ou não normal, respetivamente, e a comparação entre grupos foi feita através do teste *t* para amostras independentes, ou do teste U de Mann-Whitney, consoante apresentavam distribuição normal ou não normal, respetivamente. As variáveis categóricas foram descritas como proporção relativa e os grupos foram comparados através do teste do qui-quadrado ou do teste exato de Fisher, quando não havia casos suficientes para aplicar o teste de qui-quadrado.

RESULTADOS

Entre janeiro de 2010 e dezembro de 2020, e após

revisão dos critérios de inclusão e exclusão de mecanismos secundários de encerramento agudo do ângulo, tais como glaucoma neovascular, uveíte, trauma e *aqueous misdirection syndrome* foram registados 120 episódios de urgência relativos a doentes admitidos por crise de encerramento agudo primário do ângulo iridocorneano. A Fig. 1 discrimina o número de episódios registado em cada ano.

Dos 120 doentes incluídos, 84 (70%) eram do sexo feminino, e a idade média era de 68 ± 12 anos. A PIO média à admissão foi de 53,4 ± 12,4 mmHg. Em relação ao sistema de triagem, a maioria (66,7%) dos doentes foi triada com a cor amarela. Nenhum doente foi triado como vermelho e apenas 9,2% foram triados como laranja. Foi observado que onze doentes (9,2%) apresentavam sintomatologia não-ocular isolada como queixa principal (náuseas, cefaleias e/ou vómitos), enquanto onze doentes (9,2%) apresentavam queixas não-oculares e oculares simultaneamente (Tabela 1). Cerca de um quinto dos doentes (17,5%) estava medicado com pelo menos um medicamento potencialmente predisponente para encerramento do ângulo, sendo que a maioria (76,2%, n = 16) desses doentes estava medicada com um fármaco com ação no sistema nervoso central: antidepressivos (57,1%),[11] incluindo as classes dos inibidores seletivos e não seletivos da serotonina e/ou noradrenalina, antidepressivos tricíclicos e trazodona, antipsicóticos (9,5%),[11] agonistas dopaminérgicos, nomeadamente levodopa (0,5%),[14] anticolinérgicos (9,5%)[11] e benzodiazepinas (28,6%).[15] Verificou-se ainda que um (0,5%) doente estava medicado com indapamida[16] e outro (0,5%) com clortalidona.[17]

Em 83,3% dos casos, o primeiro especialista a observar os doentes após a triagem foi um oftalmologista enquanto 16,7% dos casos foram incorretamente triados, tendo sido inicialmente observados por outra especialidade: 13 doentes (10,8%) foram avaliados num primeiro momento por Medicina Interna, cinco doentes (4,2%) foram vistos na Emergência Médica, um doente (0,8%) foi observado por Cirurgia, enquanto a Ortopedia também observou previamente um doente (0,8%).

De seguida, foi realizada uma análise de acordo com o tipo de triagem: correta (diretamente para Oftalmologia) ou incorreta (Tabela 2). Não houve diferenças significativas entre os grupos no que concerne a idade, sexo e PIO. Houve, no entanto, diferenças estatisticamente significativas ($p < 0,001$) relativamente às queixas reportadas pelos doentes. A maioria dos doentes triados para Oftalmologia apresentava queixas oculares isoladas (93%), mas os doentes encaminhados para outras especialidades reportaram mais frequentemente queixas sistémicas isoladas ou queixas sistémicas combinadas com queixas oculares. Também foram observadas diferenças significativas no nível de

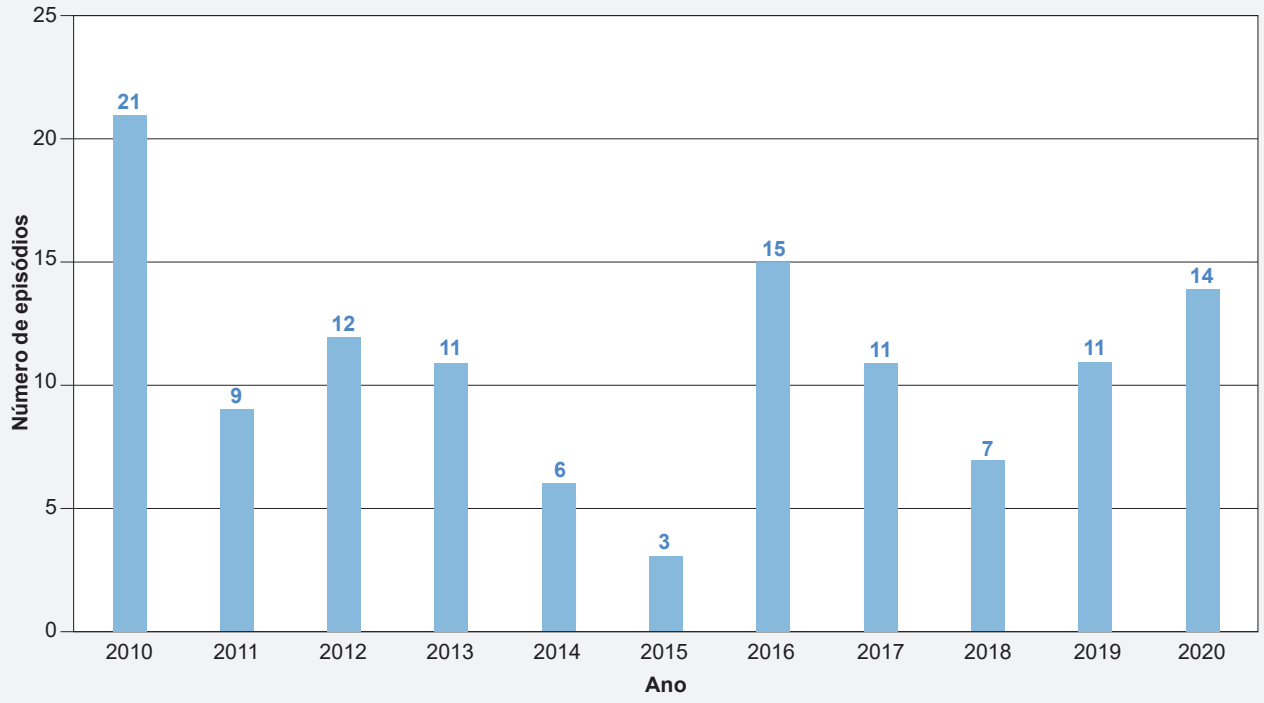

Figura 1 – Número anual de episódios de encerramento primário agudo do ângulo iridocorneano registados no Serviço de Urgência do Centro Hospitalar Universitário de São João, entre os anos de 2010 e 2020

Tabela 1 – Características demográficas e clínicas (n = 120)

Idade, média ± desvio padrão (anos)	68 ± 12
Sexo feminino, n (%)	84 (70)
Pressão intraocular à admissão, média ± desvio padrão (mmHg)	53,4 ± 12,4
Queixa principal	
Ocular	98 (81,7)
Sistémica (vómitos, cefaleias e/ou náuseas)	11 (9,2)
Ambas	11 (9,2)
Nível de triagem de Manchester, n (%)	
Azul	1 (0,8)
Verde	27 (22,5)
Amarelo	81 (67,5)
Laranja	11 (9,2)
Vermelho	0 (0)
Tempo de espera (minutos) **desde a triagem até ser observado por oftalmologia**, mediana (min., máx.)	54 (15, 871)
Tempo até iridotomia laser (minutos), mediana (min., máx.)	211 (22, 1440)
Sob medicação habitual potencialmente predisponente, n (%)	21 (17,5)
Antidepressivos (SSRI, SNRI, AT, trazodona)	12 (57,1)
Benzodiazepinas	6 (28,6)
Anticolinérgicos	2 (9,5)
Antipsicóticos	2 (9,5)
Agonistas dopaminérgicos (levodopa)	1 (0,5)
Indapamida	1 (0,5)
Clortalidona	1 (0,5)

AT: antidepressivo tricíclico; SNRI: *serotonin and norepinephrine reuptake inhibitors*; SSRI: *selective serotonin reuptake inhibitor*

triagem de Manchester, em que a maioria (95%) dos doentes triados diretamente para Oftalmologia foi triada como verde (pouco urgente) ou amarelo (urgente), sendo que a todos os doentes incorretamente triados foi atribuído um nível de triagem de amarelo (urgente) ou laranja (muito urgente) (p < 0,001). Existiu uma correlação significativa entre o nível de prioridade atribuído e o sintoma apresentado (p = 0,009). O tempo mediano até observação por Oftalmologia foi de 288 minutos (min. 45, máx. 871) num doente incorretamente triado e de 49 minutos (min. 15, máx. 404) (p < 0,001 entre grupos) em doentes corretamente triados. Da mesma forma, houve uma diferença estatisticamente significativa no tempo até realização de iridotomia laser [353 minutos (mín. 112, máx. 947) nos doentes incorretamente triados *versus* 203 minutos (mín. 22, máx. 1440) nos corretamente triados (p < 0,001)].

DISCUSSÃO

O presente estudo avaliou 120 episódios (de 120 doentes) de crise de encerramento agudo primário do ângulo iridocorneano (glaucoma agudo) observados no SU do nosso centro terciário ao longo de 11 anos. A amostra de doentes compreendeu uma percentagem de mulheres comparável com a da literatura (70% no nosso estudo *versus* 75% de acordo com a Sociedade Europeia de Glaucoma),[3] provavelmente devido ao facto de o sexo feminino apresentar uma predisposição anatómica por ter uma câmara anterior mais baixa. A média de idades foi de 68 anos, também concordante com estudos epidemiológicos prévios, sendo que o encerramento do ângulo apresenta um pico de incidência entre os 55 e os 70 anos.[9,18]

Apesar de pouco frequente, esta condição deve ser considerada uma emergência oftalmológica, para a qual o médico não-oftalmologista deverá estar atento. Sendo considerada uma emergência, esperar-se-ia a atribuição do nível vermelho na triagem de Manchester, na medida em que a sua avaliação e abordagem terapêutica deverão ser imediatas. Segundo as diretivas da Direção-Geral da Saúde,[19] o tempo de espera máximo recomendado quando atribuída a cor azul (não urgente) é de 240 minutos, a cor verde (pouco urgente) é de 120 minutos, a cor amarela (urgente) é de 60 minutos e a cor laranja (muito urgente) é de 10 minutos. Perante uma emergência (vermelho), o atendimento deverá ser imediato. Contudo, no nosso

Tabela 2 – Comparação entre os doentes corretamente triados (triados diretamente para Oftalmologia) e os incorretamente triados (triados para outra especialidade)

	Oftalmologista (n = 100, 83,3%)	**Outra especialidade** (n = 20, 16,7%)	**Valor de *p***
Idade, média ± desvio padrão (anos)	68 ± 13	69 ± 10	0,762[a]
Sexo feminino, n (%)	67 (67)	17 (85)	0,18[b]
Pressão intraocular à admissão, média ± desvio padrão (mmHg)	53,5 ± 12,3	53,2 ± 13,7	0,937[a]
Queixa principal			
Ocular	93 (93)	5 (25)	**< 0,001**[c]
Sistémica (vómitos, cefaleias e/ou náuseas)	2 (2)	9 (45)	
Ambas	5 (5)	6 (30)	
Nível de triagem de Manchester, n (%)			
Azul	1 (1)	0 (0)	**< 0,001**[c]
Verde	27 (27)	0 (0)	
Amarelo	68 (68)	13 (65)	
Laranja	4 (4)	7 (35)	
Tempo de espera (minutos) **desde a triagem até ser observado por oftalmologia**, mediana (min.- máx.)	49 (15 - 404)	288 (45 - 871)	**< 0,001**[d]
Tempo até iridotomia laser (minutos), mediana (min. - máx.)	203 (22 - 1440)	353 (112 - 947)	**< 0,001**[d]

a: teste *t* para amostras independentes; **b**: teste do qui-quadrado; **c**: teste exato de Fisher; **d**: teste U de Mann-Whitney.
Os valores estatisticamente significativos ($p < 0,05$) estão assinalados a negrito.

estudo, a maioria dos doentes (67,5%) foi triada com nível amarelo. Não obstante, é importante relembrar que o sistema de triagem de Manchester foi desenvolvido para sinalizar os doentes sob risco iminente de vida, não estando o compromisso visual previsto na elaboração do mesmo.[20] De modo semelhante e de acordo com a DGS, ainda não existem normas orientadoras ou sistemas de triagem especificamente dirigidos às queixas oculares como olho vermelho e perda súbita da acuidade visual, pelo que acreditamos que a elaboração das mesmas é da maior importância.[19]

Apesar de não haver diferenças significativas no que concerne a idade e sexo, os grupos de doentes corretamente triados para Oftalmologia e aqueles inicialmente triados para outra especialidade apresentaram diferenças importantes relacionadas com o nível de urgência atribuído, o tipo de queixas, a existência de medicação potencialmente predisponente e os tempos até observação por Oftalmologia e intervenção terapêutica com iridotomia laser. Os doentes com queixas oculares e sem queixas sistémicas foram corretamente triados para Oftalmologia, mas foram mais vezes categorizados como verde ou amarelo, enquanto os doentes que tinham pelo menos uma queixa sistémica (cefaleias, náuseas e/ou vómitos), independentemente de terem ou não queixas oculares associadas, foram mais vezes encaminhados para outra especialidade. Apesar de a estes últimos ter sido mais vezes atribuído um nível de prioridade de atendimento superior (amarelo e laranja), o tempo até serem corretamente referenciados para Oftalmologia, diagnosticados e tratados foi significativamente maior. Desta forma, depreende-se que os doentes com queixas sistémicas (com ou sem queixas oculares) tenham sido tendencialmente triados para outra área médica do SU, presumivelmente para exclusão de outros diagnósticos diferenciais para as suas queixas sistémicas. Em relação à medicação potencialmente predisponente, quase um quinto (17,5%) dos doentes estava medicado com um ou mais fármacos predisponentes para encerramento do ângulo. Os efeitos dos antidepressivos (inibidores seletivos e não seletivos da serotonina e/ou noradrenalina, tricíclicos e trazodona), anticolinérgicos e alguns antipsicóticos estão vastamente descritos na literatura,[11] e existem casos anedóticos de encerramento do ângulo com análogos da dopamina,[14] indapamida,[16] e clortalidona.[17] Questiona-se a associação entre as benzodiazepinas, uma classe farmacológica de uso bastante frequente, e o aumento do risco para encerramento do ângulo em doentes com anatomia predisponente.[15] Em teoria, estes fármacos poderiam predispor para o encerramento do ângulo através do relaxamento do esfíncter da pupila e pelo efeito anticolinérgico ligeiro.[21,22] Uma revisão sistemática refuta esta predisposição, defendida por um único caso clínico,[23] e elenca, pelo contrário, o seu efeito hipotensor, pelo que a relação causa-efeito entre o encerramento do ângulo iridocorneano e as benzodiazepinas, e sua consequente contra-indicação, constitui um tópico em debate.[24]

Este estudo apresentou limitações. Em primeiro lugar,

o facto de ser um estudo retrospetivo, que se baseia na presunção de que todos os episódios são corretamente diagnosticados. Além da natureza retrospetiva e transversal, poderá ter existido algum viés de seleção, tendo em conta que alguns dos doentes corretamente triados para Oftalmologia e com tempos de atendimento mais reduzidos tinham sido inicialmente avaliados no exterior (por exemplo, oftalmologista particular). Por outro lado, teria sido relevante avaliar a diferença de acuidade visual (e campo visual) antes e após a crise de encerramento, na tentativa de correlacionar o tempo de atendimento com a repercussão visual objetivada. No entanto, a falta desses dados na maioria dos registos não permitiu essa análise. Finalmente, o ano de 2020 inclui o início da pandemia de COVID-19. No entanto, não acreditamos que tenha influenciado significativamente os resultados, dado que esta patologia apresenta queixas severas, o que obriga o utente a procurar ajuda médica. Isto pode ser confirmado pelo número de casos detetados durante esse ano, que foi superior à média dos anos anteriores (Fig. 1). No entanto, temos de considerar a possibilidade de isso ter acontecido por menor capacidade de atendimento de outros hospitais da área de referenciação do CHUSJ.

Após revisão da literatura, este é o primeiro estudo que compara o tempo de abordagem de uma emergência oftalmológica de acordo com a triagem realizada. Como demonstrado, pode haver um atraso na identificação e orientação desta condição. A sobreposição de queixas sistémicas em doentes de idade mais avançada, sob polimedicação, pode orientar para a necessidade de exclusão de outras patologias sistémicas que poderão estar na origem das cefaleias, tais como vómitos e/ ou náuseas *de novo*. Este estudo pretende lançar o repto aos médicos não-oftalmologistas para atentarem nas queixas visuais dos doentes e nos possíveis sinais que facilmente podem ser identificados, como o olho vermelho, a turvação da córnea, a câmara anterior baixa e a midríase média com fraca (ou nenhuma) resposta pupilar à luz. Na ausência de um oftalmoscópio direto, praticamente qualquer fonte de luz permite reconhecer estes sinais.

À luz dos esforços endereçados aos colegas dos Cuidados de Saúde Primários, em 2008 foi criado o manual de "Boas Práticas na Oftalmologia – Elementos Clínicos de Avaliação e Referenciação",[25] promovido pela DGS, nomeadamente pela Comissão Coordenadora do Programa Nacional para a Saúde da Visão, e destinado, sobretudo, aos profissionais dos Cuidados de Saúde Primários envolvidos na abordagem das principais queixas e patologias oculares. Contudo, surge a necessidade de melhorar o sistema de triagem no Serviço de Urgência, e de desenvolver urgentemente normas orientadoras específicas e algoritmos de rápida consulta e orientação da patologia oftalmológica.

CONCLUSÃO

A maioria dos doentes com crise de encerramento agudo primário do ângulo iridocorneano não foi triada de acordo com o grau de prioridade apropriado segundo o sistema de triagem de Manchester. Nos doentes que foram inicialmente orientados para outra especialidade que não Oftalmologia, verificou-se um atraso significativo no diagnóstico e início do tratamento. Sendo uma condição emergente em que há perda de visão irreversível, torna-se imperativo estar atento a eventuais queixas oculares que poderão ser desvalorizadas. Apesar de ser pouco frequente, dada a sua gravidade, a otimização do processo de triagem pode minimizar a perda da função visual e maximizar a qualidade de vida destes doentes.

PRÉMIOS E APRESENTAÇÕES PRÉVIAS

O resumo do presente trabalho foi submetido para apresentação como comunicação livre no 64.º Congresso da Sociedade Portuguesa de Oftalmologia, realizado em dezembro de 2021, e no 15.º Congresso da Sociedade Europeia de Glaucoma, em junho de 2022.

CONTRIBUTO DOS AUTORES

MR, FG: Conceção e desenho de estudo; preparação, colheita e análise dos dados; redação do manuscrito; revisão e aprovação do manuscrito final.

JBB: Conceção e desenho de estudo; preparação, colheita e análise dos dados; revisão e aprovação do manuscrito final.

AFP: Preparação e colheita dos dados; revisão e aprovação do manuscrito final.

FFR, FA, SES: Revisão e aprovação do manuscrito final.

ABM: Conceção e desenho de estudo; revisão e aprovação do manuscrito final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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Translation, Cultural Adaptation and Validation of "PROMIS GI - Disrupted Swallowing" Scale for the Portuguese Language

Tradução, Adaptação Cultural e Validação da Escala "PROMIS GI - Dificuldade em Engolir" na Língua Portuguesa

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ABSTRACT

Introduction: Dysphagia is a prevalent condition (20%), and occurs more frequently in women and in older people. It negatively impacts innumerous aspects of patient's personal and professional lives. Patient-reported outcomes allow patients to directly quantify their experience regarding dysphagia and evaluate its true impact on quality of life. Among the scales available, Patient-Reported Outcomes Measurement Information System Gastrointestinal (PROMIS GI) Disrupted Swallowing stands out because it is a robust instrument that can be applied regardless of the type and etiology of dysphagia. The aim of this study was to translate, culturally adapt and validate PROMIS GI Disrupted Swallowing scale for the Portuguese-speaking population.

Methods: Firstly, the seven items of the scale were translated and transculturally reviewed following the systematic method proposed by the Functional Assessment of Chronic Illness Therapy (FACIT). Afterwards, the pre-test version of the questionnaire was administered to a convenience sample (n = 6) for semantic evaluation, with the aim of detection and subsequent correction of possible problems in the translation. The final translated and certified version of the scale was administered to 200 voluntary adult participants (n = 123 healthy; n = 77 dysphagia) in Portugal, for evaluation of reliability and validity.

Results: The Portuguese version of PROMIS GI Disrupted Swallowing presented acceptable internal consistency (coefficient of Cronbach's α of 0.919) and adequate test-retest reliability (intraclass correlation coefficient of 0.941). The translated version of the scale revealed a strong correlation with both Eckardt score ($p < 0.001$; $\rho = 0.782$) and the quality-of-life questionnaire EuroQol-5D ($p < 0.001$; $\rho = -0.551$), demonstrating evidence of convergent validity.

Conclusion: The Portuguese version of PROMIS GI Disrupted Swallowing scale presented conceptual, semantic, cultural and measurement equivalence relatively to the original items. The results attained demonstrated that the translation of this scale to Portuguese is reliable and valid for use both in clinical practice and for research purposes.

Keywords: Deglutition Disorders; Portugal; Reproducibility of Results; Surveys and Questionnaires; Translation

RESUMO

Introdução: A disfagia é uma condição prevalente (20%), mais frequente nas mulheres e nos idosos, que tem um marcado impacto negativo na qualidade de vida pessoal e profissional dos afetados. Os resultados reportados pelo doente (*patient-reported outcomes*) permitem quantificar a sua experiência perante a disfagia e avaliar o impacto real na qualidade de vida. Entre as escalas disponíveis, a *Patient-Reported Outcomes Measurement Information System Gastrointestinal* (PROMIS GI) *Disrupted Swallowing* destaca-se por ser um instrumento robusto e aplicável independentemente do tipo e causa de disfagia. Neste estudo os autores procedem à tradução, adaptação cultural e validação da escala PROMIS GI *Disrupted Swallowing* na população de língua portuguesa.

Métodos: Numa primeira fase, os sete itens da escala foram traduzidos e revistos transculturalmente de acordo com o método sistemático proposto pelo *Functional Assessment of Chronic Illness Therapy* (FACIT). A versão pré-teste do questionário foi aplicada a uma amostra de conveniência (n = 6) para avaliação semântica, para deteção e correção subsequente de possíveis problemas na tradução. A versão final traduzida e certificada foi aplicada a 200 indivíduos adultos voluntários (n = 123 saudáveis; n = 77 disfagia) em Portugal, para avaliação da confiabilidade e validade.

Resultados: A versão portuguesa da escala PROMIS GI *Disrupted Swallowing* apresenta uma consistência interna aceitável (coeficiente α de Cronbach de 0,919) e uma confiabilidade teste-reteste adequada (coeficiente de correlação intraclasse de 0,941). A versão traduzida da escala apresentou uma correlação forte com o *score* de Eckardt ($p < 0,01$; $\rho = 0,782$) e com o questionário de qualidade de vida EuroQol-5D (EQ-5D) ($p < 0,01$; $\rho = -0,551$), evidenciado validade convergente.

Conclusão: A escala PROMIS – Sintomas Gastrointestinais - Dificuldade em Engolir apresentou equivalência conceptual, semântica, cultural e de medição relativamente à escala original. Os resultados obtidos demonstraram que a versão portuguesa desta escala aparenta ser fiável e válida para aplicação tanto na prática clínica como em contexto de investigação.

Palavras-chave: Distúrbio da Deglutição; Inquéritos e Questionários; Portugal; Reprodutibilidade dos Testes; Tradução

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INTRODUCTION

Dysphagia consists in the difficulty of liquids or solids to pass from the oral cavity to the stomach. It can be classified as oropharyngeal or esophageal. The prevalence of dysphagia in the general population is around 20%,[1] and it is estimated to affect up to 50% of people over 60 years old, occurring more frequently in women and in older people than in men and in younger people.[1-3] However, it is very challenging to accurately quantify the true prevalence of this symptom.[4] Oropharyngeal dysphagia is typically due to structural, anatomic or neuromuscular abnormalities. On the other hand, esophageal dysphagia arises after swallowing and causes include intrinsic structural disease, disruption in normal motility or extrinsic compression.[1,2]

This condition can have nefarious consequences in terms of physical health such as malnutrition, dehydration, aspiration pneumonia or death caused by asphyxia,[5-6] which increase in-hospital mortality, hospital length of stay, inpatient costs and likelihood of discharge to a post-acute care facility.[4,8,9] However, the impact of dysphagia is much wider, with consequences also in terms of psychological well-being and innumerous aspects of the personal and professional lives of patients, thus reinforcing the need of an early and multidisciplinary approach.[4,10-13] In a study performed in patients with dysphagia following chemoradiation for head and neck cancer, roughly 40% reported anxiety during meals and 36% avoided eating in front of other people.[11]

The assessment of dysphagia can be performed using simple tests designed to rapidly detect signs and symptoms of swallowing disorders, such as the Eating Assessment Tool (EAT-10) and the Functional Oral Intake Scale (FOIS).[13] Patient-reported outcome (PROs) scales offer a method of quantifying the patient experience regarding his/her illness in a structured format and can be helpful for use in comparative effectiveness studies.[14-16] The measurement of PROs can improve clinical outcomes by successfully aiding in the detection and management of conditions, improving satisfaction with care and enhancing the patient–provider relationship.[17] The Patient-Reported Outcomes Measurement Information System (PROMIS®) is a standardized set of PROs that cover physical, mental, and social health. The PROMIS vision is to create highly efficient and short questionnaires that are feasible to implement in busy clinical settings while preserving reliability and validity.[17]

A recent meta-analysis identified a total of 34 dysphagia-related PROs scale studies,[15] mostly conceived for specific conditions such as achalasia or Parkinson's disease.[18-21] Among the available scales for general dysphagia, PROMIS Gastrointestinal (PROMIS GI) Disrupted Swallowing is a robust instrument when evaluating all the different domains (conceptual model, content validity, reliability, construct validity, scoring and interpretation, and burden and presentation).[15] It was validated in the North American population, it is easy to use, and it was developed with the goal of evaluating the impact caused by dysphagia in an individual patient, regardless of etiology or type of dysphagia.[17] PROMIS GI scales have not been validated, to the present moment, in a Portuguese population.

Since the original items of PROMIS were developed in English a translation is necessary in order to allow the use of these scales in countries with other native languages.[16] The PROMIS standards stipulate that all PROMIS translations should be carried out using the rigorous Functional Assessment of Chronic Illness Therapy (FACIT) translation methodology, which includes cross-cultural adaptation and linguistic validation, before allowing the application of PROMIS scales in clinical trials, multicentric studies and clinical practice.[16] Additionally, our study has included rigorous reliability verification procedures.

The objective of our study was to conduct the translation, cultural adaptation and validation of the PROMIS GI Disrupted Swallowing scale in the Portuguese language and in an adult population. The validation of the Portuguese version of PROMIS GI Disrupted Swallowing is vital for a more standardized evaluation and intervention in dysphagia, contributing for its subsequent application in research and clinical practice.

METHODS

We conducted a cross-sectional study of translation, cultural adaptation, and validation of the PROMIS GI Disrupted Swallowing scale to the Portuguese language, after obtaining permission from the PROMIS Health Organization (PHO).

PROMIS GI Disrupted Swallowing comprises seven items (questions GISX31 to GISX37) that assess the frequency of swallowing-related symptoms during the past seven days on a scale of "never" to "always".[17] It encompasses an array of symptoms described by patients ranging from pain or difficulty swallowing solid and soft foods, liquids and pills, to food getting stuck in the throat or chest when eating.[17] Each item is scored between 0 and 5 and the overall score ranges from 7 to 35 (summed score). This scale uses item-level calibrations to produce a T-score, based on the United States general population, where 50 is an estimate of the general population mean and 10 is the standard deviation. This type of scoring scale uses a response pattern scoring and is more accurate, especially when there is missing data or different groups of participants responded to different items. The participants completed the questionnaire through pen-and-paper or electronically. Participants were instructed to respond to all items.

The study was developed in three phases. The first phase included the translation process and cultural adaptation of the PROMIS GI Disrupted Swallowing scale to the Portuguese language, with verification of semantic equivalence, according to the guidelines for the process of cross-cultural adaptation of self-reported instruments.[22] The translation followed the universal and systematic method proposed by FACIT, as required by PHO.[23]

The questionnaire underwent two forward translations that were performed by two researchers, one being a native speaker of European Portuguese and the other being a native speaker of Brazilian Portuguese, and both were fluent in the Portuguese and English languages. Afterwards, a third translator, who was a native speaker of European Portuguese and was also fluent in both Portuguese and English, reconciled the two initial translations. A retro-translation of this reconciliated version was conducted by a native speaker of American English, and who was also fluent in Portuguese and uninformed about the English source of the questionnaire.

Afterwards, three independent reviewers (one linguist and two health-related quality of life research experts), two native speakers of European Portuguese and one native speaker of Brazilian Portuguese, analyzed all the previous steps and selected the most adequate translation for each one of the seven items. The translated version was sent to the PROMIS Translation coordinating center in the Department of Medical Social Sciences of Northwestern University in the United States of America for appraisal and further revision. The translation history was verified by the PROMIS Translation Director, and the Portuguese translation was harmonized with the versions in other languages. Finally, the ultimate English to Portuguese translated version was approved and submitted to the pre-test stage, in collaboration with the linguistic coordinator in Portugal.

The second phase of the process included the semantic evaluation to confirm the suitability of the translation to Portuguese-speaking populations. The approved pre-test version of the questionnaire was administered to a convenience sample of six voluntary adult participants followed in Centro Hospitalar de Lisboa Ocidental, for detection of possible problems in the translation and subsequent correction. All participants had at least basic reading and writing skills and were native speakers of Portuguese (both individuals born in Portugal and in Brazil were considered eligible participants). Participants were asked to complete the questionnaire on their own and were then asked some debriefing questions about the translated items to assess comprehension. Following the process of linguistic validation, the translation was certified by the PROMIS Translation Director at Northwestern University.

During the third phase of the process, the final version of the Portuguese PROMIS GI Disrupted Swallowing scale was applied to 200 voluntary adult participants whose native language was European Portuguese. The purpose of this phase was the evaluation of reliability and validity of the translated version of the scale. These participants were individuals from the general population or patients with dysphagia followed in Centro Hospitalar de Lisboa Ocidental. The size of the sample was considered fair according to Comrey and Lee.[24,25] The patients were also asked to fill a sociodemographic form (age, gender, education and ethnicity), Eckardt score (if dysphagia) and the Portuguese version of the quality-of-life questionnaire EuroQol-5D (EQ-5D).

The Eckardt score was used for evaluation of the severity of dysphagia. It attributes 0 to 3 points to each of the major symptoms of achalasia (dysphagia, regurgitation, chest pain and weight loss).[26]

EQ-5D is a quality-of-life index developed by the EuroQoL group that contains two pages: the EQ-5D descriptive system and the EQ-5D visual analogue scale (VAS). The first comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels of severity, which implicates a total of 243 distinct health states,[24] that can be converted to a value between -1 and 1 according to the Portuguese general population time trade-off (TTO) values for EQ-5D. VAS records the patient's self-rated health on a vertical visual analogue scale (from 0 to 100), where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcomes that reflects the patient's own judgement.

Approximately half of the study population (115 participants, both healthy and with dysphagia) did a retest 15 days after the first administration of the Portuguese version of PROMIS GI Disrupted Swallowing scale, in order to allow the subsequent study of test-retest reliability.

Statistical analysis

Descriptive statistics (central tendency and dispersion measures) were used for characterization of the sociodemographic variables of the study population and for analysis of the PROMIS GI Disrupted Swallowing initial test and retest, Eckardt score and EQ-5D (TTO and VAS values).

Testing for dimensionality was skipped due to the fact that both versions of the scale (original and Portuguese) are directly comparable. In terms of reliability, internal consistency of the items of the PROMIS GI Disrupted Swallowing scale was assessed by using Cronbach's α, with values higher than 0.5 indicating an acceptable level of reliability.[27] The test-retest reliability was analyzed by using the intraclass correlation coefficient (ICC). ICC values higher than

0.75 were considered adequate.[28]

Spearman's rank correlation coefficient was used to evaluate the relationship between the score attained in the PROMIS GI Disrupted Swallowing scale with the value of EQ-5D TTO and with Eckardt score. Coefficient estimates lower than 0.29 were deemed weak and those higher than 0.5 were considered strong.[29] Statistical tests with *p*-value less than 0.05 were considered statistically significant.

RESULTS

Translation and cultural adaptation process

The seven items of the original PROMIS GI Disrupted Swallowing scale were translated and transculturally reviewed following the systematic method proposed by FACIT. The process of translation and cultural adaptation is summarized in Fig. 1. The researchers and the certified translator discussed some specific technical concepts of the first two forward translations in order to reconcile them. A few adaptations were made to make the concepts more discernible and appropriate for Portuguese speakers both in Portugal and in Brazil. For example, in Brazilian Portuguese the term for "ice cream" is "sorvete", while in European Portuguese the term is "gelado". The consensus version includes both terms ("gelados/sorvete"). Similarly, the word "mashed" (from mashed potatoes) is spelled "purê" in Brazil and "puré" in Portugal. The solution for a universally acceptable version was to use both diacritic marks ("puré(ê) de maçã ou puré(ê) de batata").

The reconciled Portuguese version then underwent retro-translation by an independent translator without

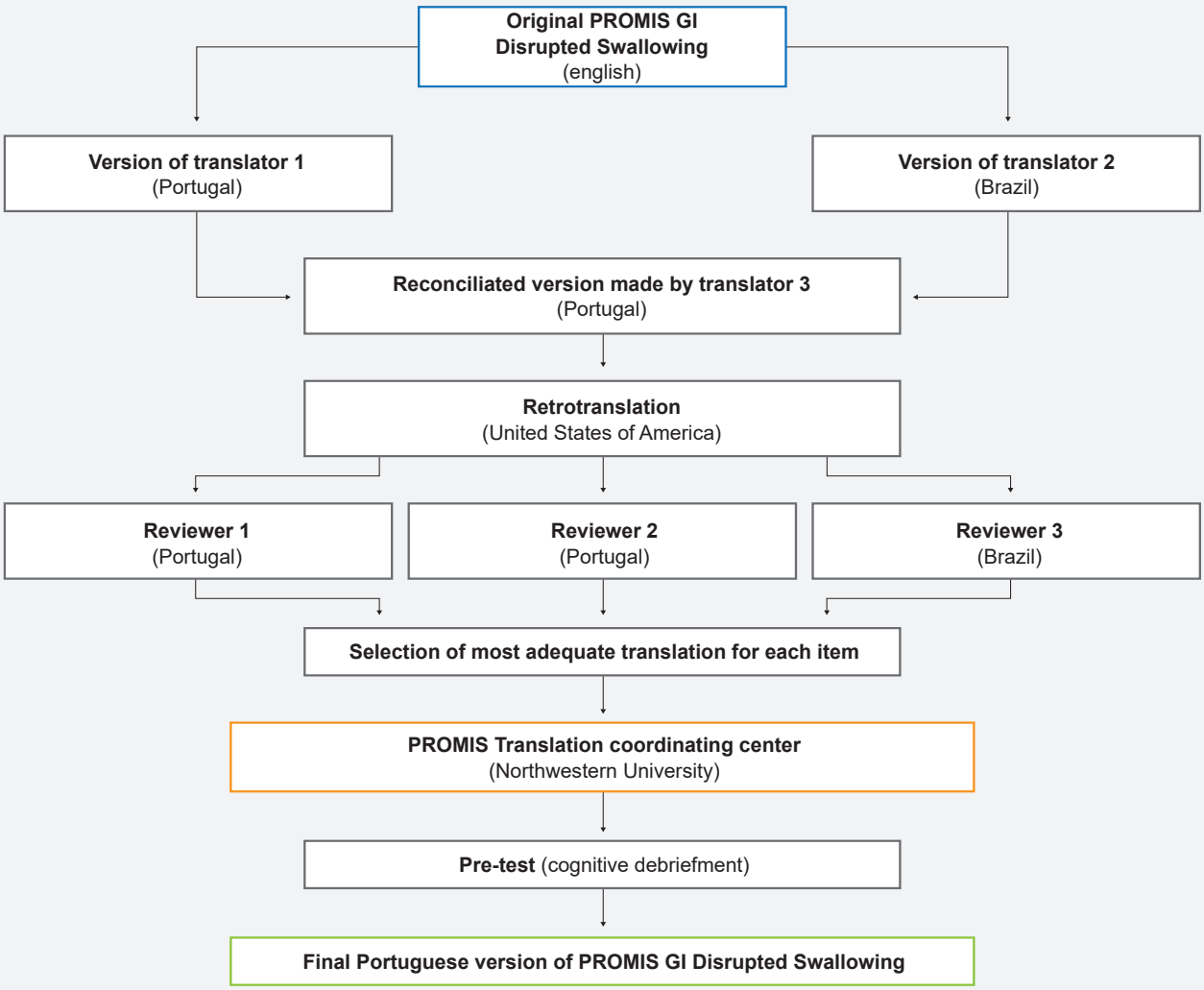

Figure 1 – Flowchart of the process of translation and cultural adaptation of PROMIS GI - Disrupted Swallowing scale to European Portuguese

access to the English source. Afterwards, three independent reviewers analyzed all the previous steps and selected the most adequate translation for each one of the seven items. Finally, the translated version was evaluated and revised by the PROMIS translations coordinating center in Northwestern University in the United States of America. Both the PROMIS Translation coordinating center and the linguistic coordinator in Portugal approved the final version of the PROMIS GI Disrupted Swallowing scale after discussion of clinical and linguistic issues (the translated questionnaire can be obtained at https://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis/available-translations). This final version was submitted to the pre-test phase.

Table 1 – Sociodemographic characteristics of the study population (n = 200)

Characteristics	Value
Age (average ± DP)	49.8 ± 16.6 years
Gender	
Male	59 (29.5%)
Female	141 (70.5%)
Education	
Primary	44 (22.0%)
Secondary	58 (29.0%)
University	85 (42.5%)
Unknown/undisclosed	13 (6.5%)
Ethnicity	
White	160 (80.0%)
Black	12 (6.0%)
Asian	1 (0.5%)
Unknown/undisclosed	27 (13.5%)
Type of participant	
Healthy	123 (61.5%)
Esophageal dysphagia	59 (29.5%)
Oropharyngeal dysphagia	18 (9.0%)

Pre-test (semantic equivalence)

The pre-test aimed to assess the cultural and semantic equivalence and the comprehension of the wording of the questions and the scale. The PROMIS GI Disrupted Swallowing instrument was tested in six individuals from the general population (three women and three men) with ages between 27 and 73 years (average age of 51 years). Five participants were native Portuguese speakers, born in Portugal, and one participant was born in Brazil and spoke Brazilian Portuguese. One participant had completed the fourth grade, one participant was a high school graduate, one had a college degree, one had a technical degree and two participants had advanced degrees. None of the participants reported any items to be difficult to understand, irrelevant or offensive. None of the participants felt the need to add anything else to the questionnaire. Cognitive debriefing for content validity was performed and no translation changes were recommended. Conceptual and semantic equivalence were confirmed in relation to the original version.

Test (measurement equivalence)

Among the 200 voluntary participants that participated in the final phase of translation, cultural adaptation and validation process of the Portuguese PROMIS GI Disrupted Swallowing scale, 123 were healthy (61.5%) and 77 had esophageal or oropharyngeal dysphagia (59 and 18 individuals, respectively). The average age was 49.8 ± 16.6 years, and most individuals were female (n = 141; 70.5%). Regarding education, nearly half of the participants did not have a college degree (n = 102; 51%) while 85 individuals went to university (42.5%). White ethnicity was the most frequently reported (n = 160; 80%). Table 1 summarizes the sociodemographic characteristics of the study population.

Table 2 shows the results attained in PROMIS GI Disrupted Swallowing test and retest (summed scores), Eckardt score and EQ-5D (TTO and VAS) among the three different groups of our study (healthy, esophageal dysphagia and oropharyngeal dysphagia). The average summed scores of PROMIS GI Disrupted Swallowing test and retest

Table 2 – Results attained in PROMIS GI Disrupted Swallowing test and retest (summed scores), Eckardt score and EQ-5D (TTO and VAS) among the three different groups of the study (healthy, esophageal dysphagia and oropharyngeal dysphagia) (n = 200)

	n	PROMIS GI Disrupted Swallowing test (summed score)*	PROMIS GI Disrupted Swallowing retest (summed score)*	Eckardt score*	EQ-5D (TTO)*	EQ-5D (VAS)*
Healthy	123 (61.5%)	8.56 ± 8.00	8.21 ± 5.21	0.1 ± 2.3	0.853 ± 2.193	85 ± 18
Esophageal dysphagia	59 (29.5%)	17.00 ± 6.32	15.39 ± 5.43	3.7 ± 2.5	0.630 ± 0.269	72 ± 19
Oropharyngeal dysphagia	18 (9.0%)	18.17 ± 5.79	16.20 ± 5.24	2.9 ± 1.8	0.481 ± 0.272	58 ± 19
Total	200 (100%)	11.92 ± 6.15	10.97 ± 5.21	1.5 ± 2.5	0.754 ± 0.266	79 ± 19

*: average ± DP

Table 3 – Distribution of the answers given to the seven questions (GISX31 to GISX37) that compose PROMIS GI Disrupted Swallowing (n = 200)

PROMIS GI Disrupted Swallowing	1	2	3	4	5	Median (Q1 - Q3)
GISX31	125 (62.5%)	24 (12.0%)	29 (14.5%)	18 (9.0%)	4 (2.0%)	1 (1 - 3)
GISX32	111 (55.5%)	44 (22.0%)	30 (15.0%)	12 (6.0%)	3 (1.5%)	1 (1 - 2)
GISX33	121 (60.5%)	32 (16.0%)	35 (17.5%)	8 (4.0%)	4 (2.0%)	1 (1 - 2)
GISX34	118 (59.0%)	25 (12.5%)	32 (16.0%)	14 (7.0%)	11 (5.5%)	1 (1 - 3)
GISX35	149 (74.5%)	23 (11.5%)	17 (8.5%)	7 (3.5%)	4 (2.0%)	1 (1 - 2)
GISX36	137 (68.5%)	25 (12.5%)	23 (11.5%)	13 (6.5%)	2 (1.0%)	1 (1 - 2)
GISX37	122 (61.0%)	36 (18.0%)	24 (12.0%)	10 (5.0%)	8 (4.0%)	1 (1 - 2)

were 11.92 ± 6.15 and 10.97 ± 5.21, respectively (the median summed score is 9 in both cases).

Table 3 displays the absolute and relative frequencies and the first quartile (Q1), median and third quartile (Q3) of the answers given to the seven items of PROMIS GI Disrupted Swallowing. Most of the inquired participants answered "1", which corresponds to "Never" in all of the items.

The set of items of the Portuguese PROMIS GI Disrupted Swallowing scale presented a coefficient of Cronbach's α of 0.919, indicating an acceptable level of reliability (shown in Table 4).

The ICC obtained regarding the test-retest reliability was 0.941 ($p < 0.001$; 95% CI: 0.916 - 0.959).

Convergent validity

Regarding the results of the other questionnaires administered to the 200 individuals, the mean Eckardt score was 1.5 ± 2.5 (median 1, minimum 0 and maximum 12). Concerning EQ-5D, the mean TTO was 0.754 ± 0.266 (median 0.767, minimum -0.035 and maximum 1) and the mean value of VAS was 79 ± 19 (median 83, minimum 5 and maximum 100) (Table 2).

The spearman's rank correlation coefficient was used to assess for convergent validity. The correlation between PROMIS GI Disrupted Swallowing and Eckardt score was positive and statistically significant ($p < 0.001$; $\rho = 0.782$).

Table 4 – Internal consistency of the Portuguese version of PROMIS GI - Disrupted Swallowing scale: Cronbach's α if item deleted

Internal consistency	n	Cronbach's α if item deleted
GISX31	200	0.905
GISX32	200	0.911
GISX33	200	0.912
GISX34	200	0.901
GISX35	200	0.901
GISX36	200	0.903
GISX37	200	0.913
Total	200	**0.919**

The values of EQ-5D TTO were also statistically correlated with PROMIS GI Disrupted Swallowing ($p < 0.001$; $\rho = -0.551$). However, the correlation was negative.

DISCUSSION

The aim of this study was to describe the process of translation, cultural adaptation and validation of PROMIS GI Disrupted Swallowing questionnaire in Portuguese, in agreement with the rigorous recommended methods proposed by international literature and including representation from major Portuguese-speaking regions.

Even though dysphagia is a prevalent symptom with major impact in the quality of life of patients, its etiology is extremely variable and the patients that report this symptom represent a very heterogeneous population. Older people are more likely to report dysphagia, with an estimated prevalence of 50% to 66% in this group and with a higher likelihood of neurologic causes, such as stroke or neurodegenerative diseases.[1,2,4] In younger populations, however, dysphagia is often associated with an underlying systemic illness, such as autoimmune diseases or eosinophilic esophagitis.[2] The use of a standardized tool in a structured format that measures the outcomes of this population in a more objective way is obviously very advantageous for epidemiological characterization and clinical intervention.

PROMIS GI Disrupted Swallowing is a reliable and validated scale that allows an efficient and quick assessment of the impact of dysphagia in an individual patient.[16] There are currently multiple international scales for evaluation and assessment of dysphagia, but none of those has been linguistically and culturally adapted and validated in Portuguese.[6,15]

The results found suggest that the Portuguese version of PROMIS GI Disrupted Swallowing is reliable and reproductible, as confirmed by the adequate coefficient of Cronbach's α and CCI scores, respectively. Furthermore, the translated version revealed a strong correlation with both the Eckardt score and the EQD-5D TTO with statistical significance, demonstrating evidence of convergent validity. These correlations were expected since individuals with

more symptoms of disrupted swallowing are more likely to have higher Eckardt scores and a more impaired quality of life.

Beyond the purpose of translation and validation, this study contributed to the development of a robust scale that could eventually be used in clinical care in Portugal for the evaluation of dysphagia. It would thus allow the assessment of the true impact of dysphagia in the physical, mental, and social health of the patient, and guide the treatment of benign conditions. Ultimately, the translated version of PROMIS GI Disrupted Swallowing could contribute to the improvement of these patients' quality of life simply by allowing them to better acknowledge the swallowing disorder.[6] There is commonly the perception that eating has a noteworthy social and cultural dimension in Portuguese-speaking countries, and this adapted questionnaire could be useful for future research on this matter.[4,7]

A limitation of the present study is the fact that the sample could have contained more individuals with dysphagia, since more than half of the sample was healthy. Moreover, further cultural adaptation may be needed in order to render the Portuguese version of PROMIS GI Disrupted Swallowing appropriate for use in countries other than Portugal and Brazil where Portuguese is the official language.

Another clear limitation relies on the fact that PROMIS GI Disrupted Swallowing was only validated for use in adults. However, dysphagia is rare in children. Also, the application of this PRO scale in the pediatric population would not be very easy, since children might lack the necessary skills to adequately manifest their own experience through this instrument.

Besides, as with other PROMIS GI scales, the seven-day recall period is a limitation since the symptoms that a patient experienced in the previous week might not reflect the true burden of dysphagia in his/her daily life.[14] Accordingly, the use of this scale for transient evaluations or as a daily diary could be helpful and more accurate in some patients. Finally, this scale is not disease specific, and there could be significant variation in performance regarding the type and etiology of dysphagia.

Finally, it is clear that the use of measures such as PROMIS GI Disrupted Swallowing questionnaire cannot obviously replace the clinical judgment, which is based on a comprehensive assessment and multidimensional evaluation of an individual patient with dysphagia. Moreover, it is essential to define the presence, location, and severity of the swallowing disruption.[13]

CONCLUSION

The translation from English to Portuguese of the PROMIS GI Disrupted Swallowing scale presented conceptual, semantic, cultural and measurement equivalence to the original items in English. The resulting translation history was verified by the PROMIS Translation Director, and the Portuguese translation and proofreading work was performed by native speakers of Portuguese (or English in the case of the back-translator) to the best of their abilities and experience. The results presented demonstrate that this instrument is reliable and valid for both research and clinical use.

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AUTHOR CONTRIBUTIONS

JPR: Study supervision and coordination, writing of the manuscript, translation and cultural adaptation, recruitment the study population and administration of the questionnaires, data analysis; statistical analysis, critical review of the manuscript.

AM: Writing of the manuscript, recruitment the study population and administration of the questionnaires, data collection, data analysis, statistical analysis, critical review of the manuscript.

CF: Translation and cultural adaptation, recruitment the study population and administration of the questionnaires, data analysis.

HC: Translation and cultural adaptation, critical review of the manuscript.

CC: Translation and cultural adaptation, data analysis.

DN: Recruitment the study population and administration of the questionnaires, data analysis.

JDC: Data analysis, statistical analysis.

RTM, MMS: 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.

COMPETING INTERESTS

AM has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Ferring Pharmaceuticals.

All other authors have declared that no competing interests exist.

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Adaptação do Questionário Standardized Patient Evaluation of Eye Dryness para Português (SPEED-Vp) numa População Não Clínica

Adaptation of the Standardized Patient Evaluation of Eye Dryness Questionnaire to European Portuguese (SPEED-Vp) in a Non-Clinical Sample

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RESUMO

Introdução: O objetivo deste estudo foi traduzir e adaptar o questionário de avaliação padronizada do paciente com secura ocular para a língua portuguesa, bem como avaliar o desempenho psicométrico da escala da versão traduzida, incluindo a sua repetibilidade e concordância entre medidas.

Métodos: O questionário original *Standardized Patient Evaluation of Eye Dryness – SPEED* foi traduzido e adaptado à cultura portuguesa, seguindo uma metodologia cientificamente válida e habitualmente utilizada no processo de adaptação de ferramentas a outras culturas e línguas. O questionário resultante da tradução para a nova língua foi sujeito a um pré-teste onde se registaram os comentários dos participantes e estes foram considerados para a versão final do questionário. Para a validação da escala da versão final do questionário traduzido participaram 89 indivíduos de uma população não clínica, com idades compreendidas entre os 18 e os 84 anos, dos quais 61% eram mulheres. Uma semana depois, o mesmo questionário foi preenchido pela segunda vez por 63 indivíduos. A confiabilidade interna do questionário foi analisada pelo alfa de Cronbach, a estabilidade temporal pelo teste-reteste e a análise da concordância entre medidas pelo método Bland-Altman.

Resultados: A consistência interna do questionário traduzido, SPEED-vP, foi alta (α = 0,871) e todos os itens do questionário contribuíram para um aumento deste índice. Esta consistência confirmou-se também alta no reteste (α = 0,856) e quando a amostra foi estratificada por idades e por sexo. O questionário SPEED-completo também apresentou alta consistência (α = 0,88). A repetibilidade do instrumento foi alta (ICC 0,933; 95% IC: 0,899 e 0,960) e o gráfico de Bland-Altman revela boa concordância entre medidas.

Conclusão: O questionário *Standardized Patient Evaluation of Eye Dryness*, na língua portuguesa (SPEED-vP) demonstrou boas propriedades psicométricas na população portuguesa. Consequentemente, a versão traduzida do questionário SPEED poderá ser usada para medir quantitativamente a presença de sintomas de olho seco, na população portuguesa.

Palavras-chave: Idioma; Inquéritos e Questionários; Portugal; Psicometria; Reprodutibilidade dos Testes; Síndromes de Olho Seco

ABSTRACT

Introduction: The aim of this study was to translate and adapt the Standardized Patient Evaluation of Eye Dryness questionnaire to European Portuguese, as well as assess the psychometric performance of the translated version, including repeatability and agreement.

Methods: The original Standardized Patient Evaluation of Eye Dryness - SPEED questionnaire was translated and adapted to the Portuguese cultural context by following a scientifically valid methodology commonly used in the process of adapting tools to other cultures and languages. The questionnaire resulting from the translation into the new language was subject to a pre-test where the comments of the participants were written and considered for the final version of the questionnaire. For the scale validation of the final version of the translated questionnaire, 89 subjects from a non-clinical population, aged 18 to 84 years, were asked to answer the questionnaire (61% were women). One week later, the same questionnaire was repeated by 63 subjects. The internal reliability of the questionnaire was analyzed by Cronbach's alpha, temporal stability by test-retest, and analysis of agreement between measures by the Bland-Altman method.

Results: The internal consistency of the translated questionnaire, SPEED-vP was high (α = 0.871) and all questionnaire items contributed to an increase in this index. This consistency was also confirmed to be high in the retest (α = 0.856) and when the sample was stratified by age and sex. The SPEED--complete questionnaire also showed high consistency (α = 0.88). The repeatability of the instrument was high (ICC 0.933; 95% CI: 0.899 and 0.960) and the Bland-Altman plot revealed good agreement between measures.

Conclusion: The Standardized Patient Evaluation of Eye Dryness in Portuguese (SPEED-vP) showed good psychometric properties for the Portuguese population. Therefore, the translated version of the SPEED-vP questionnaire could be used to quantitatively measure the presence of dry eye symptoms in the Portuguese population.

Keywords: Dry Eye Syndromes; Language; Portugal; Psychometrics; Reproducibility of Results; Surveys and Questionnaires

INTRODUÇÃO

A doença de olho seco (DOS) define-se como uma doença multifatorial da superfície ocular, caracterizada por perda de homeostase do filme lacrimal que resulta em sintomas de desconforto ocular onde a osmolaridade do filme lacrimal, a inflamação da superfície ocular e alterações neuro-sensoriais desempenham papéis etiológicos.[1] Devido à sua etiologia multifatorial, esta encontra-se associada a patologias como a diabetes, bem como a hábitos comportamentais com consequência de astenopia digital que levam a sintomas de olho seco.[2,3]

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Estima-se que a prevalência da DOS esteja entre 5% e 50% e o envelhecimento e o sexo feminino têm sido descritos como fatores de risco para o seu aumento.[4] O aumento de tempo de exposição a ecrãs digitais também tem sido apontado como um dos fatores de risco modificáveis do estilo de vida que mais se associa a sintomas de olho seco.[5]

Até ao momento não existe um teste clínico específico considerado como 'padrão de ouro' para o diagnóstico da DOS. A fraca correlação entre sinais e sintomas tem sido uma batalha desafiadora neste contexto.[6-8]

O uso de questionários de sintomas tem-se revelado útil na análise de sensações subjetivas, que não são observáveis na parte clínica objetiva.[9] O diagnóstico da DOS tem mostrado maior correlação com os sintomas do que com os sinais clínicos, o que sugere que os sintomas do paciente têm um grande peso no diagnóstico e classificação da doença.[10]

Existem vários questionários para o auxílio do diagnóstico e gestão da DOS. O questionário *Ocular Surface Disease Index* (OSDI) é o mais utilizado para ensaios clínicos e mede a frequência de sintomas, fatores ambientais e qualidade de vida relacionada com a visão.[4] Outros questionários mais recentes, com validade concorrente com o OSDI, têm surgido na investigação clínica desta condição, salientando-se os questionários *5-item Dry Eye Questionnaire* (DEQ-5) e o *Standardized Patient Evaluation of Eye Dryness* (SPEED), pela sua rapidez e facilidade de aplicação.[11]

Diversos estudos mostram que o questionário SPEED é comparável ao OSDI em vários aspetos clínicos e confiável na distinção entre participantes sintomáticos e assintomáticos. É uma ferramenta para avaliação de sintomas de olho seco padronizada, rápida e repetível com bom desempenho tanto em populações clínicas como não clínicas, que avalia a frequência e a severidade de sintomas.[6-8] Já se observa também a sua adaptação a outras culturas e línguas.[12]

O objetivo deste estudo foi traduzir e adaptar o questionário SPEED à língua e cultura portuguesa, validar psicometricamente a sua escala, e verificar a sua repetibilidade numa amostra não clínica com idades superiores a 18 anos, abrangendo diversas faixas etárias.

MÉTODOS

A proposta desta investigação obteve parecer positivo da Comissão de Ética da Universidade da Beira Interior e todos os participantes deram o seu consentimento para a participação no estudo. O desenho deste estudo foi estruturado em duas fases: a fase de tradução e adaptação cultural à língua portuguesa e a fase da validação psicométrica da escala.

O processo de tradução e adaptação cultural baseou-se nos princípios de boas práticas para o processo de tradução e adaptação cultural de questionários de relatos de pacientes.[13,14] A fase de adaptação cultural terminou com o pré-teste, que pretendeu verificar se o público-alvo compreende as perguntas e as opções de resposta propostas conforme pretendido, e se é capaz de responder a cada delas com autonomia e sem dificuldade.[15]

A validação psicométrica do questionário traduzido decorreu mediante análises de consistência interna, avaliação da estabilidade temporal e da reprodutibilidade. Para se atingirem os resultados pretendidos o questionário foi aplicado duas vezes, por dois investigadores diferentes. O intervalo temporal para o teste-reteste foi de uma semana, pois este tempo é o sugerido pela literatura para se analisar a confiabilidade de um instrumento de medida relativo ao estado de saúde.[8]

Participantes

A amostra do processo de tradução e adaptação do questionário (pré-teste) incluiu 30 indivíduos com idades compreendidas entre os 18 e os 68 anos. O tamanho amostral de 30 indivíduos é o recomendável na fase do pré-teste.[15]

Na validação psicométrica participaram 89 indivíduos, tamanho amostral superior ao recomendado por outros autores.[16] Definindo-se a probabilidade de erro tipo I (α) em 0,05 e para uma potência de teste de 90% (1-β), para se obter um índice alfa de Cronbach igual ou superior a 0,7 e tendo em conta que o questionário em análise tem oito itens, segundo a fórmula de cálculo de Bonett[16] será necessário um tamanho amostral mínimo de 19 indivíduos.

Foi utilizada uma amostra de conveniência de 89 voluntários, dividida em dois grupos de diferentes faixas etárias, um com idades compreendidas entre os 18 e os 40 anos e outro com idades superiores a 40 anos. O grupo mais jovem foi recrutado entre estudantes universitários, e os restantes participantes foram recrutados na população geral. Esta fragmentação teve como objetivo validar a interpretação do questionário em indivíduos com níveis de formação académica diferentes. Saliente-se ainda que todos os respondentes tinham como língua materna o português europeu.

Dos 89 participantes, 63 repetiram o questionário uma semana depois.

Questionário SPEED

O questionário objeto do estudo foi o SPEED, que avalia os sintomas do paciente, monitoriza as alterações dos sintomas atuais e de longo prazo (três meses), e avalia a frequência e a severidade de quatro sintomas típicos de olho seco, tais como secura/sensação de corpo estranho, dor ou irritação, ardor ou lacrimejo e olhos cansados.[8,17]

Para cada sintoma o indivíduo indica a frequência com que ocorre numa escala de Likert que é pontuada de 0 a 3, onde o 0 corresponde a "nunca", o 1 a "às vezes", o 2 a "frequentemente", e o 3 a "constantemente". Nas questões relativas à severidade, estas também são feitas com uma escala de Likert que é pontuada de 0 a 4, onde 0 representa "sem problemas", o 1 "tolerável", o 2 "desconfortável", o 3 "incómodo" e o 4 "intolerável". As respostas aos oito itens são somadas para se obter a pontuação total SPEED [$SPEED = (\sum_{frequência} + \sum_{severidade})$]. Uma pontuação total superior a 4 indica suspeita de sintomatologia de olho seco, sendo este um dos valores de corte sugerido na literatura.[7,17]

Além da frequência e da severidade dos sintomas, o questionário SPEED completo inclui também o tempo de ocorrência. Para acompanhar a evolução temporal, pode ser vantajoso utilizar o *score* SPEED-completo, e neste caso, é sugerido usar o ponto corte de 19.[8] Para o cálculo do *score* na versão completa são somadas as pontuações das vinte questões, doze relativas ao tempo de ocorrência dos sintomas, quatro relativas à frequência e quatro relativas à severidade. As questões relativas ao tempo são pontuadas numa escala dicotómica (0 corresponde a "não" e 1 corresponde a "sim"). Estas doze questões estão integradas nas categorias: "hoje", "últimas 72 horas" e "últimos 3 meses".

Procedimentos

Solicitou-se previamente aos autores do questionário original o questionário em suporte digital e a respetiva autorização para a adaptação à língua portuguesa. Uma vez conseguida essa autorização, e após obtenção de parecer positivo da Comissão de Ética para a realização do estudo, iniciou-se a operacionalização do processo.

Tradução e adaptação do questionário

O processo de tradução e adaptação cultural do questionário da sua língua original para a língua portuguesa, foi realizado em três etapas (tradução inicial; retro-tradução e revisão final) como mostra o organograma da Fig. 1.

Na fase da tradução inicial foram elaboradas três traduções independentes, por três tradutores bilingues. Seguiu-se a primeira reunião de avaliação, onde um comité formado por dois profissionais da área de saúde visual, um profissional das ciências sociais e os tradutores independentes, analisaram em profundidade as três traduções, confrontando-as também com o questionário original. O resultado da reunião foi a elaboração da primeira versão em português (SPEED-vP1) do questionário através de um consenso entre todos os membros do comité.

Na fase da retro-tradução o questionário SPEED-vP1 foi traduzido de volta para o seu idioma original (inglês) por um tradutor profissional, sem que este conhecesse a versão original, resultando uma versão retro-traduzida. Esta foi objecto de uma segunda reunião de avaliação, onde esteve presente o mesmo comité da primeira reunião e o tradutor profissional. Nesta reunião, analisaram-se, confrontaram-se e avaliaram-se o questionário original (SPEED), a primeira versão do questionário traduzido (SPEED-vP1) e o questionário retro-traduzido, resultando em pequenas alterações de sintaxe, que se integraram numa nova versão (SPEED-vP2).

Para a revisão final realizou-se um pré-teste, através da aplicação da versão SPEED-vP2 a 30 indivíduos com idades entre os 18 e os 68 anos, para determinação das dificuldades de compreensão e interpretação do conteúdo dos diferentes itens. Às opções de resposta para cada item foi acrescentada a opção de resposta "não entendo a questão". Também se pediu aos voluntários que comentassem as questões que lhes suscitassem dúvidas. Após análise dos resultados deste pré-teste, elaborou-se o *layout* final do questionário de sintomas visuais na versão portuguesa (SPEED-vP).

Validação psicométrica do questionário

Para a validação psicométrica do instrumento adaptado à língua portuguesa, 89 indivíduos de uma população não clínica responderam à versão SPEED-vP do questionário. O questionário foi distribuído em papel e cada um dos voluntários respondeu individualmente. Uma semana depois, 63 indivíduos responderam uma segunda vez ao mesmo questionário.

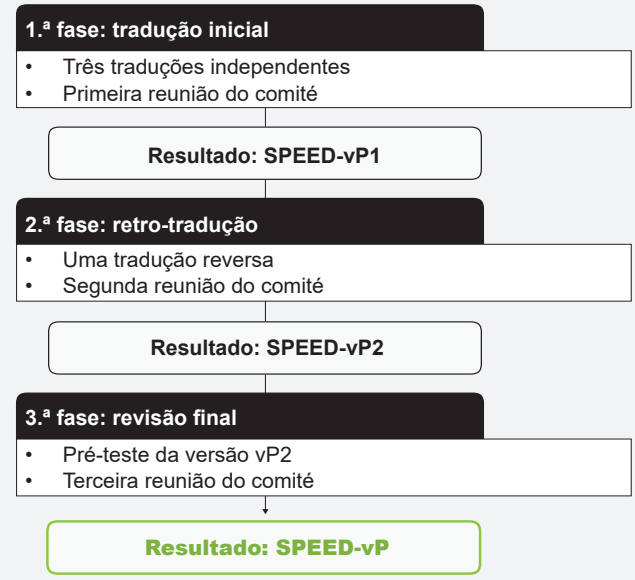

Figura 1 – Etapas do processo de tradução e adaptação do questionário SPEED para a língua portuguesa (SPEED-vP)

Tratamento estatístico

Todos os procedimentos estatísticos foram efetuados com o *software* estatístico IBM® SPSS *Statistics* versão 26.

A fiabilidade da escala do questionário, sendo este um instrumento de medida constituído por uma escala de Likert, foi avaliado através do coeficiente a de Cronbach. Este coeficiente avalia a consistência interna de um conjunto de itens, ou seja, expressa até que ponto as respostas são suficientemente coerentes (relacionadas entre si), de modo a concluir-se que todas medem o mesmo parâmetro e que todas são somáveis numa pontuação única. Valores inferiores a 0,6 são considerados inaceitáveis, valores entre 0,6 e 0,8 são considerados altos e superiores a 0,8 são considerados muito altos.[18]

A estabilidade temporal e a fiabilidade do questionário estudaram-se através de diversos testes. Foram estudadas as diferenças entre duas medidas pelo teste dos sinais para analisar as diferenças da pontuação do questionário em dois momentos da avaliação. Foi usado o coeficiente de correlação intraclasse (ICC) para avaliar o grau de fiabilidade entre avaliações em dois momentos diferentes. A interpretação do ICC baseou-se nas sugestões de outros autores, segundo as quais os valores inferiores a 0,4 foram considerados inaceitáveis, de 0,41 a 0,6 como tendo boa reprodutibilidade, de 0,61 a 0,80 como tendo alta reprodutibilidade e de 0,81 a 1,0 como tendo reprodutibilidade excelente.[19] A concordância entre as medidas foi ainda analisada graficamente, com os limites de concordância de Bland-Altman.[20]

RESULTADOS

Tradução e adaptação do questionário

Na primeira e segunda fase do processo de tradução e adaptação à língua portuguesa, as incongruências verificadas entre as traduções independentes foram discutidas na primeira e na segunda reunião, respetivamente, tendo sido corrigidas através de consenso entre os elementos do comité.

Na terceira fase, o resultado da aplicação do pré-teste não revelou dificuldades na interpretação de nenhum dos itens do questionário traduzido. No entanto, uma pequena percentagem dos respondentes (10%) pediu esclarecimentos quanto à possibilidade de poder selecionar mais do que um sintoma na primeira questão, que revelou pouca clareza. Além disso, alguns respondentes também questionaram sobre o significado do termo "nesta visita". Dado que estas questões foram colocadas apenas por indivíduos do grupo com mais de 40 anos, o comité entendeu que se deveria ajustar a linguagem, dando maior clareza ao conteúdo. A Tabela 1 lista as alterações efetuadas nesta fase.

A nova versão foi testada num grupo pequeno de indivíduos com mais de 50 anos (n = 8), não tendo suscitado qualquer dúvida.

O final deste processo resultou na versão final do questionário em versão portuguesa (SPEED-vP) cujo *layout* se encontra no Apêndice 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18597/Apendice_01.pdf).

Validação psicométrica do questionário

Para a validação de escala do instrumento traduzido, analisaram-se as respostas dos questionários estratificando a amostra por grupo etário e por sexo. A Tabela 2 apresenta as características gerais destes grupos. Indica-se ainda o resultado da inferência estatística para as diferenças de pontuação do questionário, entre as duas amostras, obtido pelo teste de Mann-Whitney. Avaliou-se a consistência interna da escala, para a amostra total e para as diferentes estratificações efetuadas, bem como na amostra que repetiu o questionário. A pontuação SPEED-vP representa a soma dos quatro sintomas, avaliados em frequência e em severidade. A pontuação SPEED-vP completo integra também a componente relativa ao tempo de ocorrência.

O estudo das diferenças da pontuação SPEED-vP e SPEED-vP completo, através do teste Mann-Whitney, não evidencia diferenças estatisticamente significativas entre as faixas etárias ($p > 0,05$), nem se registaram diferenças estatisticamente significativas entre homens e mulheres ($p > 0,05$).

O alfa de Cronbach indica que a consistência interna, tanto para o score do SPEED-vP como para o SPEED-vP completo, apresenta um índice de fiabilidade muito alto (α

Tabela 1 – Adaptação linguística e cultural após pré-teste

Original	Consenso da 1.ª reunião	Consenso após pré teste
Report the type of SYMPTOMS you experience and when they occur:	Selecione o tipo de SINTOMAS que experienciou e quando ocorreram:	Para cada um dos SINTOMAS, indique se o experienciou e quando aconteceu.
At this visit	**Nesta visita**	**Hoje**
Report the FREQUENCY of your symptoms using the rating list below:	Selecione a FREQUÊNCIA dos seus sintomas usando a escala em baixo:	Para cada um dos sintomas, selecione a FREQUÊNCIA com que ocorre, usando a escala em baixo:
Report the SEVERITY of your symptoms using the rating list below:	Selecione a SEVERIDADE dos seus sintomas usando a escala em baixo:	Para cada um dos sintomas, selecione a SEVERIDADE com que ocorre, usando a escala em baixo:

Tabela 2 – Estatísticas descritivas, teste de diferenças e consistência interna

		Amostra total	Faixa etária ≤ 40 anos	Faixa etária > 40 anos	Homens	Mulheres	Re-teste
Tamanho amostra (n)		89	55	34	35	54	63
Idade (anos)		36,3 ± 19,3	22,1 ± 2,8	59,4 ± 9,7	36,4 ± 18,3	36,3 ± 20,1	34,4 ± 19,7
SPEED-vP		7,3 ± 5,0	7,6 ± 4,7	6,9 ± 5,6	7,5 ± 6,1	7,2 ± 4,2	7,2 ± 4,4
SPEED-vP completo		11,0 ± 7,02	11,2 ± 6,2	10,6 ± 8,3	11,3 ± 8,2	10,8 ± 6,2	11,2 ± 6,8
Mann-Whitney (*p-value*)	**SPEED-vP**	---	0,733		0,363		---
	SPEED-vP completo		0,820		0,368		
Alfa de Cronbach	**SPEED-vP**	0,871	0,852	0,894	0,920	0,812	0,856
	SPEED-vP completo	0,880	0,842	0,915	0,904	0,856	0,893

> 0,8) tanto para a amostra total como para as diferentes estratificações efetuadas, como ainda no re-teste (Tabela 2).

Nas análises de correlação item-total verificou-se uma correlação moderada entre todos os itens relativos à frequência e à intensidade, sugerindo que podem ser somados, tanto para a pontuação SPEED-vP como SPEED-vP completo. Na análise da consistência interna total verificou-se que todos os itens contribuem para uma maior consistência, tanto para a pontuação SPEED-vP como para o SPEED-vP completo. A Tabela 3 apresenta o resultado desta análise.

A fiabilidade temporal e reprodutibilidade do instrumento mediu-se através de uma análise teste-reteste, pelo estudo das diferenças entre os dois momentos (teste dos sinais), pela análise de concordância entre as duas medidas (gráfico de Bland-Altman) e pelo ICC entre observadores.

Tabela 3 – Fiabilidade: consistência interna item por item da versão portuguesa do questionário SPEED-vP

Item		SPEED- vP		SPEED-vP completa	
		Correlação item-total corrigida	Alfa de Cronbach se o item fosse eliminado	Correlação item-total corrigida	Alfa de Cronbach se o item fosse eliminado
Hoje	1			0,402	0,741
	2			0,313	0,742
	3			0,283	0,742
	4			0,367	0,739
72 horas	1			0,543	0,735
	2			0,488	0,737
	3			0,472	0,736
	4			0,490	0,735
3 meses	1			0,518	0,735
	2			0,516	0,735
	3			0,342	0,739
	4			0,257	0,741
Frequência	1	0,643	0,854	0,706	0,723
	2	0,660	0,853	0,693	0,724
	3	0,610	0,857	0,612	0,726
	4	0,550	0,864	0,536	0,727
Severidade	1	0,597	0,859	0,675	0,720
	2	0,699	0,847	0,712	0,719
	3	0,619	0,856	0,644	0,723
	4	0,668	0,851	0,641	0,719
	Total do instrumento		0,871		0,88

A média das diferenças da pontuação total do questionário SPEED-vP e SPEED-vP completo, entre a primeira e a segunda avaliação, é de 0,14 ± 2,2 e -0,15 ± 3,4 respetivamente, o que indica um viés mínimo entre as duas administrações (teste dos sinais; p = 0,635; 0,671) representando uma boa fiabilidade temporal. O ICC inter-observadores foi de 0,933 (95% IC: 0,899 e 0,960) o que representa um grau de concordância excelente.

O gráfico de Bland Altman (Fig. 2), mostra que a média das diferenças, tanto para a pontuação SPEED-vP (Fig. 2A) como para a pontuação SPEED-vP completo, (Fig. 2B) apresenta um valor próximo de zero e as variações obtidas encontram-se maioritariamente dentro do intervalo de confiança a 95%. A regressão linear da diferença das médias mostra que não existe viés de proporção (SPEED-vP completo: p = 0,795; SPEED-vP: p = 0,661).

DISCUSSÃO

O objetivo deste estudo foi traduzir e adaptar culturalmente o questionário SPEED para a língua portuguesa e avaliar as propriedades psicométricas da versão traduzida, incluindo a repetibilidade numa amostra não clínica de uma ampla faixa etária. Os resultados do estudo indicam que a versão portuguesa do questionário SPEED é uma ferramenta de fácil aplicação e revelou boas propriedades psicométricas, representando uma ferramenta de medida confiável. A alta consistência interna das respostas obtidas no questionário (α > 0,8) e a alta correlação intraclasse (ICC > 0,9) indicam que a versão SPEED-vP apresenta um grau de confiabilidade excelente.

O processo de tradução e adaptação cultural do questionário original para a nova língua cumpriu os padrões de boas práticas segundo o proposto na literatura.[13,14] Foram usados métodos qualitativos e quantitativos para identificar e abordar vários problemas durante as fases de tradução e adaptação cultural. O recurso a três tradutores independentes, que se desconheciam mutuamente, revelou-se muito útil porque permitiu confrontar e discutir três versões diferentes. A inclusão de membros de diferentes áreas de formação no comité de avaliação permitiu confrontar várias opiniões de profissionais familiarizados quer com a área da saúde, quer com as ciências sociais. Os debates resultantes das discrepâncias encontradas e a busca de soluções consensuais revelaram-se fundamentais para o processo da equivalência semântica. O pré-teste foi fundamental para a adaptação cultural, permitindo adaptar a linguagem e assim assegurar que todos os estratos etários e sociais compreendessem a ferramenta.

Observou-se que o grupo total de participantes recrutados para o presente estudo apresentou uma grande variação nas pontuações do SPEED, desde a ausência de sintomas até quadros mais graves, mas com valores médios semelhantes aos encontrados por outros autores em amostras não clínicas selecionadas aleatoriamente.[12]

O envelhecimento e o sexo são considerados como potenciais fator de risco para sintomatologia de olho seco.[4] Na validação psicométrica da escala no presente estudo, a amostra foi estratificada por faixa etária e por sexo. A análise da consistência interna para cada um dos grupos apresentou resultados que variaram de 0,812 a 0,920, indicando que a consistência interna do questionário SPEED-vP é excelente para todos os estratos populacionais avaliados.

Apesar de o objetivo deste trabalho não ser o diagnóstico da DOS, verificou-se que a pontuação SPEED na amostra em estudo não evidenciou diferenças significativas nem de género, nem entre as diferentes faixas etárias. Um estudo de meta-análise relativo ao tema confirmou que a prevalência de DOS aumenta com a idade. No entanto, observa-se que este aumento é mais evidente para os sinais do que para os sintomas.[4] Por outro lado, estudos realizados em estudantes universitários revelam uma taxa de sintomas de olho seco bastante elevada[7,21] e estudos recentes afirmam que nos pacientes jovens a DOS é caracterizada pela redução da camada lipídica, pela diminuição do pestanejo e por sintomas mais graves.[22] Além disso, alguns fatores tais como realização de tarefas de lazer, uso prolongado de ecrãs digitais e *e-learning* podem promover a ocorrência de olho seco em qualquer idade, mas os sintomas encontram-se com mais frequência em jovens do que em indivíduos com mais de 60 anos.[5,23] Quanto ao sexo, nem sempre existe consenso sobre diferenças notórias entre homens e mulheres, encontrando-se também estudos que registam taxas de prevalência idênticas em homens e mulheres.[24] Num estudo de meta-análise confirmou-se que as mulheres apresentaram maior prevalência de DOS do que os homens, embora essas diferenças se tornem significativas apenas com a idade.[4]

De uma forma geral, a versão final do questionário SPEED na língua portuguesa revelou ser um instrumento confiável e repetível na avaliação dos sintomas de olho seco na população adulta. A consistência interna do questionário apresentou valores excelentes e cada um dos itens contribuiu significativamente para a pontuação total, o que indica a importância de manter os oito itens que constituem o questionário original. Este achado vai ao encontro do reportado noutros estudos realizados em populações não clínicas, com o questionário SPEED noutros idomas.[7,12]

A concordância entre as avaliações (ICC) foi de 0,933 (95% IC: 0,899 e 0,960) o que indica que o questionário SPEED-vP apresenta uma excelente reprodutibilidade.[19,20] A média das diferenças, bem como o estudo da variância entre os dois momentos de avaliação, revelam um viés mínimo entre as duas administrações aplicadas com um

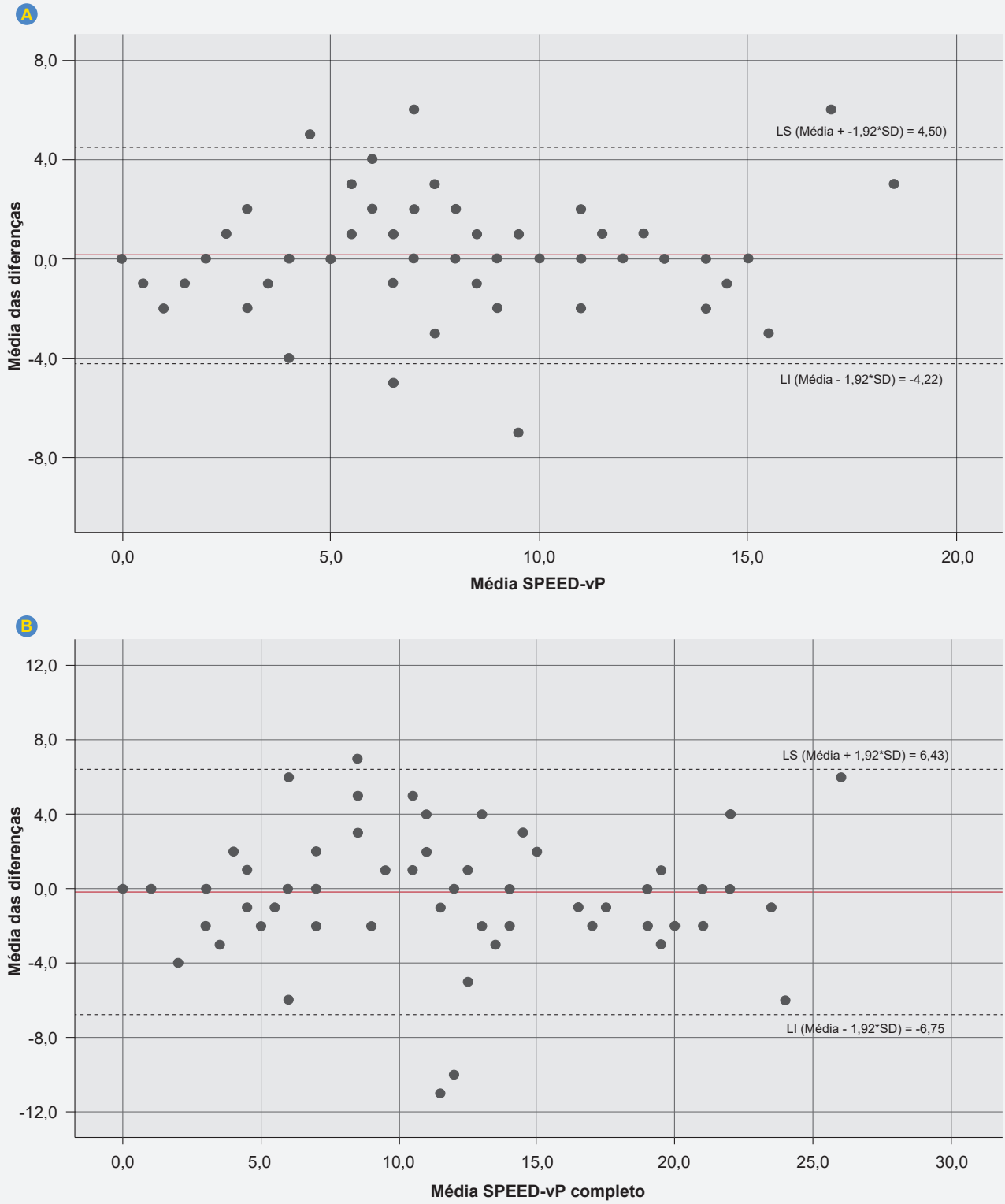

Figura 2 – Gráfico de Bland-Altman para estudo da concordância entre medidas. A linha a vermelho marca a média das diferenças. As linhas a ponteado marcam os limites de concordância no intervalo de 95%. (A) refere-se ao SPEED-vP; (B) refere-se ao SPEED-vP completo.

intervalo de uma semana, dados concordantes com os resultados de outros estudos em que se aplicou o questionário original.[8]

Pontos fortes e limitações

Como pontos fortes do presente estudo destacam-se: o questionário SPEED é universalmente aceite e cientificamente válido, e foi adaptado para o português europeu segundo as diretivas internacionais aplicáveis a ferramentas desta natureza; as características da amostra utilizada para a validação cultural deste questionário abrangem diferentes estratos etários e sociais suscetíveis de garantir uma melhor adaptação cultural da ferramenta; as propriedades psicométricas obtidas indicam que poderá ser utilizado de forma confiável, na população portuguesa.

A principal limitação do estudo relaciona-se com a ausência do registo de dados clínicos dos participantes. Outro aspeto que, em certa medida, está relacionado prende-se com o ponto de corte mais indicado para a população portuguesa. O desenho deste estudo não permitiu calcular o melhor ponto de corte para a interpretação dos resultados, tendo-se usado por defeito os valores indicados pelo autor do questionário. Esta limitação poderá ser ultrapassada num trabalho futuro, com a validação clínica do questionário.

CONCLUSÃO

Considerando que o objetivo principal do estudo consistiu na tradução e adaptação cultural do questionário *Standardized Patient Evaluation of Eye Dryness* para a população portuguesa (SPEED-vP), este considera-se atingido. As propriedades psicométricas obtidas confirmam as características do questionário original. A escala de medida revelou elevados níveis de fiabilidade interna (alfa de Cronbach), de estabilidade temporal (teste-reteste) e concordância entre medidas, indicando ser uma ferramenta fiável e reprodutível para quantificar os sintomas de olho seco na população portuguesa. O questionário SPEED é descrito como uma ferramenta para avaliação de sintomas de olho seco padronizada, rápida e repetível. Dadas as propriedades psicométricas observadas na validação da versão portuguesa, consideramos estar perante uma ferramenta simples e de fácil utilização, que representa uma mais-valia para a prática clínica como meio auxiliar de diagnóstico da DOS.

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CONTRIBUTO DOS AUTORES

AS: Contribuição substancial no desenho do estudo; recolha de dados; tratamento estatístico; interpretação de dados; escrita do artigo.

SL: Contribuição substancial no desenho do estudo; recolha de dados; tratamento estatístico; escrita do artigo.

AN: Contribuição substancial no desenho do estudo; interpretação de dados; revisão crítica.

MC, PM, AN: Contribuição substancial no desenho do estudo; escrita do artigo; interpretação de dados; revisão crítica.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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European Portuguese Version of the Multidimensional Fatigue Symptom Inventory-Short Form: Validation Study

Validação da Versão Portuguesa do Inventário Multidimensional de Sintomas de Fadiga-Forma Reduzida

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ABSTRACT

Introduction: Appropriate management of fatigue relies upon comprehensive assessment instruments and timely delivery of targeted interventions. The aims of this study were to translate a commonly used English-language measure of fatigue in cancer patients (the Multidimensional Fatigue Symptom Inventory–Short-Form, or MFSI-SF) into European Portuguese and to evaluate the psychometric properties (internal consistency reliability, factorial structure, and discriminant, convergent and criterion concurrent validity) of the translated measure for use with Portuguese patients.

Methods: After translation and adaptation of the MFSI-SF to European Portuguese, 389 participants (68.38% women), with a mean age of 59.14 years, completed the study protocol. This sample included 148 patients in active cancer treatment from a cancer center and a community sample composed of 55 cancer survivors, 75 patients with other chronic diseases, and 111 healthy controls.

Results: The European Portuguese version of the Multidimensional Fatigue Symptom Inventory-Short Form (IMSF-FR) showed strong internal consistency (Cronbach's alpha = 0.97, McDonald's omega = 0.95). An exploratory factor analysis indicated that the items loaded in a 5-factor model in subscales were similar to the original version. Strong correlations between the IMSF-FR and other measures of fatigue and vitality confirmed convergent validity. Discriminant validity was supported by weak-to-moderate correlations between the IMSF-FR and measures of sleepiness, propensity to sleep, and lapses of attention and memory. The IMSF-FR accurately distinguished cancer patients from healthy controls and was able to differentiate clinician rated levels of performance among cancer patients.

Conclusion: The IMFS-FR is a reliable and valid tool to assess cancer-related fatigue. By providing integrated comprehensive characterization of fatigue, this instrument may assist clinicians implementing targeted interventions.

Keywords: Chronic Disease; Fatigue; Neoplasms; Portugal; Psychometrics

RESUMO

Introdução: A gestão apropriada da fadiga depende do desenvolvimento de instrumentos de avaliação compreensivos que permitam identificar os sintomas que devem ser alvo de intervenção. Os objetivos deste estudo foram traduzir uma medida internacional sobejamente usada na avaliação da fadiga (o *Multidimensional Fatigue Symptom Inventory–Short-Form*, ou MFSI-SF) para português-europeu e avaliar as propriedades psicométricas (consistência interna, estrutura fatorial, e validade discriminante, convergente e de critério, concorrente) daquele instrumento para pacientes portugueses.

Métodos: Após a tradução e adaptação do MFSI-SF para português-europeu, 389 participantes (68,38% mulheres), com uma média de idades de 59,14 anos, completaram o protocolo de estudo. Esta amostra incluiu 148 pacientes oncológicos em tratamento ativo de um hospital de oncologia e uma amostra comunitária composta por 55 sobreviventes oncológicos, 75 pacientes com outras doenças crónicas e 111 controlos saudáveis.

Resultados: A versão portuguesa do *Multidimensional Fatigue Symptom Inventory-Short Form* (IMSF-FR) revelou uma forte consistência interna (alfa de Cronbach = 0.97, ómega de McDonald = 0.95). A análise fatorial exploratória indicou que os itens seguem um modelo de cinco fatores em subescalas idênticas à versão original. A validade convergente foi confirmada por relações fortes entre o IMSF-FR e outras medidas de fadiga e vitalidade. A validade discriminante foi sustentada por correlações fracas-a-moderadas entre o IMSF-FR e outras medidas de sonolência, propensão para a sonolência, e lapsos de atenção e memória. O IMSF-FR conseguiu distinguir corretamente doentes oncológicos e participantes saudáveis e predizer a capacidade funcional dos doentes oncológicos.

Conclusão: Os resultados sugerem que o IMFS-FR é um instrumento válido e fiável para avaliar a fadiga em doentes oncológicos e outros doentes crónicos. Ao permitir uma caraterização integrada e compreensiva da fadiga, este instrumento pode assistir os profissionais de saúde a implementar intervenções específicas para a constelação de sintomas exibida.

Palavras-chave: Doença Crónica; Fadiga; Neoplasias; Portugal; Psicometria

INTRODUCTION

Cancer-related fatigue (CRF) has been defined as a persistent and distressing sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with normal functioning resulting from cancer or its treatment.[1] During the active treatment phase, fatigue affects up to 25% to 99% of patients, including patients undergoing chemotherapy, radiation, hormonal, surgical and/or biological therapies.[2-7] CRF usually increases during cancer treatments and decreases in the year that follows their completion. However, for about 25% to 33% of cancer survivors, CRF persists for months, years, or even decades after successful treatment completion.[8-10]

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Fatigue has been conceptualized as a multidimensional construct both in its etiology and expression. Encompassing a constellation of physical, cognitive and/or emotional manifestations that are not relieved by rest or sleep,[11,12] CRF may be influenced by demographic, medical and psychosocial factors, including depression[13] and sleep disturbances.[14] Cancer-related fatigue is associated with a myriad of negative consequences during and after cancer treatment, including emotional disorders, hampered quality of life, and disruptions in cognitive performance, interpersonal and self-care abilities.[15-18] Fatigue may lead to dose reduction or regimen discontinuation, compromising antineoplastic treatment.[19] Cancer-related fatigue may also predict shorter survival.[20] Notwithstanding such prevalence and harmful consequences, CRF is under-recognized, under-reported, under-assessed and under-treated.

Due to its subjective nature, patient self-report tools are the gold standard measures to assess fatigue.[1] However, there are no multidimensional measures to assess fatigue in Portuguese-speakers. Furthermore, measures of fatigue were never evaluated specifically for use with Portuguese-speaking cancer patients. With this paper we intend to provide a Portuguese version of a well-known, validated multidimensional tool to assess fatigue in nonclinical and clinical samples, including cancer patients. The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF[20,21]) is a theoretically broad albeit brief instrument when compared to other multi-dimensional measures. By capturing the wide spectrum of symptomatic profiles associated with fatigue and minimizing the burden of patients who may find it challenging to complete a longer instrument, this tool might prove to be valuable for research and clinical use with Portuguese-speakers.

To address the issues raised above, we sought to translate the MFSI-SF to European Portuguese and evaluate its psychometric performance to establish its research and clinical utility. We first assessed the factorial structure of the European Portuguese version of the MFSI-SF to see if our results replicated the original factor analysis. Second, we assessed the reliability (via internal consistency) and validity (via convergent, discriminant, and criterion concurrent validity) of this translated measure for use with Portuguese patients.

METHODS

Ethics and legal compliance

All procedures were in accordance with the Helsinki Declaration and were approved by the Ethics Committee of the Faculty of Psychology and Educational Sciences of the University of Coimbra, and by the Ethics Committee, Legal Committee and Administration Board (number 93/DC/CA) of the Centro Hospitalar do Médio Tejo (CHMT). Informed consent was obtained from all participants involved in the study.

Procedures

Translation and adaptation to European Portuguese followed Hambleton's recommendations.[22] Two authors of the manuscript separately performed an initial translation, originating two translated versions which were then discussed, item by item, and harmonized to the European Portuguese cultural setting. The version arising from that discussion was presented to five experts in oncology and/or fatigue with vast clinical experience (one family physician, one psychiatrist, two psycho-oncologists, and one professor of Psycho-Oncology). After the expert review, a pre-final version was preliminarily tested with a non-probabilistic representative sample of the cancer population through the thinking aloud method.[23] The results of this pilot-test suggested that the final Portuguese version of the MFSI-SF was comprehensible. Lastly, a bilingual expert not involved in the study performed a back-translation to English to ensure that the Portuguese version correctly approximated the original meaning of the instrument's items.

Participants and data collection

For the current study, following a cross-sectional design, 389 participants were recruited (68.38% women) with 59.14 ± 11.60 (28 - 87) years, including patients undergoing cancer treatment (oncologic group) and a community sample. The oncologic sample (ONC) was collected from December 2021 to February 2022 at the Oncology daycare ward of the CHMT. All participants signed a written informed consent form before completing the survey. The community sample included three groups who completed an online survey (available November 2021-February 2022): healthy participants (H), participants diagnosed with a chronic disease other than cancer (CD), and cancer survivors (SUR). Criteria for inclusion in the study was 1) having at least 18 years of age, 2) being able to read Portuguese, and 3) providing written informed consent. The demographic, disease and treatment characteristics of the study participants are presented in Table 1. There were no statistically significant differences in age across the different groups F (326.09) = 2.45, p = 0.06.

Most cancer survivors (n = 21, 38.18%) had completed active cancer treatment more than five years before, 20 (36.36%) had completed treatment one to five years prior, seven (12.73%) had finished treatment six months to one year before, and seven had finished treatment less than six months before. Common diagnoses in the chronic disease group included respiratory disease (n = 13), hypertension (10), thyroid disease (9), chronic pain (8), heart disease (8), diabetes (6), and gastrointestinal disease (5).

Table 1 – Demographic and medical characteristics of patients undergoing active cancer treatment, cancer survivors, chronic disease patients, and healthy participants

	Active cancer treatment (ONC, n = 148)	Cancer survivors (SUR, n = 55)	Chronic disease (CD, n = 75)	Healthy group (H, n = 111)
Age	60.82 ± 10.19	59.24 ± 14.09	59.08 ± 11.76	56.89 ± 11.67
Sex				
F	95 (64.19%)	38 (69.09%)	60 (80.00%)	73 (65.77%)
M	53 (35.81%)	17 (30.91%)	15 (20.00%)	38 (34.23%)
Marital status				
Married	108 (72.97%)	40 (72.73%)	52 (69.33%)	71 (63.96%)
Divorced	20 (13.51%)	6 (10.91%)	12 (16.00%)	20 (18.02%)
Widowed	13	2	3	9
Single	7	7	8	11
Employment status				
Retired	70 (47.30%)	26 (47.27%)	36 (48.00%)	45 (40.54%)
Working	7 (4.73%)	23 (41.82%)	26 (34.66%)	58 (52.25%)
On leave	63 (42.57%)	5	4	1
Unemployed	6	1	7	7
Homemaker/student	2	-	2	-
Primary diagnosis				
Breast	61 (41.22%)	20 (36.36%)		
Colorectal	30 (20.27%)	6 (10.91%)		
Prostate	8	8		
Hematological	11	3		
Gynecologic	4	5		
Skin	4	3		
Stomach	6	1		
Others	24	9		
Cancer treatment				
Surgery	108 (38.99%)	44 (38.94%)		
Chemotherapy	106 (38.27%)	25 (22.12%)		
Radiotherapy	27	26		
Immunotherapy	15	4		
Hormonotherapy	18	12		
Pharmacotherapy	3	2		

Measures

All participants completed a self-reported survey comprising demographic information (age, marital status, and education level) and medical questions. Noncancer participants were asked if they had been diagnosed with any chronic disease (and, if so, their diagnosis). For cancer patients, medical questions included type of cancer and treatments performed.

Eastern Cooperative Oncology Group (ECOG) Performance Status Rating (PSR) Scale[24]

The ECOG is a single-item scale assessing their overall ambulatory ability and physical status (where 0 = fully active; 3 = in bed at least 50% of the time), was previously filled by a clinician for cancer patients.

Multidimensional Fatigue Symptom Inventory-Short Form [Portuguese version (IMSF-FR)][20,21]

The MFSI-SF is a 30-item self-reported instrument that

provides five empirically derived dimensions of fatigue: general fatigue, emotional fatigue, physical fatigue, mental fatigue, and vigor. Each subscale has six items rated on a 5-point Likert scale, with higher scores indicating more fatigue. Respondents indicate the extent to which they have experienced each symptom during the previous week (0 = not at all; 4 = extremely). Ratings are summed to obtain scores for each subscale. A total fatigue score can be calculated by subtracting the vigor subscale score from the sum of the four fatigue subscales. The original version of the MFSI-SF has demonstrated to be a valid and reliable scale [general (α = 0.96), emotional (α = 0.92), physical (α = 0.87), mental fatigue (α = 0.91) and vigor (α = 0.90)].[21] The European Portuguese version of the tool is henceforth referred to as the IMSF-FR.

Mood States Fatigue Scale (POMS-F)[25,26]

In this 7-item measure assessing the feeling of weariness and low energy, participants indicated the extent to which they had experienced each feeling during the previous week on a 5-point Likert scale (0 = not at all; 4 = extremely). The global score ranges from 0 – 28, with higher scores indicating more fatigue. In the current study the Cronbach's alpha (α) and McDonald's omega (ω) coefficients were 0.93 for the total sample.

Medical Outcomes Study 36-Item Short Form – Vitality Scale (SF-36 VT)[27,28]

For this 4-item measure, respondents were asked to rate on a 6-point Likert scale (1 = all the time; 6 = none of the time) the degree to which they felt energetic or worn out during the preceding four-week period. The transformed score ranges between 0 - 100, with a higher score denoting greater vitality. Its α and ω coefficients in the present study were 0.88 and 0.89, respectively, for the total sample.

Epworth Sleepiness Scale (ESS)[29,30]

This 8-item questionnaire was used to assess the unintended propensity to daytime sleepiness. Respondents were asked to indicate their usual chances of dozing off in eight distinct everyday situations on a 4-point scale (0 = no probability; 3 = high probability of dozing). The ESS score ranges from 0 - 24. Higher scores denote a higher sleep propensity (normal range is 0 - 10, scores of 11 - 12 indicate mild sleepiness, 13 - 15 moderate sleepiness and 16 - 24 severe sleepiness). Cronbach's α coefficient was 0.83 and McDonald's ω was 0.86.

Daytime Sleepiness Perception Scale (DSPS-4)[31]

Respondents evaluated their subjective perception of sleepiness through DSPS-4. A composite score, ranging from 0 - 16, is obtained summing up the ratings of the four Likert-type items, each scored from 0 (never) to 4 (always). The higher the score, the higher the perception of sleepiness. α and ω coefficients were 0.82 and 0.83, respectively.

Cognitive Failures Questionnaire (CFQ)[32,33]

In this 25-item questionnaire measuring the frequency of everyday lapses of memory, cognition and attention, respondents rated the frequency of their slips during the previous six months on a 5-point scale (0 = never; 4 = very often). The summing of ratings yields a score from 0 - 100, with higher scores denoting more cognitive failures. In this study, both its α and ω coefficient was 0.94 for the entire sample.

Hospital Anxiety and Depression Scale (HADS)[34,35]

Symptoms of anxiety and depression were measured through the HADS, a questionnaire with seven items each for depression and anxiety subscales. Scoring for each item ranges 0 - 3 and total scores range from 0 - 21, with scores < 7 indicating non-cases, 8 - 10 mild symptoms and scores > 15 denoting severe symptoms. Cronbach's α and McDonald's ω were 0.86 for the anxiety and 0.79 for the depression subscale.

Statistical methods

Data were analyzed using the 22nd version of IBM® SPSS. Descriptive statistics (frequencies and means) were generated to characterize the sample according to sociodemographic and medical parameters. The factorial structure of the IMSF-FR was assessed via an exploratory factor analysis, considering the Portuguese version has never been tested. Principal axis factoring followed by an oblimin rotation was performed using five factors for extraction. Reliability was estimated by Cronbach's α and McDonald's ω coefficients as measures of internal consistency, computed for each of the five empirically derived subscales and the total score. Item homogeneity was investigated by corrected item-total correlations. The construct validity of the IMSF-FR (convergent *versus* discriminant approach) was evaluated through the Pearson product-moment correlation coefficients of the IMSF-FR total score, as well as each of the 5 subscale scores, with other measures administered in the protocol. Convergent validity was examined by computing correlations between the IMSF-FR and the POMS-F and the SF-36 VT scales (we predicted the IMSF-FR would be moderately to highly correlated with these measures of fatigue). We predicted the HADS, ESS, DSPS-4 and CFQ, measures of concepts related to fatigue used to examine the discriminant validity, would be moderately correlated with the IMSF-FR. Correlations were interpreted as small ($0.1 \leq |r| \leq 0.29$), medium ($0.3 \leq |r| \leq 0.49$), and as large ($|r| \geq 0.5$) following Cohen's criteria.[36]

Criterion concurrent validity was evaluated by comparing IMSF-FR scores between cancer patients and noncancer controls and determining the relationship between the IMSF-FR subscale scores and the Performance Status among cancer patients. ANOVAs, *post-hoc* tests, partial *eta* squared (η_p^2) and Pearson's *r* were computed. We anticipated cancer patients would report greater fatigue than noncancer controls. For the latter approach, patients with cancer were categorized according to ECOG PSR Scale (0 = fully ambulatory, 1 = restricted in physical strenuous activity but ambulatory, 2 to 3 = capable of limited self-care), and a MANOVA was performed. We expected a poorer performance status would be associated with greater fatigue.

RESULTS

Scale structure

The Keyser-Meyer-Oklin value was 0.96 and the Barletts' test reached statistical significance. Factors explained 55.03, 7.41, 7.05, 3.60, and 2.43% of the variance, respectively. Factor 1 included items 2, 4, 6, 16, 19, 26 (corresponding to the Physical Subscale) and 17 (Table 2). Factor 2 was comprised of items 5, 7, 9, 22, 24 and 29, corresponding to the Vigor Subscale. Factor 3 comprised items 1, 11, 15, 20, 25 and 27, corresponding to the Mental Subscale. Factor 4 comprised items 3, 8, 13, 21, 23, 30, corresponding to the Emotional Subscale. Factor 5 comprised items 12, 10, 18, 14 and 28, corresponding to the General Subscale, except for item 17, which loaded primarily on Factor 1.

Reliability and item homogeneity

The overall α Cronbach coefficient of the IMSF-FR was 0.97 [total sample (ONC + H: α = 0.96, SUR + CD: α = 0.97)], with corrected item-total correlations ranging from 0.57 to 0.86. McDonald's ω for the total IMSF-FR score was 0.95 in the total sample (ONC + H: ω = 0.93, SUR: ω = 0.95, CD: ω = 0.94).

Cronbach's α and McDonald's ω coefficients for the subscales Emotional Fatigue (total sample: α and ω = 0.94; ONC: α and ω = 0.94; SUR: α = 0.91, ω = 0.93; CD: α and ω = 0.93; H: α and ω = 0.90), General Fatigue (total sample: α and ω = 0.96; ONC, SUR, CD: α and ω = 0.95; H: α and ω = 0.94), Mental Fatigue (total sample: α = 0.92, ω = 0.93; ONC: α and ω = 0.94; SUR: α and ω = 0.92, CD: α and ω = 0.89; H: α = 0.88, ω = 0.89), Physical Fatigue (total sample: α and ω = 0.92; ONC: α and ω = 0.88; SUR: α = 0.90, ω = 0.91; CD: α and ω = 0.91; H: α = 0.90, ω = 0.89) and Vigor (total sample, SUR: α = 0.90, ω = 0.89; ONC: α = 0.88, ω = 0.89; CD: α and ω = 0.88; H: α and ω = 0.85) suggest all scales have strong internal consistency.

Validity

As for convergent validity, we found strong correlations

Table 2 – Factor structure of the IMSF-FR

Items	Factors				
	1	2	3	4	5
26 (heavy body)	0.87				
16 (weak arms)	0.82				
4 (weak legs)	0.81				
2 (muscles ache)	0.78				
17 (sluggish)	0.77				(-0.76)
19 (ache)	0.76				
6 (heavy head)	0.72				
7 (lively)		0.85			
5 (cheerful)		0.80			
29 (cal)		0.75			
9 (relaxed)		0.75			
24 (energetic)		0.73			
22 (refreshed)		0.66			
27 (forgetful)			0.89		
15 (attention)			0.85		
20 (concentrate)			0.84		
1 (remembering)			0.82		
25 (mistakes)			0.75		
11 (confused)			0.75		
30 (distressed)				0.87	
21 (depressed)				0.84	
13 (sad)				0.82	
23 (tense)				0.80	
3 (upset)				0.79	
8 (nervous)				0.73	
12 (worn out)					-0.96
10 (pooped)					-0.94
14 (fatigued)					-0.94
18 (run down)					-0.92
28 (tired)					-0.90
Factor correlation					
1		-0.45	0.52	0.40	-0.79
2			-0.39	-0.56	0.55
3				0.54	-0.58
4					-0.54

Extraction methods: Principal axis factoring. Rotation method: Oblimin with Kaiser-Normalization. Except for item 17, only the principal loadings are presented. Factor 1, Physical subscale. Factor 2, Vigor subscale. Factor 3, Mental subscale. Factor 4, Emotional Subscale. Factor 5, General subscale (except item 17).
Factor 1 included items 2, 4, 6, 16, 19, 26 (corresponding to the Physical subscale) and 17 (Table 2). Factor 2 was comprised of items 5, 7, 9, 22, 24 and 29, corresponding to the Vigor subscale. Factor 3 comprised items 1, 11, 15, 20, 25 and 27, corresponding to the Mental subscale. Factor 4 comprised items 3, 8, 13, 21, 23, 30, corresponding to the Emotional subscale. Factor 5 comprised items 12, 10, 18, 14 and 28, corresponding to the General subscale, except for item 17, which loaded primarily on Factor 1.

between the MFSI-SF subscales and the POMS-F; and between the IMSF-FR subscales and the SF-36 VT (Table 3). For discriminant validity there were significant but correlations with small-to-medium effect sizes between the Fatigue subscales and the ESS, the DSPS-4 and the CFQ – except for CFQ and the Mental subscale, which were highly correlated. Contrary to hypotheses, correlations between the HADS and the IMSF-FR subscales were strong, albeit somewhat lower than the correlations between the IMSF-FR and other measures of fatigue. We found a strong correlation between the HADS and Emotional fatigue.

The total IMSF-FR score was significantly higher in the group of cancer patients (M_{ONC}: 42.93 ± 26.69) than in chronic disease patients (M_{CD}: 23.60 ± 23.98), cancer survivors (M_{SUR}: 22.91 ± 25.34) and healthy controls (M_H: 8.96 ± 19.07), and the magnitude of this difference was large (H = 101.61, $p < 0.001$, $\eta_p^2 = 0.25$). Games-Howell *post-hoc* tests indicated that the mean score for cancer patients was significantly different compared to the other groups (ONC > CD,SUR > H). There were also statistically significant differences in all MFSI-SF subscale scores for the four subsamples: Emotional [M_{ONC}: 11.31 ± 6.81; M_{SUR}: 7.60 ± 5.59; M_{CD}: 8.57 ± 6.15; M_H: 5.36 ± 4.91: (H = 53.39, $p < 0.001$, $\eta_p^2 = 0.14$, *post-hoc*: ONC > SUR,CD,H; CD > H)], General [M_{ONC}: 15.16 ± 6.87; M_{SUR}: 8.64 ± 6.61; M_{CD}: 8.43 ± 6.20; M_H: 5.04 ± 5.24: (H = 122.94, $p < 0.001$, $\eta_p^2 = 0.31$, *post-hoc*: ONC > CD, SUR > H)], Mental [M_{ONC}: 9.04 ± 6.87; M_{SUR}: 7.13 ± 5.53; M_{CD}: 7.16 ± 4.85; M_H: 5.10 ± 4.37: (H = 21.53, $p < 0.001$, $\eta_p^2 = 0.07$, *post-hoc*: ONC, CD > H)], Physical [M_{ONC}: 13.07 ± 6.48; M_{SUR}: 7.69 ± 6.00; M_{CD}: 8.19 ± 5.75; M_H: 4.03 ± 4.54: (H = 116.18, $p < 0.001$, $\eta_p^2 = 0.29$, *post-hoc*: ONC > CD, SUR > H)], and Vigor [M_{ONC}: 5.64 ± 5.63; M_{SUR}: 8.15 ± 4.81; M_{CD}: 8.75 ± 4.77; M_H: 10.57 ± 4.33: (F = 21.35, $p < 0.001$, $\eta_p^2 = 0.14$, *post-hoc*: ONC < SUR < CD, H)]. Statistically significant differences between the oncologic and healthy groups were found for every IMSF-FR item. These differences were associated with moderate-to-large effect sizes [η_p^2 ranging from 0.06 to 0.37, except items 1 ($\eta p^2 = 0.02$) and 3 ($\eta p^2 = 0.05$)].

Also concerning concurrent validity, a significant main effect of performance status was found for the total score and every subscale of the IMSF-FR (Table 4). Follow-up multiple comparisons using Tukey's range test indicated significant increases in fatigue for each successively lower level of performance status for General, Physical and Vigor subscales, as well as for the IMSF-FR total score. The Games-Howell *post-hoc* tests indicated the same tendency for the Emotional, but not the Mental subscale.

DISCUSSION

In this study, we first set out to adapt the English-language Multidimensional Fatigue Symptom Inventory-Short Form to European Portuguese and explore its factorial structure. An exploratory factor analysis of the IMSF-FR

Table 3 – Correlations of MFSI-SF subscales with other measures

MFSI-SF	Correlation coefficient (r)						
	POMS-F	SF-36 VT	HADS anxiety	HADS depression	ESS	DSPS-4	CFQ
Total Fatigue	0.82***	-0.77***	0.70***	0.70***	-0.09	0.26***	0.37***
Emotional Fatigue	0.65***	-0.60***	0.76***	0.71***	-0.09	0.23***	0.33***
General Fatigue	0.88***	-0.078***	0.56***	0.58***	-0.13*	0.21***	0.27***
Mental Fatigue	0.59***	-0.057***	0.58***	0.61***	0.08	-0.31***	0.55***
Physical Fatigue	0.75***	-0.071***	0.51***	0.53***	-0.09	0.22***	0.30***
Vigor	-0.60***	0.61***	-0.61***	-0.62***	0.14**	-0.13**	-0.18**

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

Table 4 – Mean MFSI-SF scale scores at each level of ECOG PSR

IMSF-FR/ECOG	0 (n = 37)	1 (n = 80)	2 + 3 (n = 85)	Test		Effect size
	Mean ± SD			*F*	*Post-hoc* test	η_p^2
Total	10.37 ± 22.84	37.91 ± 22.76	49.26 ± 27.64	33.91***	0 > 1 > 2 + 3	0.26
Subscales						
Emotional	5.89 ± 5.07	10.03 ± 5.74	12.67 ± 7.05	H = 26.45**	0 < 1 < 2 + 3[a]	0.14
General	6.41 ± 6.75	13.27 ± 6.36	16.60 ± 6.43	31.01***	0 < 1 < 2 + 3	0.24
Mental	5.32 ± 5.14	8.49 ± 6.24	9.91 ± 6.89	H = 13.17**	0 > 1 and 2 + 3[a]	0.06
Physical	5.14 ± 4.84	11.96 ± 6.21	14.18 ± 6.15	29.85***	0 < 1 < 2 + 3	0.23
Vigor	12.38 ± 6.28	5.83 ± 3.73	4.09 ± 4.68	40.99***	0 > 1 > 2 + 3	0.29

F: ANOVA; *H:* Kruskal-Wallis; a: Games-Howell (homogeneity of variances not assumed); η_p^2: partial eta squared.
**$p < 0.01$; ***$p < 0.001$

supported the 5-factor structure, as identified in the original 83-item version and the further validation studies,[20,21] corresponding to the Physical, Vigor, Mental, Emotional and General subscales of the 30-item MFSI-SF. Principal loadings were in the expected subscales for all items, except for item 17 ("I feel sluggish"), which loaded primarily in the Physical subscale instead of the General Fatigue subscale. As previously noted, some of the factors were highly correlated, and several items had secondary loadings in other factors, suggesting the factors of the IMSF-FR share variance and are not completely distinct.[20,21]

In agreement with previous validation studies, we found very good estimates of internal consistency for all subscales and the total score of the IMSF-FR in all subsamples (cancer patients, survivors, chronic disease, and healthy participants). The correlation pattern indicated the POMS-F and the fatigue subscales of the IMSF-FR, as well as the Vigor subscale and the Vitality scale of the SF-36, measured similar constructs (supporting convergent validity), while the IMSF-FR and the ESS, the DSPS-4 and the CFQ measured different constructs (supporting discriminant validity). Although the correlations we found between the HADS and the IMSF-FR were strong, they were lower than the correlations with other measures of fatigue (apart from the correlation between the Emotional Fatigue subscale and the HADS). This could mean emotionally distressed participants were prone to experience higher levels of fatigue. Even though findings opposed our hypothesis, they are in line with previous studies bearing on the correlations between the MFSI-SF and depression and anxiety measures.[37] Lukas *et al*[38] have reported a correlation between Total Fatigue score and the HADS total of 0.74. The mean correlation of eight studies reporting the associations of Total Fatigue with another measure of depression was 0.77.[37]

Concurrent validity analyses showed every item and subscale of the IMSF-FR could accurately differentiate between cancer patients and healthy participants in terms of fatigue. Furthermore, fatigue scores were significantly higher according to performance status measured by ECOG. This shows the IMSF-FR can accurately distinguish between clinician rated levels of performance ratings.

Study limitations

Overall, our results suggest that the IMSF-FR is a valid and reliable measure to assess fatigue in Portuguese-speaking patients with different diagnoses and sex. However, our sample was heterogeneous in terms of medical conditions. Future studies should determine the extent to which the factor structure of IMSF-FR is confirmed for specific groups with different health status/diagnoses, as response patterns may differ. Due to sample size limitations, we could not compare IMSF-FR scores among cancer types. Our oncologic sample was composed predominantly of women, precluding adequate numbers to make sex comparisons, although it should be noted there were no significant differences in sex across the sub-samples. The one-time administration prevented us from computing test-retest reliability.

Clinical implications

Our results highlight the research and clinical value of the IMSF-FR, the European Portuguese version of the MFSI-SF. By assessing fatigue using a multidimensional approach, this instrument may help clinicians to identify patterns within individuals and select targeted interventions for managing fatigue. The IMSF-FR may be incorporated into routine clinical assessments, throughout cancer treatments, to compare groups in studies of fatigue, or to obtain baseline data in patients initiating treatments in which fatigue is a common effect.

CONCLUSION

This paper established the psychometric properties of a measure of fatigue for use with European Portuguese-speaking cancer patients. As cultural background may shape the meaning of fatigue, examining the properties of cross-cultural measures is paramount to establish its accurate assessment. The European Portuguese version of the MFSI-SF revealed strong internal consistency and favorable convergent and discriminant validity. Concurrent validity analyses showed the IMSF-FR can accurately distinguish cancer from noncancer participants, as well as between clinician rated levels of performance.

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AUTHOR CONTRIBUTIONS

MIC: Conception, data collection; data analysis and interpretation; drafting the article.

KS, MCC: Discussion; critical revision.

AAG: Conception; critical revision.

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

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A Preliminary Psychometric Case Study of the Music in Dementia Assessment Scales: European Portuguese Version (Midas-PT)

Um Estudo de Caso Psicométrico Preliminar da Music in Dementia Assessment Scales: Versão em Português Europeu (Midas-PT)

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ABSTRACT

Introduction: Music in Dementia Assessment Scales (MiDAS) is a standardized outcome measure aiming to capture the effects of music-based interventions in patients with dementia. It is a unique instrument regarding its specificity, with the potential to enhance research in the field of music in dementia care. The aim of this study was to report a preliminary psychometric study of the translated and adapted instrument to European Portuguese (MiDAS-PT).
Methods: Care home residents with dementia attended bi-weekly group music-based interventions, for five weeks. Intervention coordinators and care home staff completed MiDAS ratings at every session and the Quality-of-Life Scale (QoL-AD) at three time-points. Inter-rater reliability, test-retest reliability, internal consistency, concurrent validity (QoL-AD) and construct validity were evaluated.
Results: A total of 529 forms were completed (staff = 235, therapist = 294). Low therapist inter-rater and test-retest reliability, good internal consistency, low concurrent validity, and good construct validity were found. There were high factor loadings between the five MiDAS items (Interest, Response, Initiation, Involvement, and Enjoyment).
Conclusion: This preliminary investigation indicated acceptable psychometric properties on a range of attributes, but more research is needed in order to definitely establish the psychometric value of the scale.
Keywords: Dementia/therapy; Music Therapy; Neuropsychological Tests; Portugal; Psychometrics; Reproducibility of Results; Surveys and Questionnaires

RESUMO

Introdução: A *Music in Dementia Assessment Scales* (MiDAS) é um instrumento estandardizado para avaliar os efeitos de intervenções terapêuticas baseadas na música em doentes com demência. Dada a sua especificidade e características, é uma escala particularmente interessante e importante na investigação do uso terapêutico da música na demência. O objetivo deste estudo foi reportar um estudo psicométrico preliminar do instrumento traduzido e adaptado para Português Europeu (MiDAS-PT).
Métodos: Um grupo de doentes com demência, residentes em lar, frequentou sessões de intervenções terapêuticas baseadas na música em grupo, bissemanais, durante cinco semanas. Os coordenadores da intervenção e profissionais de saúde do lar aplicaram a MiDAS em todas as sessões e a *Quality-of-Life Scale* (QoL-AD) em três momentos. Foram avaliadas a fiabilidade inter-observadores, a fiabilidade teste-reteste e a validade de construto.
Resultados: Foram completados um total de 529 formulários (funcionários = 235, terapeutas = 294). Foram identificadas baixa fiabilidade inter-observadores e teste-reteste, boa consistência interna, baixa validade concorrente e boa validade de construto. Verificou-se uma elevada correlação entre os cinco itens da escala (Interesse, Resposta, Iniciativa, Envolvimento e Satisfação) na análise fatorial.
Conclusão: Esta investigação preliminar demonstrou propriedades psicométricas aceitáveis em variados atributos, sendo necessária investigação adicional para estabelecer definitivamente o valor psicométrico do instrumento.
Palavras-chave: Demência/tratamento; Inquéritos e Questionários; Musicoterapia; Portugal; Psicometria; Reprodutibilidade dos Testes; Testes Neuropsicológicos

INTRODUCTION

People living with dementia (PwD) experience not only cognitive symptoms but also less well known behavioral and psychological symptoms of dementia (BPSD), like agitation, disinhibition, irritability, and psychosis. The management of those symptoms remains an exceptional challenge for clinicians and carers.[1] The frequent use of sedatives and physical restraint is associated with sub-optimal efficacy and important adverse effects, such as increased risk of cardiovascular events and mortality.[2-9] Non-pharmacological interventions are recommended as first line approaches for BPSD prevention and management,[10-13] but its widespread applicability is not yet fully established.[14-20]

Music-based interventions (Mbi) – including formal music therapy and other less strictly defined therapeutic music activities, which are performed for the purpose of obtaining health benefits, but without the intervention of a trained music therapist – seem to have a positive effect in mood and behavior of PwD, at least in the short term.[15,18,21,22] Various forms of Mbi have become increasingly popular in dementia care – highlighting that music is widely accepted as beneficial

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for the general wellbeing of PwD, potentially helping them to adapt, enabling the connection with people around them, the environment and society[17] – but robust evidence on their effectivity is lacking.

Mbi are especially difficult to describe fully and transparently, because of particular aspects such as the complexity of the music stimuli and the interpersonal component of the intervention.[23] The scarcity of standardized and adequate outcome measures also contributes to the dearth of robust evidence.[24] Author derived non-validated instruments are frequently used, and standardized measures are commonly derived from other disciplines. Those allow for comparisons between the effects of Mbi and other interventions but might fail in capturing the essence of the Mbi effects and what can specifically be created and/or changed for PwD.[19]

There is a need for robust, standardized, dementia specific instruments, that allow researchers to capture a holistic picture of the therapy process and effects of Mbi, specially tailored to be used with patients with major cognitive deficits. The Music in Dementia Assessment Scales (MiDAS) has been specifically developed for this purpose.[25] Additionally, it does not focus exclusively on capturing the reduction of clinical symptoms – like most non-music therapy outcome measures – but encompasses a wider range of well-being indicators (Interest, Response, Initiation, Involvement, and Enjoyment).

In previous work, we reported the translation and cross-cultural adaptation of MiDAS to European Portuguese.[26] Face and content validity were examined at this stage. The MiDAS Portuguese Version (MiDAS-PT) was approved by the authors of the original instrument and is publicly available at http://www.midas.aau.dk.

We aimed to report a preliminary psychometric study of MiDAS-PT, in order to validate its use for research and clinical purposes.

METHODS

This preliminary psychometric study is an exploratory work from a larger PhD project aiming to investigate the administration of Mbi to PwD in the acute setting.

MiDAS was administered repeatedly to PwD who participated in a Mbi, in order to investigate inter-rater reliability, test-retest reliability, internal consistency and construct validity. Concurrent validity was assessed using the Quality of Life in Alzheimer's disease scale (QoL-AD),[27] akin to what has been done for the original MIDAS version psychometric study.[28]

Two psychiatry trainees with experience in dementia care were responsible for delivering the Mbi and rating the MiDAS Therapist Version. Four registered nurses, who provided regular daily care to the residents, completed the MiDAS Staff ratings and Qol-AD.

Training and clarifications on how to use the instruments were delivered through a single individual meeting with a researcher.

Design

Bi-weekly group Mbi was provided to care home residents with dementia. Before a participant attended the Mbi, a staff member who was familiar with all the residents was asked to complete a MiDAS BEFORE rating based on the average presentation of the resident on the day. An "AFTER" form was completed by the same staff member a few hours after the Mbi.

Both intervention coordinators completed a "BEFORE" form and a "DURING" form immediately after each session. The "BEFORE" rating was based on the observation of the resident during the first five minutes of the session, while the "DURING" rating was based on the observation of the most clinically significant five minutes of that session.

The intervention coordinators and care home staff completed MiDAS ratings at every session. Quality of Life in Alzheimer's disease (QoL-AD)[27] was completed at baseline, mid-treatment, and end-treatment by a staff member.

Music-based intervention

The intervention consisted of semi-individualized sessions of music listening, lasting 30 to 45 minutes, during which patients were encouraged to sing, dance and engage with each other freely. Music was delivered through loudspeakers in a quiet room where patients had the option to sit in a circle. Musical preferences were assessed through informal interviews with the participants and their main carers. The most frequently chosen music types were: popular Portuguese music, traditional Portuguese music/folklore, fado and religious music. In total, 10 sessions were held, over a period of five weeks, and took place every Monday and Friday midmorning.

Participants

Elderly residents from one semi-private Portuguese care home were assessed for eligibility (n = 45). Being a typical Portuguese care home, located in an urban area, the institution offers non-specialized care to elders with and without dementia. The inclusion criteria were having a clinical diagnosis of dementia and being capable of giving informed consent to participate (or having a legal representative). Significant hearing impairment was the only exclusion criteria applied. The recruitment process is illustrated in Fig. 1. From the 17 potential participants approached, 12 accepted to participate. Most were females (n = 10), widowed (n = 6) or married (n = 4), with a mean age of 79 years old (min - 69; max - 87). All had moderate to severe Alzheimer's type dementia and had been institutionalized for more than one

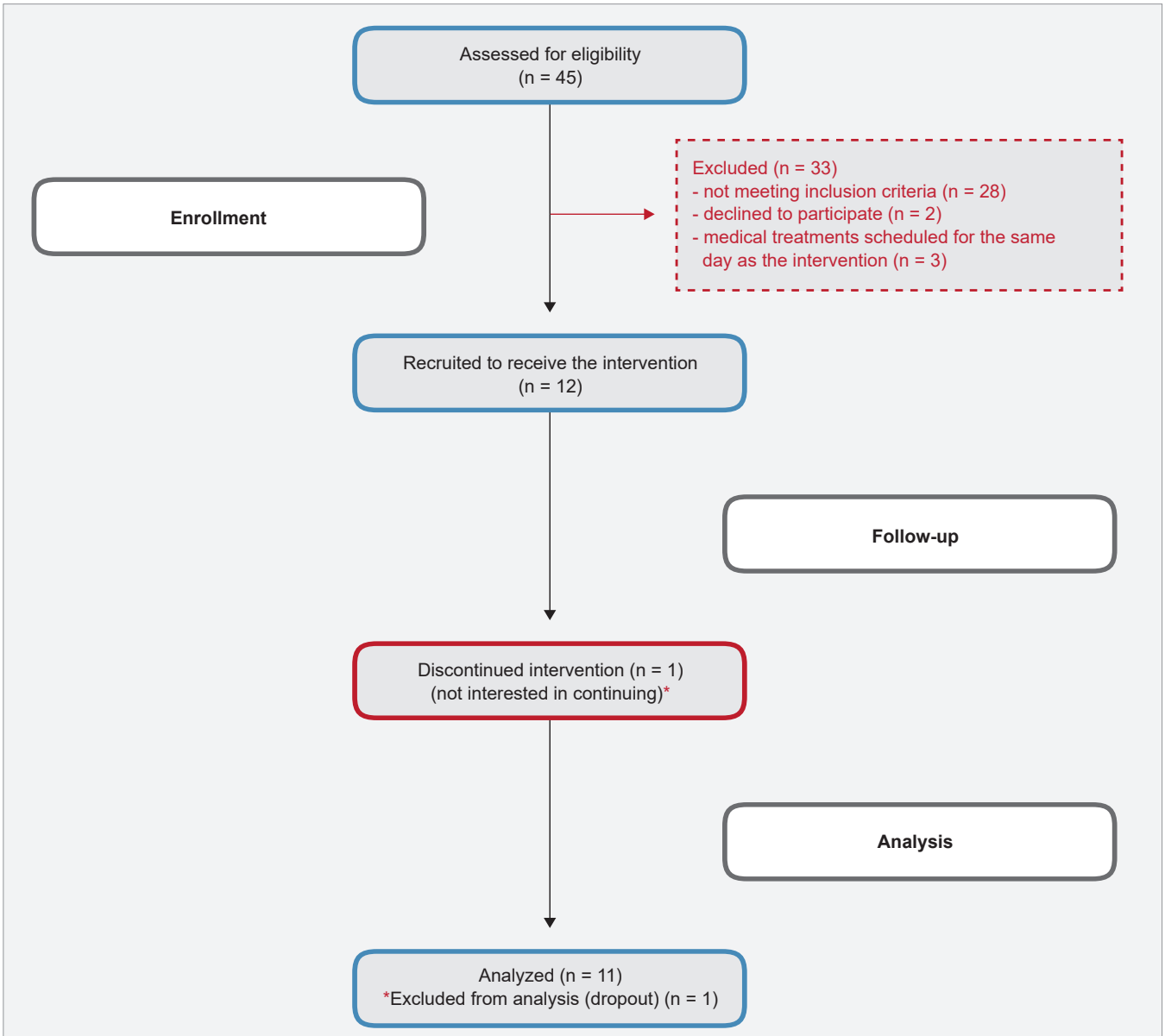

Figure 1 – CONSORT 2010 flow diagram (modified)

year (mean admission time: 2 years; min: 1,5 years; max: 4 years).

Instruments

Music in Dementia Assessment Scales (MiDAS)

MiDAS consists of five visual analogue scales (VAS), each capturing a different dimension of the music intervention's effect: Interest, Response, Initiation, Involvement and Enjoyment.

The original English version was rigorously developed using qualitative methods and consensus approaches[25] and a preliminary psychometric evaluation indicates adequate psychometric properties on a range of attributes (high therapist inter-rater reliability; adequate staff test-retest reliability; adequate concurrent validity; and good construct validity) even though sample size was small.[28]

The response to each dimension of the scale is marked vertically on a 10 cm line and then converted to a score ranging from 0 to 100, with higher scores representing better effects. This may be illustrated with additional information regarding whether the person had some important reactions beyond the usual, through free text, and six optional behaviors can also be selected (agitated/aggressive; withdrawn/low in mood; restless/anxious; relaxed; attentive/

interested; cheerful/smiling).

MiDAS has two versions, one to be completed by a staff member and the other for the music therapist. In the staff version, an assessment is carried out several hours "BEFORE" and "AFTER" the music therapy, on the same day, ideally by the same caregiver, who knows the person with dementia well. In the music therapist version, the music therapist marks the participant's response to the music therapy itself, with a retrospective assessment of the participant's behavior in both the beginning of the Mbi and at the clinically most relevant time "DURING" the intervention. The staff version can be used to assess the effect of music therapy based on the staff's subjective assessment and the music therapist version can provide more information about changes in the clinical context itself. The two forms should then be analyzed separately to mutually inform each other.[25]

Quality of life in Alzheimer's disease (QoL-AD)

QoL-AD[27] is a Likert scale, originally developed as a disease-specific scale for Alzheimer's disease, consisting of 13 items, including physical health, mood, family, ability to do chores around the house, and life as a whole. It can be used as a self-rating scale, or as a proxy measure completed by a carer, to evaluate a broad concept of well-being.

Statistical analysis

Statistical analysis was conducted with SPSS version 26 and R version 4.0.4. Inter-rater reliability, test-retest reliability, internal consistency, concurrent validity, and construct validity of MiDAS were evaluated, akin to the original MiDAS psychometric evaluation study.[28] Due to the small sample size, repeated observations of the same residents at different times were treated as unique observations when evaluating inter-rater reliability, concurrent validity, and construct validity. This approach was also used in the original MiDAS psychometric evaluation.

"Reliability analysis" consisted of the estimation of intraclass correlation coefficient (ICC) for inter-rater reliability and test-retest reliability. An ICC case 2 two-way random effects model with absolute agreement (McGraw and Wong, 1996)[29] was used. Since these analyses depend on a normal distribution of variables, normality tests were performed for Mbi first moment ("BEFORE") evaluations, excluding missing data. Asymmetry coefficient, Kurtosis coefficient and the Kolmogorov-Smirnov test were calculated.

Internal consistency was examined using Cronbach's α.

Concurrent validity was examined with Spearman's correlation coefficient.

Construct validity was evaluated through exploratory factor analysis. Both principal component analysis (PCA) and principal axis factoring (PAF), a descriptive method applicable when normality cannot be established, were performed. Two different approaches were used to estimate correlation coefficients. In factorial analysis Test 1, repeated observations of the same residents at different times were treated as unique observations and factorial analysis test 2 was conducted on the mean MiDAS scores of each participant. Due to the small sample size of this pilot study, squared multiple correlation (SMC) for each variable were used. To confirm the adequacy of the factorial analysis, visual inspection of the multiple scatter diagram, estimation of the diagonal values of the anti-image correlation matrix and calculation of Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity[30] were performed. Squared multiple correlations (R^2) were also calculated, in order to determine the commonality and the adequacy of the factor analysis, according to the suggestion of Field.[31]

Ethical considerations

The present study complies with the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Medicine of the University of Porto. All participants (or their legal representatives) provided written informed consent. Patients could decline to participate in any specific session, without the need for justification.

RESULTS

The 10 Mbi sessions were held as planned, but participant attendance varied, as illustrated in Table 1. As a substantial proportion of missing data (> 40%) was found, it was not possible to use 'multiple imputation' to work around the problem, as suggested by Jakobsen *et al*.[32]

A total of 529 MiDAS forms (staff = 235, therapist = 294) and 30 QoL-AD were completed. The mean of each of the five VAS items was calculated for both moments ("BEFORE" and "AFTER/DURING" respectively) as shown in Table 2. The mean total scores were: "BEFORE" 26.9 (SD 21.3); "AFTER/DURING" 60.3 (SD 30.9).

Table 1 – Attendance per session

Session	Participants	Therapist	Staff
1	7	1	1
2	10	2	1
3	8	2	1
4	8	1	1
5	8	2	1
6	10	2	1
7	8	2	1
8	9	2	1
9	8	2	1
10	7	2	1

Table 2 – Mean of each VAS item

	Item	Mean	SD	n
BEFORE	Interest	27.0	20.3	232
	Response	30.1	21.6	232
	Initiation	23.7	20.6	232
	Involvement	23.8	21.2	232
	Enjoyment	29.7	22.3	232
	Total	13.3	100.0	232
AFTER/DURING	Interest	58.3	29.6	225
	Response	63.8	29.7	225
	Initiation	57.1	31.6	225
	Involvement	58.3	31.9	225
	Enjoyment	64.3	31.0	225
	Total	30.5	147.4	225

Reliability

The results of inter-rater reliability and test-retest reliability are shown on Table 3.

Since the asymmetry coefficient value was far from zero (0.27), as well as the Kurtosis coefficient (2.05), the distribution of the scores was not considered normal. The Kolmogorov-Smirnov test [D (575) = 0.09, $p < 0.001$], also confirmed this assumption. In order to normalize the symmetry and Kurtosis of the original scores, the square root transformation of the original data was conducted to evaluate ICC. Tests on original and transformed data were then performed to assess if there were any major differences between the results.

Inter-rater reliability*:* the analysis was carried out based on the observations produced by the two intervention coordinators. Since the differences between the results of the transformed data and the original data were not significant (ICC differences: range - 0.063 to 0.052, mean: 0.014, SD: 0.047) the original scores were retained. Analyzing the ICC scores ("BEFORE"), all items assumed values below 0.5, thus suggesting a low level of reliability. In the second moment of evaluation ("DURING"), the values were higher and statistically significant ($p < 0.05$), although in general still below the average level of reliability (0.6).

Test-retest reliability*:* 94 paired therapist forms were used, and all scores obtained by each pair for all contiguous sessions over time were compared. The differences between the results of the transformed and the original data were also not significant (ICC differences: range 0.07 to 0.14, mean: 0.1, SD: 0.027) and thus original scores were used. In this case, although the ICC assumes values higher than those obtained in the previous test, they are mostly below 0.6.

Internal consistency

Cronbach's α values revealed high correlations (α = 0.982) between the five VAS items (n = 457). The values regarding the initial observations of the intervention coordinators were 0.957 (n = 115), and for their second moment of evaluation 0.976 (n = 140). In the case of staff, the values were 0.974 (n = 117), "BEFORE" and 0.970 (n = 83), "AFTER".

Concurrent validity

QoL-AD was administered at the beginning (session 1), in the middle (session 5) and at the end (session 10) of the collection process, prior to the intervention. The three results (n = 30) were combined to assess the overall correlation, resulting in a Spearman ordinal correlation coefficient of 0.079 ($p = 0.714$). Similarly, Spearman's correlation coefficients for each of the three moments were neither acceptable nor significant: 0.566 (beginning), 0.116 (middle) and -0.008 (final), in relation to the scores assigned by intervention coordinators and staff ("BEFORE").

Table 3 – Inter-rater reliability and test-retest reliability (original data)

	BEFORE		DURING	
	Inter-rater ICC (n = 45) IC	Test-retest ICC (n = 94) IC	Inter-rater ICC (n = 62) IC	Test-retest ICC (n = 119) IC
Interest	0.283* (0.015; 0.519)	0.470** (0.297; 0.612)	0.559** (0.214; 0.751)	0.628** (0.507; 0.725)
Response	0.263* (-0.009; 0.505)	0.464** (0.291; 0.608)	0.477** (0.25; 0.652)	0.593** (0.464; 0.697)
Initiation	0.236 (-0.054; 0.489)	0.361** (0.174; 0.524)	0.694** (0.538; 0.803)	0.742** (0.65; 0.813)
Involvement	0.211* (-0.049; 0.457)	0.592** (0.445; 0.709)	0.528** (0.077; 0.756)	0.700** (0.596; 0.781)
Satisfaction	0.161 (-0.108; 0.417)	0.432** (0.254; 0.582)	0.583** (0.241; 0.767)	0.591** (0.462; 0.696)

ICC case 2 model: two-way random ANOVA, absolute agreement, single measures; CI: 95% confidence interval
*$p < 0.05$; **$p < 0.001$

Construct validity

Factorial analysis test 1

This analysis was performed based on the scores attributed by the intervention coordinators ("BEFORE"), organized by item. Individual scores were treated as single observations. The visual inspection of the multiple scatter diagram of the five items allowed us to consider that the relationships between the variables with each other are approximately linear. The KMO value was 0.910, which exceeds the 0.6 value suggested by Pallant.[33] The Bartlett's sphericity test was statistically significant ($p < 0.001$), thus allowing the decomposition into factors of the correlation matrix through a PCA. The diagonal values of the anti-image correlation matrix were all greater than 0.887, which is considered good, and therefore it was not necessary to remove any variables to perform the analysis.

PCA*:* the correlation matrix (Table 4) between the five items allowed us to verify that all correlations were statistically significant ($p < 0.01$) and greater than 0.773. The lowest correlation was between Initiation and Response. Factors (principal components) with eigenvalues greater than 1 were selected. Five components were extracted, but only the first was retained, which explained 85.6% of the variance. This fact allowed us to conclude about the existence of a single latent variable.

PAF*:* the results were similar to those obtained by PCA. The first factor explained 85.6% of the variance. The factor matrix had a very similar structure to the PCA component matrix: the item best associated with factor 1 was Interest and the worst associated was Initiation.

Factorial analysis test 2

This analysis was also performed based on the scores attributed by the intervention coordinators ("BEFORE"), organized by item. The averages of the assigned scores were calculated, per item. Due to the small sample size, R2-scores were calculated and since they were consistently higher than 0.5 for the five items of the VAS – varying between 0.924 and 0.980, with an average of 0.9616 – which exceeds the recommendation of the average level of communalities of 0.7 MacCallum *et al*,[34] a factorial analysis could be performed. The visual inspection of the multiple scatter diagram between the five items indicated the relationships between the variables were approximately linear. Regarding the quality of the correlations, the value of the KMO measure was 0.806, which exceeds the value of 0.6 suggested by Pallant.[33] The Bartlett's sphericity test was statistically significant ($p < 0.001$), thus allowing the decomposition into factors of the correlation matrix through the PCA. The diagonal values of the anti-image correlation matrix were all greater than 0.752, which is considered good, avoiding the need to remove any variable from the analysis.

The results of test 2 were similar to the previous factor analyses (Table 5). The first factor explained 95.8% of the variance and the component matrix had a very similar structure to that of the previous factor analyses: the item best associated with factor 1 was Interest and the worst associated was Initiation.

DISCUSSION

This preliminary psychometric evaluation of MiDAS-PT revealed good indicators regarding internal consistency and construct validity, with reliability and concurrent validity falling below expectations. However, some crucial aspects of the study methodology need to be cautiously considered, especially when comparing results with the psychometric

Table 4 – Factor loadings (principal component analysis) – test 1 (n = 115)

	Interest	Response	Initiation	Involvement	Satisfaction
Interest	1				
Response	0.882**	1			
Initiation	0.785**	0.773**	1		
Involvement	0.848**	0.819**	0.787**	1	
Satisfaction	0.847**	0.860**	0.763**	0.832**	1

Identical results for PCA and PAF
**$p < 0.001$ (two tailed)

Table 5 – Factor loadings (principal component analysis) – test 2 (n = 10)

	Interest	Response	Initiation	Involvement	Satisfaction
Interest	1				
Response	0.984**	1			
Initiation	0.942**	0.923**	1		
Involvement	0.959**	0.961**	0.968**	1	
Satisfaction	0.953**	0.950**	0.917**	0.918**	1

**$p < 0.001$ (two tailed)

study of the original version of MiDAS.

Inter-rater reliability and Test-retest reliability were analyzed through the calculation of ICC for the observations of the intervention coordinators only (since there weren't enough paired staff forms) – with a case 2 two-way random effects model with absolute agreement. The premise of absolute agreement might prevent the identification of agreement only at certain levels. The impossibility to analyze reliability for Staff – who know the PwD better and could thus be more consistent when rating MiDAS items – might have also impacted negatively on our reliability estimation.

The analysis of Table 3 indicates that reliability (inter-rater and test-retest) was always better in the second moment of observation, thus possibly indicating that the scale has better discriminative properties when there is some change in the basal state of the subjects – perhaps in the moment "BEFORE" the Mbi people with dementia were too withdrawn and apathetic to allow for fine discrimination in MiDAS items. For instance, regarding inter-rater reliability, almost all the scores in the second moment of observation were above the 0.5 threshold and the values reached statistical significance. Therefore, the scale might have better reliability for this second moment of evaluation.

Another important observation is that the test-retest reliability was significantly better than inter-rater reliability, for all items and in both moments of observations. This indication of better repeatability by the same observer than concordance between raters could be explained by the lack of training and proficiency of raters, since this is expected to affect the repeatability to less extent and the concordance between raters to greater extent. Importantly, in the second moment of observation, almost all items reached the value of 0.6, indicating a reasonable test-retest reliability.

In the preliminary psychometric study of the original version of MiDAS,[28] a low staff inter-rater reliability has also been reported. Despite this variability among raters, the test-retest reliability for this group was adequate, possibly indicating that the repeated use of the scale increased the consistency with which the instrument is used. A high inter-rater reliability among intervention coordinators was identified in this study, as expected, since they were quite familiar with the scale. We believe this corroborates the hypothesis that the scale is reliable, that appropriate training is provided.

Internal consistency measures the degree of correlations between the items on the same test. For this purpose, we calculated Cronbach's α values considering all observations and then separately, for therapist and staff and in both moments of observation. Results were similar for all the analyses and a very good internal consistency was admitted with all correlation coefficients being significantly above 0.8.

One observation that could help explain the counter-intuitive low inter-rater and test-retest reliability, with a good internal consistency according to Cronbach's α, is that the reliability tests used were based on the assumption of absolute agreement. Therefore, it is possible that there was some concordance that was not identified. There might be a correlation in the evaluations of different raters and in different ratings from the same rater, with better and worse scores being systematically attributed to the same patients, but without an absolute concordance in the scores. This is a point that deserves further exploration in future investigations, with appropriate methodology.

Concurrent validity investigates if a test correlates well with a measure that has previously been validated for the same construct, or, more often, presumably related constructs. In the psychometric study of the original version of MiDAS, QoL-AD has been used to evaluate this parameter. For replicability and comparison purposes we decided to use the same scale. In the original study, the concurrent validity of MiDAS in comparison with Qol-AD was only reasonable. This was not unexpected, since the scales were not designed to capture exactly the same construct. In our investigation of MiDAS-PT, concurrent validity was even lower. This might be related with the smaller size of our sample or with less training/familiarity of our raters with the scales. Notwithstanding, in our opinion, it would be preferable to use a more similar scale for concurrent validity, such as the recently developed Music Therapy Engagement scale for Dementia (MTED).[35] The latter evaluates musical experiences of PwD, while Qol-AD does in fact measure a slightly different construct and is not a scale prepared for repeated use in a short period of time.

Construct validity refers to the degree to which a test measures what it is supposed to be measuring – the construct that one wants to capture and measure. Factorial analysis is one of the methodologies commonly used to do so. Specifically, it enables the confirmation of the relationships between the test items and to identify the total number of dimensions represented on the test. It is commonly accepted that a good correlation between items and the identification of only one dimension indicates the scale has been properly developed in order to discriminate a certain construct. We performed two sets of factor analysis to accommodate the limitation of using repeated observations of the same residents as independent observations. As for the preliminary psychometric study of the original version of MiDAS, PCA and PAF were performed in original and transformed data and a second factorial test was performed using the average of the assigned scores per item of each participant, instead of treating all individual form scores as single observations. Different strategies confirmed the between item correlations and the one-dimensionality of the

scale. Moreover, in order to be extra cautious, we hypothesized that the intervention could affect the interrelations between items, just like the mix of different raters (therapist and staff). In agreement with that hypothesis, we performed factorial analysis using only the forms from the "BEFORE" observation of intervention coordinators.

Finally, it can be argued that when the correlation between the different items of a scale is too high it can also indicate that they are too similar to discriminate their characteristics from each other. As explained by the original authors of MiDAS, having one construct (engagement with music) and using the total score of the five VAS items as the main outcome does not decrease the clinical relevance of MiDAS.

Strengths and limitations of the study

A rigorously translated and adapted Portuguese version of MiDAS was used, under the supervision of its original developers and of experts in dementia care. Statistical advice was obtained from a statistician with extensive experience in psychometric studies.

The main limitation of this study is its small sample size. Relatively low session attendance also decreased the power of the study. The fact that not all raters were previously familiar with the instruments can be a point of criticism as well, and one that helps contextualize the results and thus should be carefully addressed in future studies. Additionally, it was not possible to fully explore the reliability of staff rating.

The use of a more standardized therapeutic music intervention by a licensed music therapist could have produced different and more reproducible results, despite the fact that the MiDAS developers have suggested it could be used by non-music therapists

These are all points that should be better addressed in future studies in order to more accurately estimate the psychometric characteristics of the instrument. We suggest future studies to use evidence-based music therapy protocols to deliver Mbi as well as proficient raters of the scale. Subgroup analyses according to dementia severity (mild/moderated or severe) would also be interesting.

CONCLUSION

MiDAS-PT is the first instrument available in European Portuguese that was designed to evaluate the effects of Mbi in dementia care. This preliminary psychometric investigation suggests that MiDAS-PT has acceptable properties on a range of attributes even though the sample size was small and raters were not proficient users of the scale.

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AUTHOR CONTRIBUTIONS

LS: Study concept and design, acquisition of data, data analysis and manuscript writing.

BM: Acquisition of data and preparation of the manuscript.

OM, LF: Analysis and interpretation of data and manuscript revision.

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

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Extracorporeal Membrane Oxygenation in an Adolescent with Multisystem Inflammatory Syndrome in Children

Oxigenação por Membrana Extracorporal num Adolescente com Síndrome Inflamatória Multissistémica Pediátrica

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ABSTRACT

Multisystem inflammatory syndrome in children is a rare and potentially life-threatening disease that is associated with SARS-CoV-2 infection, characterized by hyperinflammation and multiorgan involvement. Cardiovascular involvement is common, including myocardial dysfunction often leading to cardiogenic shock. We present the case of a 17-year-old boy with fever, odynophagia, maculopapular rash and abdominal pain who developed a cardiogenic shock. Due to progressive deterioration of cardiac function despite optimized vasoactive support, veno-arterial extracorporeal membrane oxygenation support was initiated 12 hours after admission, with successful decannulation after seven days and discharge after 23 days, with normal cardiac function. The patient received corticosteroids and intravenous immunoglobulin. Early recognition and intensive care support are crucial for ensuring a successful outcome in severe cases of multisystem inflammatory syndrome. In cases of severe cardiogenic shock, extracorporeal membrane oxygenation support can be critical for survival and rapid recovery.
Keywords: Adolescent; COVID-19/complications; Extracorporeal Membrane Oxygenation; SARS-CoV-2; Shock, Cardiogenic; Systemic Inflammatory Response Syndrome

RESUMO

A síndrome inflamatória multissistémica em crianças é uma doença rara e potencialmente fatal, e que está associada à infeção por SARS-CoV-2 e caracterizada por hiperinflamação e pelo envolvimento de múltiplos órgãos. As manifestações cardiovasculares são comuns, incluindo a disfunção miocárdica, podendo apresentar-se como choque cardiogénico. Apresentamos o caso de um rapaz de 17 anos com febre, odinofagia, exantema maculopapular e dor abdominal, que desenvolveu choque cardiogénico. Apesar do suporte vasoativo otimizado, verificou-se a deterioração progressiva da função cardíaca, pelo que 12 horas após a admissão se iniciou o suporte através de oxigenação por membrana extracorporal venoarterial. O doente foi descanulado com sucesso após sete dias e teve alta após 23 dias, com função cardíaca normal, tendo realizado tratamento com corticosteroides e imunoglobulina intravenosa. O reconhecimento precoce e o suporte em cuidados intensivos são cruciais para garantir o tratamento adequado em casos de síndrome inflamatória multissistémica. O suporte por oxigenação por membrana extracorporal pode ser fundamental para a sobrevivência e rápida recuperação perante choque cardiogénico grave.
Palavras-chave: Adolescente; Choque Cardiogénico; COVID-19/complicações; Oxigenação por Membrana Extracorporal; SARS-CoV-2; Síndrome de Resposta Inflamatória Sistémica

INTRODUCTION

Although most children with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appear to be asymptomatic or have a mild clinical course, some cases may have complications such as the multisystem inflammatory syndrome in children (MIS-C) also known, in Europe, as pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), which was observed for the first time in April 2020.[1-3] MIS-C is characterized by hyperinflammation and multiorgan involvement and can share clinical features with other syndromes like Kawasaki disease (KD) or toxic shock syndrome.

In these cases, pediatric patients present persistent high-grade fever, skin rash, multisystem organ dysfunction and elevated acute inflammatory markers, which could not be explained by an alternative diagnosis and that was temporally related to SARS-CoV-2 infection, with or without PCR evidence of infection (Table 1).[2,4,5] Despite being rare, severe MIS-C cases can be potentially life-threatening if associated with cardiogenic or distributive shock. Refractory shock may require venoarterial extracorporeal membrane oxygenation (VA-ECMO) for circulatory and respiratory support.[6-12]

Early recognition of this new entity and prompt referral to a pediatric intensive care unit (PICU) in cases of hemodynamic instability is crucial for ensuring a successful outcome. We report a case of an adolescent with severe MIS-C with cardiogenic shock and myocardial dysfunction who required VA-ECMO.

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Table 1 – Case definitions of Multisystem Inflammatory Syndrome in Children from the World Health Organization and Centers for Disease Control and Prevention.[16,17]

CDC case definition	WHO case definition
4 criteria:	**All 6 criteria must be met:**
1. Age < 21 years	1. Age 0 to 19 years
2. Clinical presentation consistent with MIS-C, including **all** of the following: 1. Fever (> 38º C for ≥ 24 hours) or report of subjective fever lasting ≥ 24 hours 2. Laboratory evidence of inflammation; including, but not limited to, **any** of the following: elevated CRP, elevated ESR, elevated fibrinogen, elevated procalcitonin, elevated D-dimer, elevated ferritin, LDH, elevated IL-6 level, neutrophilia, lymphocytopenia, hypoalbuminemia 3. Multisystem involvement: • **Two or more** organ systems involved: cardiovascular (eg, shock, elevated troponin, elevated BNP, abnormal echocardiogram, arrhythmia); respiratory (eg, pneumonia, ARDS, pulmonary embolism); renal (eg, AKI, kidney failure); neurologic (eg, seizure, stroke, aseptic meningitis); hematologic (eg, coagulopathy); gastrointestinal (eg, abdominal pain, vomiting, diarrhea, elevated liver enzymes, ileus, gastrointestinal bleeding); dermatologic (eg, erythroderma, mucositis, other rash) 4. Severe illness requiring hospitalization	2. Fever for ≥ 3 days 3. Clinical signs of multisystem involvement (**at least 2** of the following): • Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet) • Hypotension or shock • Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/ BNP) • Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer) • Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain) 4. Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin) 5. No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes 6. Evidence of SARS-CoV-2 infection • Any of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; contact with an individual with COVID-19
3. No alternative plausible diagnosis	
4. Recent or current SARS-CoV-2 infection or exposure	
5. **Any** of the following: positive SARS-CoV-2 RT-PCR; positive serology; positive antigen test; COVID-19 exposure within the 4 weeks prior to the onset of symptoms	

CDC: Centers for Disease Control and Prevention; WHO: World Health Organization; MIS-C: multisystem inflammatory syndrome in children; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; IL-6: interleukin 6; BNP: brain natriuretic peptide; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; COVID-19: coronavirus disease 2019; PT: prothrombin time; PTT: partial prothrombin time.

CASE REPORT

A 17-year-old white boy with irrelevant past medical history presented to the emergency department with a four-day history of persistent high-grade fever, odynophagia, non-pruritic rash and abdominal pain. The physical examination revealed skin pallor, maculopapular rash, and an erythematous throat. Laboratory findings included an elevated C-reactive protein of 143 mg/L and the patient was admitted for monitoring. Nasopharyngeal swab RT-PCR for SARS-CoV-2 and a rapid antigen detection test for group A streptococci were negative. There was a maternal history of SARS-CoV-2 infection seven months earlier and COVID-19 cases in school during the previous weeks.

One day after admission, the patient developed cardiogenic shock (blood pressure 90/60 mmHg with transient improvement after fluid resuscitation of 10 mL/kg) with decreased left ventricular systolic function (LVSF) - ejection fraction (EF) of 45%, and subsequent acute pulmonary edema. Severe hypoxia was evident and invasive mechanical ventilation was necessary. Dobutamine infusion was started due to hemodynamic instability with severe cardiogenic shock. Ceftriaxone and clindamycin were initiated to cover for possible septic shock /toxic shock syndrome and the patient was transferred to the PICU.

On admission, he presented bilateral conjunctival injection, inguinal and cervical lymphadenopathy, bilateral maculopapular rash on the knees, ankles, and elbows, erythematous micropapular rash on the trunk, a petechial rash on his feet and knees and hand edema (Figs. 1 to 3). The echocardiography revealed worsening LVSF (EF 33%) with normal coronary arteries; the electrocardiogram showed negative T-waves (inferior and left precordial leads). Blood tests revealed neutrophilia and lymphopenia, elevated acute inflammatory markers, acute kidney injury, elevated

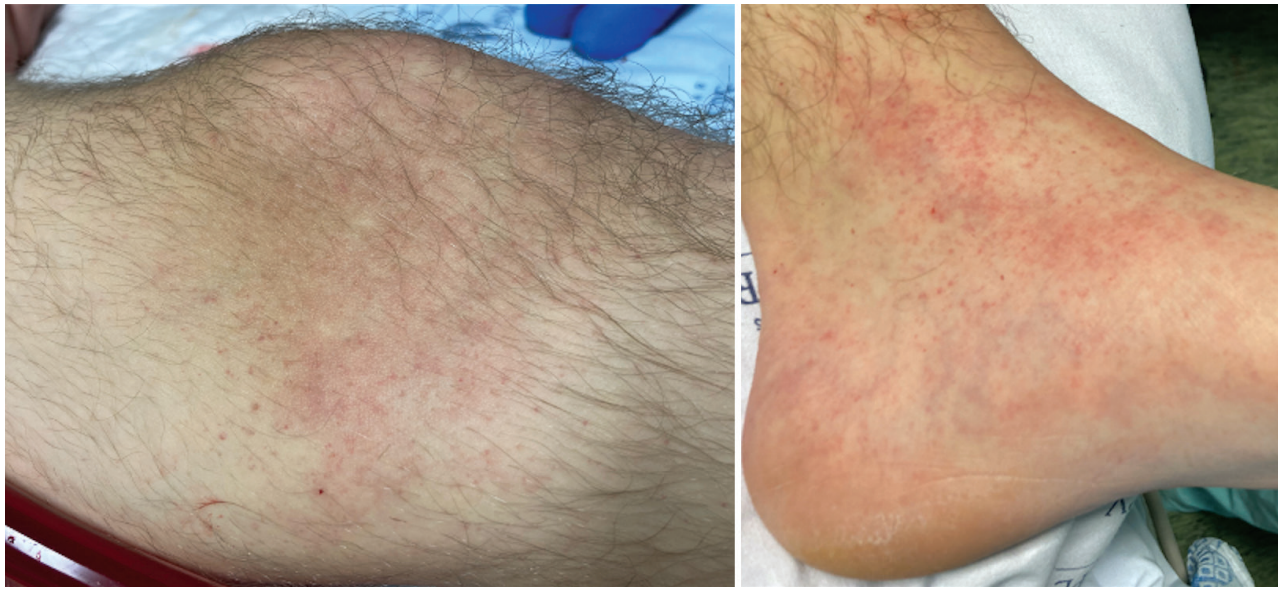

Figure 1 – Maculopapular and petechial rash on PICU day one

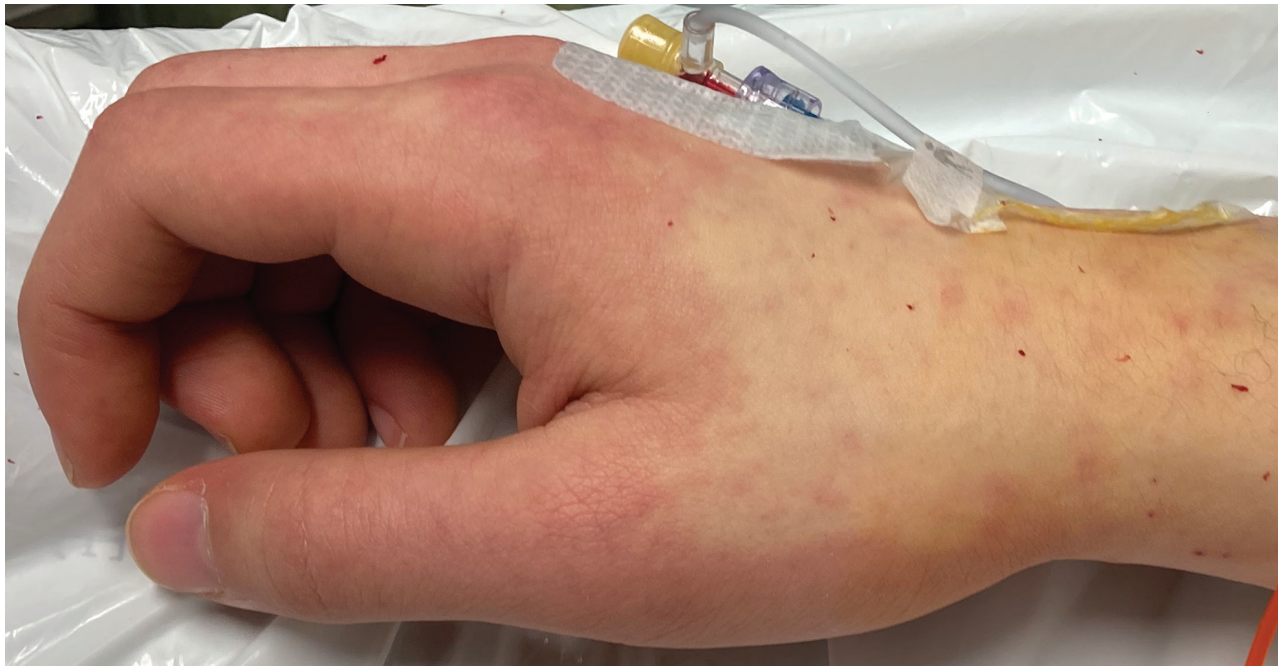

Figure 2 – Hand edema on PICU day one

NT-proBNP and troponin T (Table 2). Due to suspicion of MIS-C, methylprednisolone (1 mg/kg/day) was started shortly after admission. Prophylactic acetylsalicylic acid (100 mg/day) was initiated because of severe left ventricle (LV) dysfunction.

Despite optimized respiratory and inotropic support (dobutamine 10 mcg/kg/min, epinephrine 0.3 mcg/kg/min and norepinephrine 0.05 mcg/kg/min) there was a progressive clinical (blood pressure 82/44 mmHg) and cardiac deterioration (EF 23%, cardiac index 1.69 L/min/m2) with severe lactic acidosis (pH 7.13; lactate 13 mmol/L) and P/F ratio of

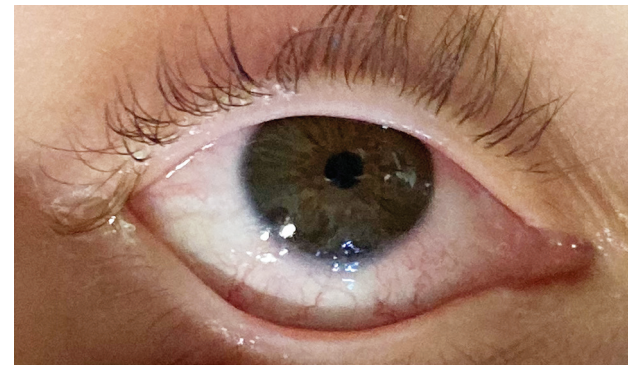

Figure 3 – Conjunctival injection on PICU day one

Table 2 – Laboratory findings

	Normal values	Peak value (PICU day)
NT-proBNP, pg/mL	< 300	34.389 (D1)
Troponin T, ng/L	< 14	119 (D9)
Creatinine kinase, U/L	39 - 308	59 (D4)
D-dimer, ug/mL	0.0 - 0.5	2.76 (D1)
C-reactive protein, mg/L	< 5	315 (D2)
Procalcitonin, ng/mL	< 0.5	4.4 (D2)
Erythrocyte sedimentation rate, mm/h	≤ 10	120 (D6)
Fibrinogen, mg/dL	200 - 400	968 (D1)
Interleukin-6, pg/mL	≤ 1.5	132 (D1)
Ferritin, ng/mL	13 - 110	501 (D1)
Albumin, g/dL	3.5 - 5.2	*2.4 (D3)
Triglycerides, mg/dL	< 150	129 (D6)
Hemoglobin, g/dL	13.0 - 17.5	14.5 (D1)
White blood cell count, x 10^9/L	4 - 11	33.7 (D1)
Neutrophil count, x 10^9/L	1.9 - 7.5	31.6 (D1)
Lymphocyte count, x 10^9/L	1.0 - 4.8	*0.5 (D1)
Platelets, x 10^9/L	150 - 450	*124 (D1)
Serum creatinine, mg/dL	0.7 - 1.2	1.3 (D1)
Blood urea nitrogen, mg/dL	7 - 22	20.5 (D1; D3)
Lactate dehydrogenase, U/L	100 - 250	327 (D1)
Alanine aminotransferase, U/L	0 - 41	146 (D7)
Aspartate aminotransferase, U/L	0 - 40	160 (D7)
Gamma-glutamyltransferase, U/L	0 - 60	164 (D6)
RT-PCR SARS-CoV-2	––	neg (D1)
SARS-CoV-2 IgG, UA/mL SARS-CoV-2 IgM	Cut-off < 0.1	5.2 (D1) neg (D1)
Blood culture	––	neg (D1)

neg: negative; pos: positive; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NT: not tested; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; *nadir value; –– : non applicable

64. Therefore, VA-ECMO was initiated 12 hours after admission. Cannulation was performed uneventfully via left femoral artery and right jugular vein. Immunomodulation therapy was escalated with administration of intravenous immunoglobulin (IVIG, 2 g/kg). The patient improved over the first 48 hours and was gradually weaned from circulatory support. Sustained apyrexy and progressive improvement of skin lesions and conjunctival injection were observed since day two of ECMO run and desquamation of the fingertips since day four. A diagnosis of MIS-C was confirmed after a positive serology for SARS-CoV-2. Blood cultures were negative and antibiotic therapy was stopped after five days. Electrocardiogram normalized by day five. The patient was decannulated on day seven (EF 60% - 70%; NT-proBNP decreasing). The procedure was complicated by femoral artery laceration and hemorrhagic shock requiring fluid resuscitation and transfusion of red cell concentrate. Two days later he was successfully extubated to room air.

Since serial transthoracic echocardiograms revealed increased LV myocardial thickness, carvedilol was started. During hospitalization, changes in the coronary arteries, namely aneurysms, were not visualized. Acetylsalicylic acid was suspended on day 19. Twenty-four-hour Holter monitoring was normal. A cardiac magnetic resonance imaging (MRI) performed at discharge (day 23) showed a non-dilated LV with normal function, mild increase in parietal myocardium thickness, and evidence of acute diffuse myocardial edema consistent with acute myocarditis. One month after discharge the patient only maintained bilateral conjunctival injection. The echocardiogram showed

reduction of parietal myocardial thickness. Corticosteroid therapy was suspended after one month and cardiac MRI was normal eight months later. Currently, the patient has annual follow-up in cardiology, with normal electrocardiogram and echocardiogram.

DISCUSSION

Multisystem inflammatory syndrome in children occurs mainly in previously healthy children and adolescents, although asthma and obesity are common comorbidities.[5,7-9] Unlike KD, patients with MIS-C have a median age of 8 to 11 years and cardiac involvement is more common.[5,9,14] Even though our patient was older than usual for MIS-C diagnosis, both the clinical presentation and the laboratory findings were in agreement with the literature in these cases.[15-17] KD was excluded based on patient age, gastrointestinal symptoms, and elevation of inflammatory and cardiac biomarkers higher than usually seen in KD.

Myocardial dysfunction is frequent and coronary artery dilatation or aneurysm and arrhythmias may develop over time.[8-10] In children, the mechanism of myocardial dysfunction is associated with a dysregulated late inflammatory response.[5,7] A multicenter study in Europe reported 35 cases of MIS-C with cardiogenic shock, LV dysfunction and severe inflammatory state; 28 required inotropic drugs and 10 required ECMO.[7] ECMO has been reported in other series with good outcomes.[5,11-13]

In our case, NT-proBNP was significantly elevated at admission (34.39 pg/mL), which has been shown to correlate with worse clinical outcomes and the need for intensive care support.[10] Due to persistent and severe LV dysfunction despite optimized inotropic support and corticosteroid therapy, VA-ECMO was started shortly after PICU admission. IVIG was only administered after the patient was on VA-ECMO support to prevent fluid overload complications and worsening of pulmonary edema. The use of IVIG and corticosteroids correlates with rapid improvement of LV systolic function (median of two days).[5,7,9] Other studies found no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus corticosteroids, or corticosteroids alone.[18] In addition, tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, has been shown to be effective in a cohort of severe COVID-19 adult patients. However, trials including children are ongoing and it is not currently recommended as standard of care.[19]

Since coronary artery involvement may develop in the convalescent stage, there should be close follow-up after discharge in order to optimize cardiac outcomes.[9]

Notwithstanding multisystem organ disfunction seen in MIS-C patients, most children and adolescents show a rapid and full recovery. Death is uncommon, compared with the COVID-19 adult population.[10]

Early diagnosis and immunomodulation therapy are essential to prevent complications such as acute heart failure. In children with prolonged and unexplained fever, NT-proBNP should be evaluated and, if elevated, urgent cardiac evaluation should be performed.[7] IVIG and corticosteroids play an important role and early ECMO support can be critical for survival and rapid recovery from acute heart failure.

PREVIOUS PRESENTATIONS

This case report was presented as a poster at the 31st Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care, on 15th – 18th June 2021.

AUTHOR CONTRIBUTIONS

CG, CL: Data collection, analysis and interpretation, draft and critical review of the paper.

SP, AS, CC, FA: Data analysis and interpretation, critical review of the paper.

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.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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EDITORIAL
PERSPECTIVA
ARTIGO ORIGINAL
ARTIGO DE REVISÃO
CASO CLÍNICO
IMAGENS MÉDICAS
NORMAS ORIENTAÇÃO
CARTAS

Rare Presentation of Primary Hyperparathyroidism in a Young Woman

Apresentação Rara de Hiperparatiroidismo Primário numa Mulher Jovem

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ABSTRACT

Even though primary hyperparathyroidism (PHPT) is a common endocrine disorder, due to better and more regular screening, the usual presentation is only seen in less than 15% of cases of PHPT. The authors present the case of a young female patient with a previous medical history of depression and nephrolithiasis, with one year of bone pain, that had become progressively worse and disabling. In the initial work-up, several lytic bone lesions and moderate hypercalcemia were found, leading to admission of the patient in the Internal Medicine ward for investigation and treatment. The ensuing investigation revealed PHPT due to hyperfunctioning parathyroid adenoma. The patient underwent a parathyroidectomy and at the follow-up assessment two months after discharge, she reported no symptoms and a computer tomography scan showed regression of the lytic lesions. This case is a reminder that severe symptomatic PHPT, a rare form in developed countries nowadays, still exists, and even though it is a medical condition, collaboration with surgical specialties is necessary to ensure the best possible treatment and prognosis.
Keywords: Bone Diseases/etiology; Hypercalcemia; Hyperparathyroidism, Primary/complications

RESUMO

Embora o hiperparatiroidismo primário (HPTP) seja uma doença endócrina comum, com a evolução e a melhoria dos métodos de rastreio, a apresentação clássica é apenas observada em menos de 15% dos casos. Os autores apresentam o caso de uma jovem com antecedentes de síndrome depressiva e nefrolitíase, com história de um ano de dor óssea, incapacitante e de agravamento progressivo. Na avaliação inicial, é de realçar a deteção de lesões ósseas líticas graves e hipercalcemia moderada, o que levou ao internamento da doente para investigação e tratamento. O estudo seguinte possibilitou o diagnóstico de HPTP por adenoma da paratiroide hiperfuncionante. A doente foi submetida a paratiroidectomia e na reavaliação dois meses depois da alta apresentava-se assintomática e com regressão das lesões líticas na imagem de tomografia computorizada. Este caso serve para relembrar que as manifestações muito sintomáticas de HPTP, embora raras nos países desenvolvidos, ainda existem e, que embora sejam quase sempre benignas, a abordagem multidisciplinar com as especialidades cirúrgicas é essencial para a melhor abordagem terapêutica e para um melhor prognóstico.
Palavras-chave: Doenças dos Ossos/etiologia; Hipercalcemia; Hiperparatiroidismo Primário/complicações

INTRODUCTION

Even though primary hyperparathyroidism (PHPT) is a common endocrine disorder that has been known for more than 100 years, its presentation has been changing over time, especially in the last four decades in developed countries.[1-3]

Primary hyperparathyroidism is usually characterized by the presence of hypercalcemia and inappropriately normal or elevated parathyroid hormone (PTH) levels.[3,4] It is more common in female patients.[3,4] A few decades ago, the most common presentation was severe bone and kidney disease, but nowadays, due to increased testing for calcium and PTH levels, it is usually diagnosed in asymptomatic patients.[1,2]

CLINICAL CASE

The authors present the case of a young female patient, 32 years old, who went to the Emergency Room (ER) in the previous year several times, due to bone pain and mobility impairment.

This patient had a medical history of nephrolithiasis, in the last three years, with several episodes of renal colic. In addition, she was treated in the previous year for depression by her Family Physician. She had been prescribed an oral contraceptive pill and an anxiolytic drug on demand. Moreover, she had always been autonomous, and worked as a call-center operator.

In the last year, the patient came several times to the ER due to intense thoracic and lumbar pain, referring already to persisting generalized mild osteoarticular and muscular pain, associated with asthenia. In the last two weeks, the pain became progressively worse. She also reported nausea with vomiting, and polydipsia in the last few days. On the day of admission, she presented intense and completely disabling hip pain in the last three days, placing her in a wheelchair.

The physical examination showed dehydrated mucous membranes, pain on palpation of the 8th to 10th right ribs and pain during mobilization of the lower limbs. In addition, there was a small, painless, and mobile nodule on palpation of the anterior neck and a small, elastic, painless retroareolar

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nodule in the right breast. There were no other relevant findings to the case.

The arterial blood gas test presented high ionized calcium (1.99 mmol/L – Reference range 1.12 - 1.32 mmol/L); the initial blood tests confirmed moderate hypercalcemia (14.7 mg/dL – Reference range 8.6 - 10.0 mg/dL), high alkaline phosphatase (447.UI/L – Reference range 35 – 105 UI/L) and elevated C reactive protein (3 mg/dL – Reference range < 0.5 mg/dL). The complete blood count and renal function were normal, without other relevant changes. The electrocardiogram was normal, in sinus rhythm with 76 beats per minute, without repolarization or QT interval changes.

The hip x-ray and computer tomography (CT) presented several lytic images in the iliac bones and femurs, with cortical thinning and associated soft tissue component – which suggested the possibility of secondary lesions (Figs.1 and 2).

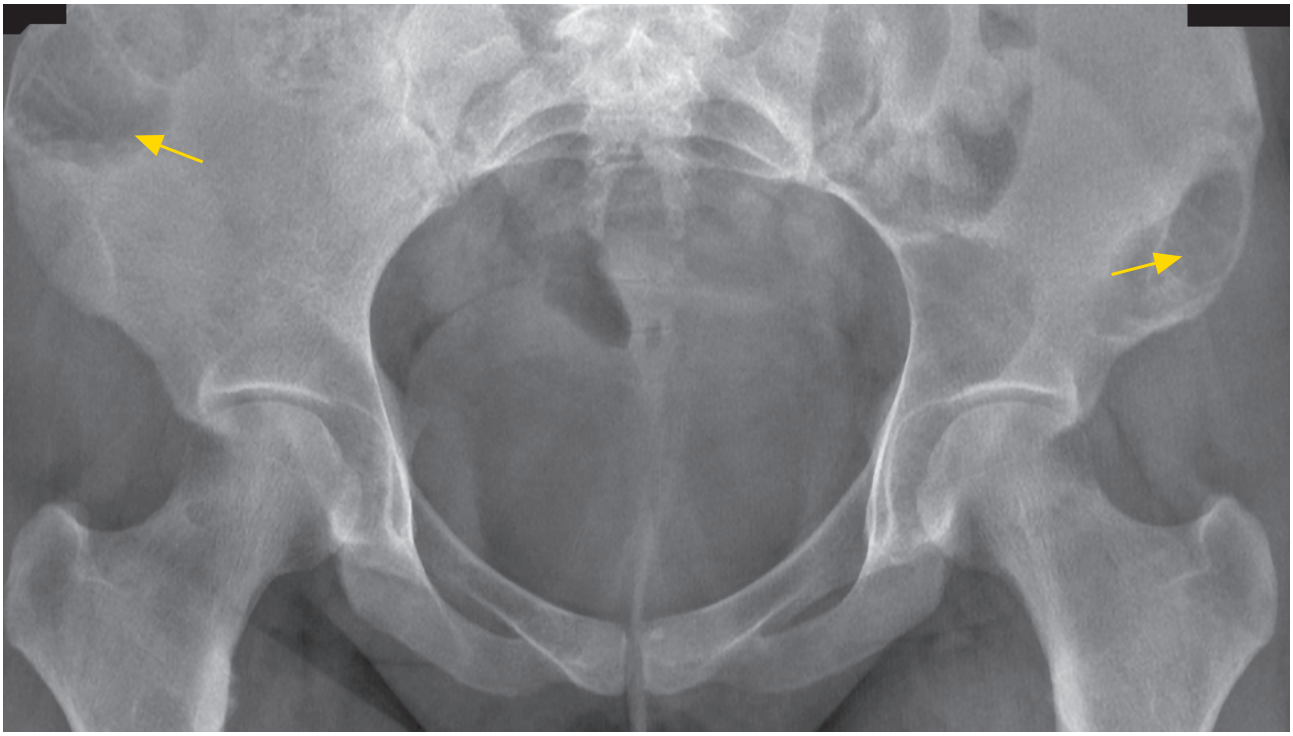

Figure 1 – Hip x-ray (yellow arrows – lytic bone lesions on iliac bone)

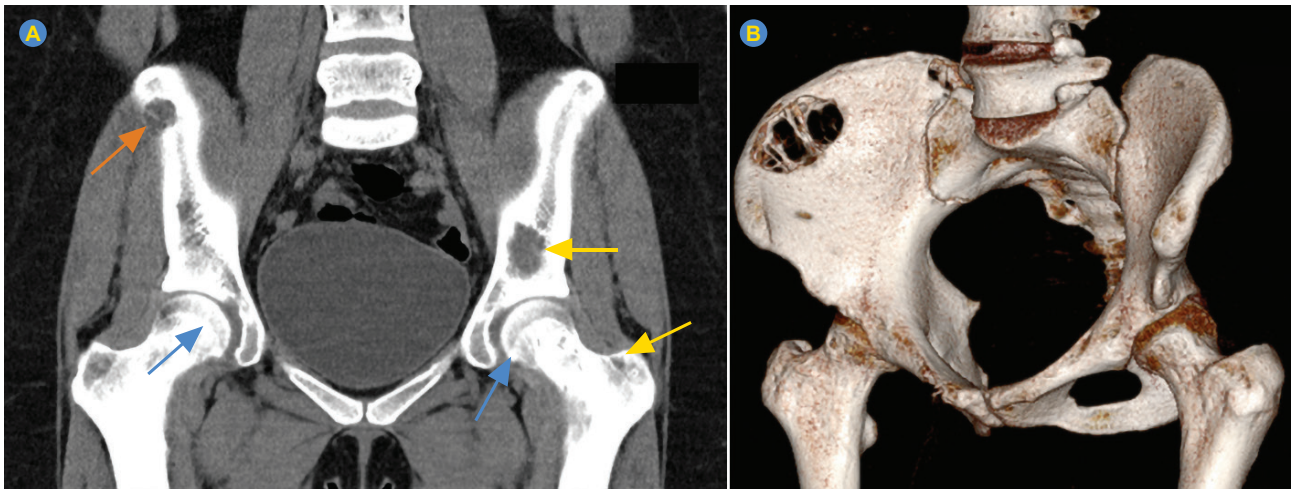

Figure 2 – (A) Hip CT (yellow arrows – lytic bone lesions on iliac bone and femurs; blue arrows – cortical thinning; orange arrow – soft tissue component) and (B) 3D reconstruction of hip CT images

The patient was admitted to the Internal Medicine ward to start a clinical investigation as well as symptomatic treatment.

Due to chronic, moderate, not very symptomatic hypercalcemia, intense fluid therapy was started, in addition to furosemide, analgesic therapy and bed rest.

The mammography and breast ultrasound showed a benign breast nodule. The neck ultrasound and aspiration biopsy suggested a nodule of the parathyroid gland. A full body CT showed no lesions suggestive of cancer or metastasis, other than a cervical nodule suggestive of a parathyroid gland nodular lesion and showed several scattered lytic bone lesions on the ribs, vertebral bones, scapula, and iliac bones. The head X-ray revealed a 'salt-and-pepper' pattern. The head CT presented several bone lesions, more indicative of brown tumors instead of lytic lesions (Fig. 3). The more complete blood tests showed hypophosphatemia and elevated levels of PTH (688 pg/mL – Reference range 15 – 65 pg/mL), with no other findings, namely no other endocrine or immunologic changes. This investigation allowed the diagnosis of symptomatic PHPT.

With the collaboration of General Surgery to help identify the precise location of the parathyroid nodule, the patient underwent a perfusion scintigraphy revealing hyperfunctioning parathyroid tissue, probably a parathyroid adenoma, of the right superior parathyroid gland. She underwent a parathyroidectomy, without any immediate intercurrences, presenting a drop higher than 50% in the values of PTH in the ten minutes after excision, meaning curative resection. The histological examination of the resected tissue confirmed the diagnosis of PHPT due to a hyperfunctioning parathyroid adenoma.

Finally, during the post-operative period, the patient presented hungry bone syndrome (persistent hypocalcemia post-op due to prolonged exposure to PTH, which leads to high bone turnover with bone resorption that suddenly shifts towards osteoblastic activity after the hormone removal),[5] and required to start intravenous and oral calcium supplementation. After almost two months of hospital admission, the patient was released, only with oral calcium supplementation and an indication for physical rehabilitation.

At the two-month follow-up, lytic bone lesions were much smaller and less expressive in the CT, as expected (Fig. 4), and the patient fully recovered her functional capacity.

DISCUSSION

This case presents a young woman with two different but still interconnected pathological findings: osteolytic lesions and hypercalcemia.

The main concern about this initial presentation was the possibility that it was caused by cancer.[4] However, in the presence of hypercalcemia and osteolytic lesions, other different diagnoses must be considered, and PHPT is one of them.

Fortunately, the full investigation revealed a benign condition, but with a presentation rarely seen nowadays – symptomatic PHPT, which is only present today in less than

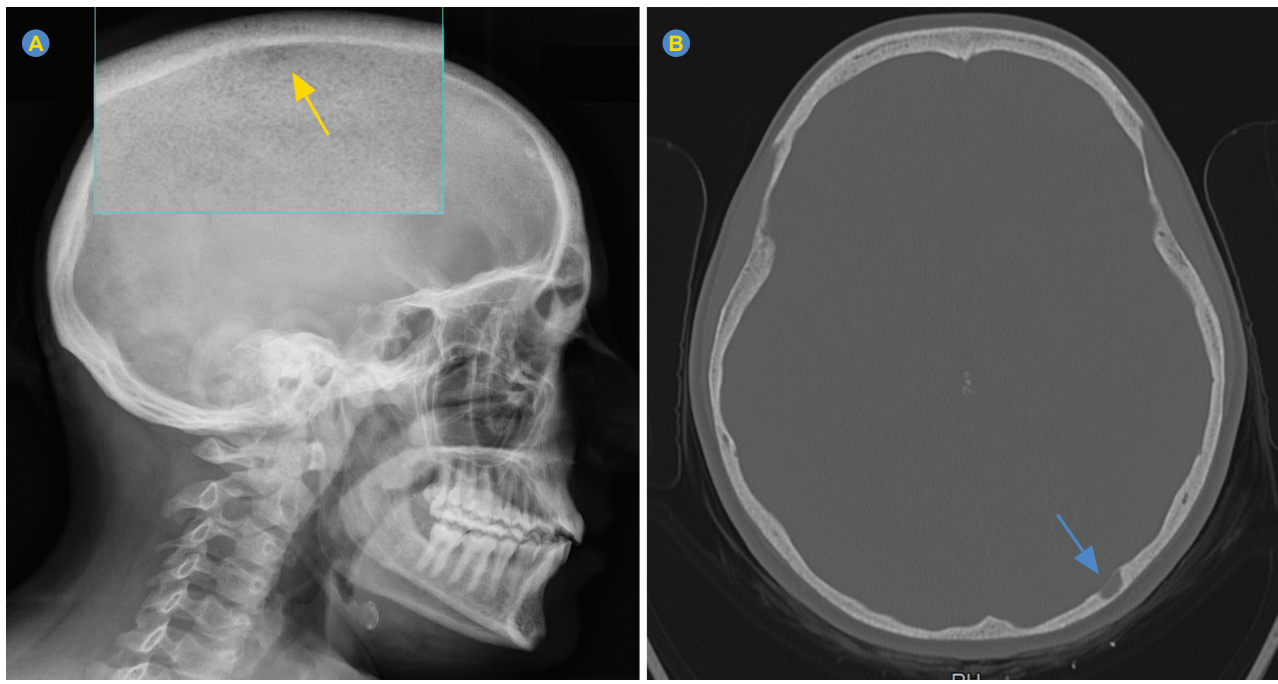

Figure 3 – (A) Head x-ray (yellow arrow – salt-and-pepper pattern) and (B) head CT (blue arrow – brown tumor)

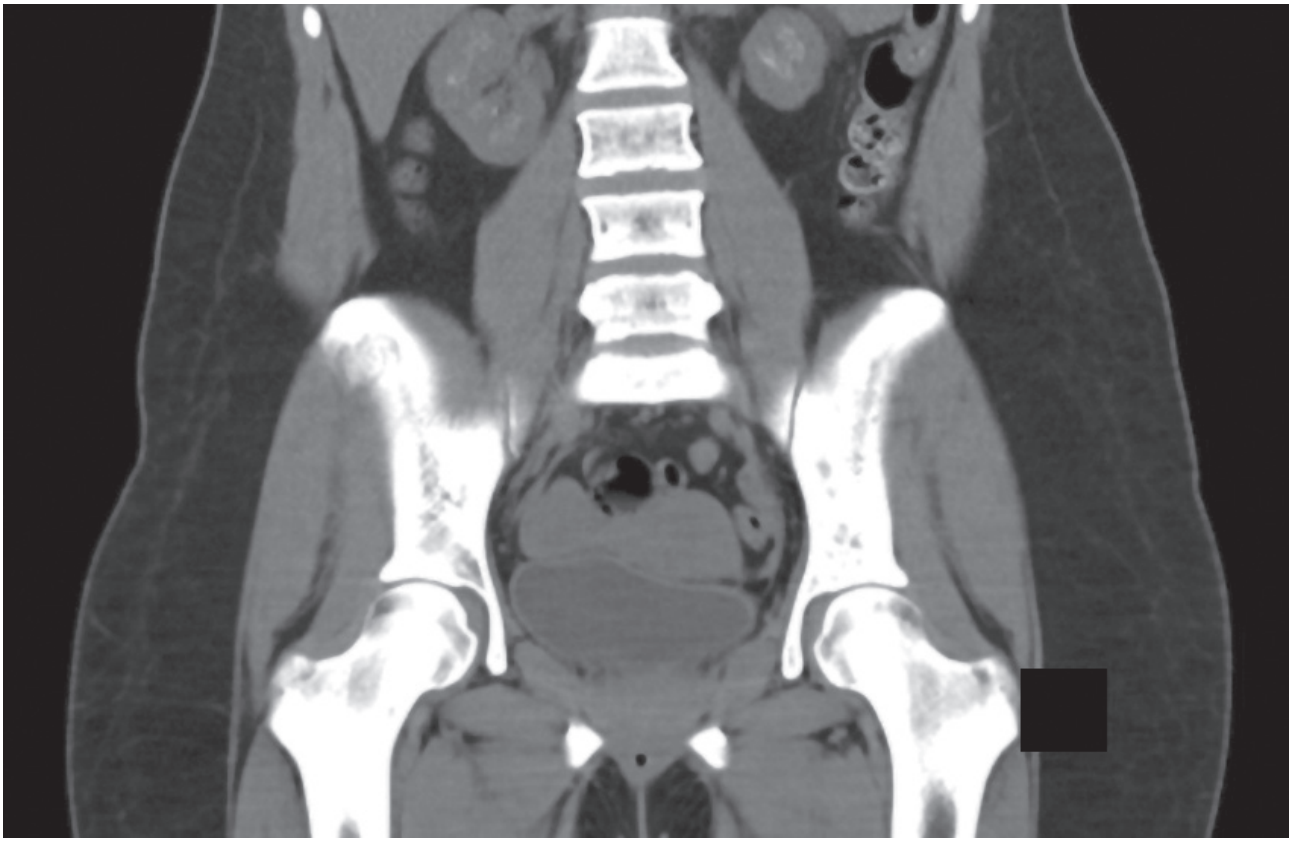

Figure 4 – Hip CT (two-month follow-up)

15% of PHPT patients.[3]

The 'classic' symptoms of PHPT target the bone and kidney.[2,4,7] 'Salt-and-pepper' pattern skull demineralization, distal clavicle tapering, subperiosteal bone resorption, cysts, and brown tumors – together they are described as osteitis fibrosa cystica.[2,4,6] The main renal complication is nephrolithiasis, being much more prevalent than in the normal population.[2,4]

There are also neurocognitive changes (such as depression, fatigue, and anxiety)[2,4] and effects in the cardiac and gastro-intestinal tract.[4]

After diagnosis, it was also possible to associate this disease with the patient's history of kidney stones, fatigue, and depression for more than a year.

Parathyroidectomy of the hyperfunctioning parathyroid tissue is the curative approach[2,4,6]; it is advised in younger patients with symptomatic PHPT or with severe hypercalcemia or renal disease.[2-4,6]

After the surgical procedure, the identified gland hyperplasia was successfully removed, confirming the diagnosis of PHPT due to a hyperfunctioning single parathyroid gland, which is the most common cause of PHPT.[3,4]

CONCLUSION

The aim of this article is to raise awareness to the fact that severe symptomatic PHPT still exists in developed countries, is an entity that should be considered every time hypercalcemia is found. and is mostly associated with skeletal and kidney disease. Despite being a medical condition, collaboration with surgical specialties is necessary to ensure the best possible treatment and prognosis.

PREVIOUS AWARDS AND PRESENTATIONS

This clinical case was presented as an Oral Communication at the 24th National Congress of Internal Medicine on May 30, 2018.

AUTHOR CONTRIBUTIONS

IMA: Draft, writing and critical review of the manuscript.
AIB: Writing and critical review of the manuscript.
IBC, AMB: Critical review of the manuscript.
SM: Study design and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki

Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Cytomegalovirus and Herpes Simplex Virus Co-Infection: Recurrence in a Kidney Transplant Recipient

Coinfecção por Citomegalovírus e Vírus Herpes Simples: Recorrência em Doente Transplantado Renal

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Keywords: Coinfection; Cytomegalovirus Infections; Herpes Simplex; Kidney Transplantation/adverse effects
Palavras-chave: Coinfecção; Herpes Simples; Infecções por Citomegalovirus; Transplante de Rim/efeitos adversos

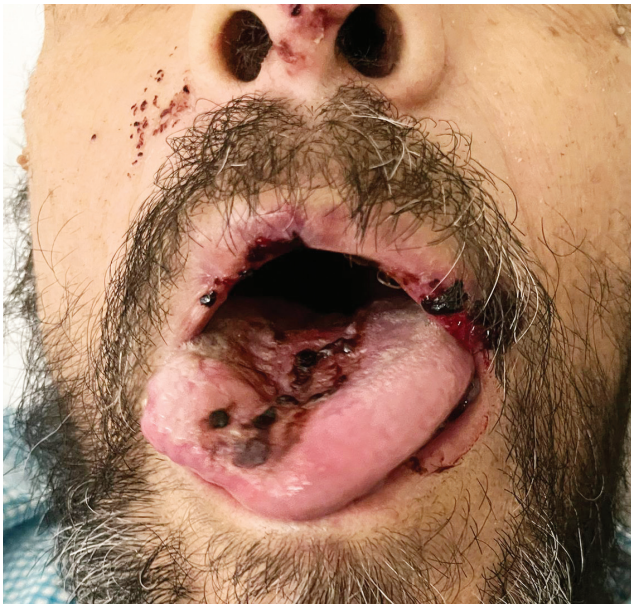

Figure 1 – Initial presentation with painful and hemorrhagic lesions in the tongue, lips and oral mucosa

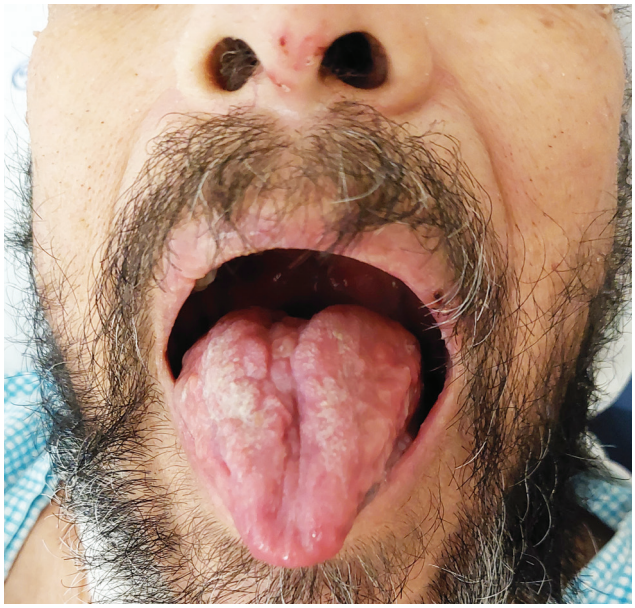

Figure 2 – Almost complete resolution of the lesions at day seven of treatment with ganciclovir

A 54-year-old male kidney transplant recipient, and receiving immunosuppressive treatment with tacrolimus, mycophenolate mofetil and prednisolone and a previous history of cytomegalovirus (CMV) disease. He was admitted with painful and hemorrhagic oral lesions (Fig. 1), associated with rapidly deterioration of health status, fever, dysphagia, and odynophagia. A swab of the oral lesions identified Herpes simplex 1 virus by Polymerase Chain Reaction. High blood CMV viral load and oral tissue biopsy confirmed the diagnosis of CMV disease with herpetic co-infection. The patient was started on ganciclovir with significant clinical improvement on day seven (Fig. 2).

CMV disease is a common clinical infection in solid organ transplant recipients[1] despite various prophylaxis strategies.[2] Ganciclovir is preferred as initial treatment. Renal function and CMV viral load should be monitored at weekly intervals to guide the duration of therapy.[3] The authors want to raise awareness to the possibility of recurrence of CMV disease and its co-infection with HSV in immunosuppressed patients.

AUTHOR CONTRIBUTIONS

MBS: Draft of the case description and discussion.
AG, GC: Critical review of the work.

PROTECTION OF HUMANS AND ANIMALS

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

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PATIENT CONSENT

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COMPETING INTERESTS

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Portuguese Consensus on Acute Porphyrias: Diagnosis, Treatment, Monitoring and Patient Referral

Consenso Português de Porfirias Agudas: Diagnóstico, Tratamento, Monitorização e Referenciação

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ABSTRACT

Acute porphyrias are a group of rare genetic metabolic disorders, caused by a defect in one of the enzymes involved in the heme biosynthesis, which results in an abnormally high accumulation of toxic intermediates. Acute porphyrias are characterized by potentially life-threatening attacks and, for some patients, by chronic manifestations that negatively impact daily functioning and quality of life. Clinical manifestations include a nonspecific set of gastrointestinal, neuropsychiatric, and/or cutaneous symptoms. Effective diagnostic methods are widely available, but due to their clinical heterogeneity and non-specificity, many years often elapse from symptom onset to diagnosis of acute porphyrias, delaying the treatment and increasing morbidity. Therefore, increased awareness of acute porphyrias among healthcare professionals is paramount to reducing disease burden. Treatment of acute porphyrias is centered on eliminating the potential precipitants, symptomatic treatment, and suppressing the hepatic heme pathway, through the administration of hemin or givosiran. Moreover, properly monitoring patients with acute porphyrias and their relatives is fundamental to preventing acute attacks, hospitalization, and long-term complications. Considering this, a multidisciplinary panel elaborated a consensus paper, aiming to provide guidance for an efficient and timely diagnosis of acute porphyrias, and evidence-based recommendations for treating and monitoring patients and their families in Portugal. To this end, all authors exhaustively reviewed and discussed the current scientific evidence on acute porphyrias available in the literature, between November 2022 and May 2023.
Keywords: Consensus; Porphyria, Acute Intermittent/diagnosis; Porphyria, Acute Intermittent/therapy; Porphyrias/diagnosis; Porphyrias/therapy; Portugal; Referral and Consultation

RESUMO

As porfirias agudas são um grupo de doenças metabólicas raras, causadas pela deficiência numa das enzimas envolvidas na biossíntese do heme, originando uma elevada e anormal acumulação de intermediários tóxicos. As porfirias agudas são caracterizadas por crises potencialmente fatais e, em alguns doentes, por manifestações crónicas que têm um impacto negativo no funcionamento diário e na qualidade de vida. As manifestações clínicas incluem um amplo espetro de sintomas gastrointestinais, neuropsiquiátricos e/ou dermatológicos. Existem métodos de diagnóstico eficazes amplamente disponíveis, mas devido à heterogeneidade e inespecificidade das manifestações clínicas, muitas vezes decorrem vários anos desde o início dos sintomas até ao diagnóstico das porfirias agudas, atrasando o tratamento e aumentando a morbilidade. Assim, o aumento da consciencialização para as porfirias agudas entre os profissionais de saúde é considerado fundamental para reduzir o impacto da doença. O tratamento centra-se na eliminação dos potenciais precipitantes, tratamento sintomático e supressão da via hepática de síntese do heme, através da administração de hemina ou givosiran. Além disso, a monitorização adequada dos doentes com porfirias agudas e dos seus familiares é crucial para prevenir crises agudas, hospitalização e complicações a longo prazo. Considerando isto, um painel multidisciplinar elaborou um consenso nacional, com o objetivo de fornecer orientações para o diagnóstico rápido e eficiente das porfirias agudas, assim como recomendações, baseadas em evidência científica, para o tratamento e monitorização de doentes com estas patologias e as suas famílias, em Portugal. Para tal, a evidência científica atual sobre porfirias agudas disponível na literatura foi exaustivamente revista e discutida por todos os autores entre novembro de 2022 e maio de 2023.
Palavras-chave: Consenso; Encaminhamento e Consulta; Porfirias/diagnóstico; Porfirias/tratamento; Porfiria Aguda Intermitente/diagnóstico; Porfiria Aguda Intermitente/tratamento; Portugal

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INTRODUCTION

Porphyrias are a group of rare, genetic metabolic disorders caused by a defect in an enzyme of the heme biosynthesis pathway, leading to the accumulation of specific heme precursors.[1,2] Porphyrias can be categorized as acute or non-acute photocutaneous porphyrias, characterized by intermittent neurovisceral attacks or moderate to severe cutaneous photosensitivity, respectively.[3-5]

Acute porphyrias comprise three autosomal dominant disorders, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), and the rare autosomal recessive disorder aminolevulinic acid dehydratase deficiency porphyria (ADP).[3,5,6]

Acute porphyrias are characterized by potentially life-threatening acute attacks, which most frequently consist of pain accompanied or preceded by neuropsychiatric symptoms and peripheral neuropathy. In VP and HCP, cutaneous blistering can also occur in sunlight-exposed skin. Recurrent acute attacks increasingly predispose patients to chronic symptoms and long-term complications may occur during the natural course of acute porphyrias.[7-9]

PATHOPHYSIOLOGY

Acute porphyrias are caused by a genetic mutation leading to a partial deficiency in one of four specific enzymes in the heme biosynthetic pathway. In detail, ADP is caused by an abnormal function of ALA dehydratase; AIP is caused by a deficiency in the hydroxymethylbilane synthase; HCP is caused by a defect in the coproporphyrinogen oxidase, and VP is caused by a deficiency in the protoporphyrinogen oxidase.[3,5,6]

The defective function of these enzymes is an essential but not a sufficient condition to develop acute porphyria. In fact, the activity of aminolevulinic acid synthase 1 (ALAS1), the first and rate-limiting enzyme in the heme biosynthetic pathway in the liver, is determinant for the development of acute porphyria. The ALAS1 activity can be induced directly or indirectly by several environmental and physiological factors, such as certain drugs, stress, infection, caloric restriction, alcohol use, smoking, and fluctuating levels of female sex hormones.[3,5]

ALAS1 upregulation associated with the deficiency in one of the downstream enzymes leads to an abnormal and toxic accumulation of porphyrins and their precursors, namely aminolevulinic acid (ALA) and porphobilinogen (PBG). The increased release of these intermediates into the circulation can cause injuries to the nervous system and other organs.[3,5,10]

EPIDEMIOLOGY

Acute porphyrias have a combined prevalence rate of approximately five cases per 100 000 subjects worldwide.[5,10-12] AIP is the most common type, with an estimated prevalence rate of the disease-related mutations varying from 1:1299 to 1:1700 in the general population.[13,14] In European countries, the incidence rate was calculated as 0.13, 0.08, and 0.02 new cases/year per million inhabitants for AIP, VP, and HCP, respectively, and the prevalence rate was determined as 5.4 and 3.2 per million inhabitants for AIP and VP, respectively.[12] ADP is an extremely rare porphyria, with fewer than 10 cases described in the literature.[3] In Portugal, the incidence and prevalence rates of acute porphyrias are currently unknown.

The clinical penetrance of acute porphyrias is low, estimated at 1% for the patients with an AIP mutation, suggesting a critical role of modifying genes and/or environmental factors for triggering the acute attacks.[13,14]

DIAGNOSIS

Acute porphyrias are rare and characterized by a non-specific range of manifestations, and therefore many patients remain undiagnosed or are often misdiagnosed with other medical conditions. A population-based study reported an up to 15-year delay from symptom onset to diagnosis of acute porphyrias.[15] An earlier diagnosis is fundamental for rapid and effective treatment, reduced healthcare costs and improved outcomes.[16]

Clinical and laboratory findings

Acute attacks

Acute attacks may occur in all acute porphyrias and are clinically indistinguishable. Patients usually present a non-specific constellation of signs and symptoms caused by dysfunction across the autonomic, central, and peripheral nervous systems (Fig. 1). Classically, abdominal pain, peripheral neuropathy, and changes in mental status constitute the symptomatic triad of an acute attack.[6,7,17]

Severe abdominal pain is often the initial symptom of an attack, and it is the most common symptom reported by patients (74% - 100%). Pain typically lasts hours to several days, and gradually abates. The pain pattern is diffuse, colicky in nature, and it is commonly accompanied by nausea and vomiting (42% - 88%) and constipation (50%). The abdominal examination is often unremarkable. Pain in the back, legs, arms or chest is common (72% - 77%).[6,7,18]

Behavioral changes can precede an acute crisis and a myriad of psychiatric symptoms can occur during an attack. Among patients with acute porphyrias, 20% to 58% have neuropsychiatric symptoms before and during acute exacerbations. The broad spectrum of psychiatric manifestations includes irritability and subtle mood disturbances, anxiety, behavioral and sleep disorders, severe depression, psychosis, personality changes, catatonia, and dementia.[19-21] The

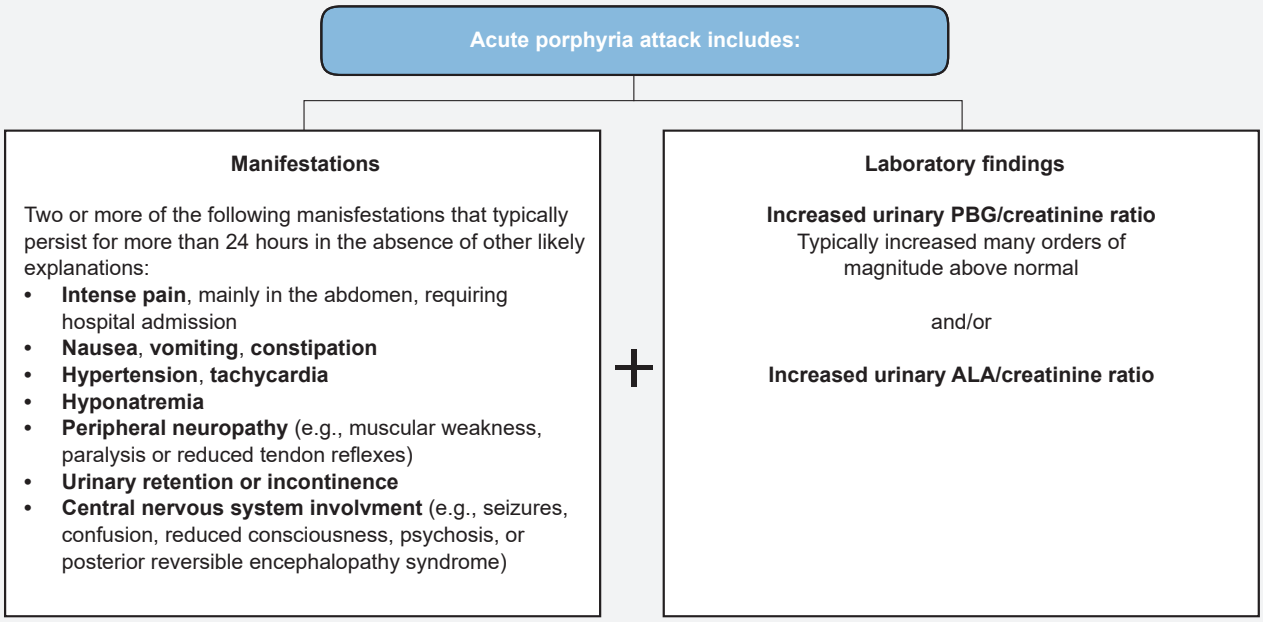

Figure 1 – Key manifestations and specific laboratory findings indicating an attack of acute porphyria

same patient may have variable psychiatric manifestations in each attack.[22]

Patients may also experience motor weakness and sensitivity changes typically mild in severity, which improve as the pain resolves. Rarely, progressive motor weakness may evolve to complete paralysis, incontinence or urinary retention, swallowing difficulties and respiratory failure.[5,20,23]

Hyponatremia is a common feature (25% - 60% of acute attacks), and a marker of the severity of the crisis. Hyponatremia is mainly due to hypothalamic involvement, resulting in the syndrome of inappropriate diuretic hormone secretion (SIADH).[24] Other non-specific laboratory abnormalities such as hypomagnesemia, mild aminotransferases elevations, anemia, leukocytosis, and increased C-reactive protein, can also be detected.[4,25,26]

Seizures occur in up to 20% of AIP patients, and they are often associated with severe hyponatremia.[2,20,27] Cases of porphyria-induced posterior reversible encephalopathy syndrome have been reported.[28]

Increased sympathetic activity leads to tachycardia, excess sweating, and hypertension, which occur in about 60% of acute attacks. Cardiac dysrhythmias occur in rare situations.[7]

Most patients experience either none or only a few acute attacks during their lifetime; yet a few patients experience recurrent attacks (≥ four attacks/year) and/or have severe and chronic symptoms.[12,29] By definition, symptomatic patients are those who have experienced at least one acute porphyria attack within the last two years; whereas asymptomatic patients are those who have experienced at least one acute porphyria attack in the past but have had no acute porphyria related manifestations during the last two years. Asymptomatic patients can be further distinguished as patients in remission or high excreters, according to the urine PBG/creatinine ratio – lower or higher than four times the upper limit of normal, respectively.[6]

Cutaneous manifestations

Variegate porphyria and HCP can be associated with photocutaneous skin lesions, which result from the overproduction and skin accumulation of photoreactive porphyrins.[30] Skin manifestations can occur either alone or during acute symptoms, and in 60% of VP patients these may be the only sign of the condition.[31,32]

Clinically, bullae, blisters or vesicular lesions are limited to sun-exposed skin, such as the back of hands and feet, face, neck, and legs. Other cutaneous manifestations include skin fragility, hypertrichosis, and increased pigmentation of sun-exposed areas. Cutaneous manifestations change seasonally, being more intense in the summer and in the autumn.[31]

Chronic symptoms

Most symptomatic patients with acute porphyria have complete resolution of their symptoms between attacks, although those with multiple recurrent attacks may develop chronic symptoms. In a four-year natural history study, almost 75% of patients reported chronic symptoms between

attacks.[33] In a different observational study, chronic symptoms were reported in 85% of AIP patients with sporadic attacks (< four attacks/year) and 46% of patients with latent AIP (no attacks).[34]

Chronic pain is usually the most commonly reported symptom, followed by tiredness, anxiety, nausea and sleeping disorders.[29,34-36] Chronic manifestations negatively impact many aspects of daily living, and health-related quality of life is considerably reduced in patients with acute porphyria.[29,34,36]

Long-term complications

Subclinical liver disease is common in acute porphyria and manifests as progressive transaminitis, fibrosis, cirrhosis, or hepatocellular carcinoma leading to premature death. In a recent systematic review enrolling 7381 patients with porphyria, primary liver cancer was diagnosed in 4.8% of patients, of whom 3.3% (of the total) had hepatocellular carcinoma.[37] Advanced liver fibrosis and cirrhosis are not a prerequisite for the development of hepatocellular carcinoma in patients with acute porphyria.[37,38]

Chronic kidney disease is also common, particularly in symptomatic AIP patients. In a 10-year cohort study, chronic kidney disease occurred in up to 59% of the symptomatic AIP patients, with a decline in glomerular filtration rate of ~1 mL/min/1.73 m^2 annually.[39] Among these patients, 2.7% developed end-stage renal disease.[39] Additionally, a recent study reported a five-fold higher risk of advanced chronic kidney disease in patients with acute porphyria than in the general population.[40] Porphyria-associated kidney disease is typically presented as chronic tubulointerstitial damage and chronic fibrous intimal hyperplasia associated with focal cortical atrophy.[41,42]

The decline of renal function may also be related with chronic hypertension. In fact, in the abovementioned 10-year study, hypertension was present in 62% of symptomatic patients.[39] Moreover, hypertension can also occur with normal renal function. Chronic hypertension was more frequent in the symptomatic cases (71% - 73%), than in the asymptomatic control group (26%).[43]

Ultimately, death can occur in acute attacks and as an outcome of long-term complications.[44,45]

Laboratory diagnosis

First-line testing

In symptomatic patients, first-line biochemical diagnosis consists of a single random urine screening for PBG, ALA, and porphyrins. The use of Hoesch Test, with Erhlich reagent is a rapid test for screening PBG in urine.[46] The optimal time to collect a urine sample is during or shortly after an attack, when PBG or ALA levels will have peaked. Reddish, purple, or brown urine color is common during acute attacks, and urine may darken further upon exposure to light. The urine sample should be protected from light and frozen (preferentially) or refrigerated for transport and storage. Results should be normalized to the creatinine concentration for a more reliable interpretation (please consult the article by Stein *et al*[6] for detailed considerations in the interpretation of the urine PBG/creatinine ratio).[6,17,46,47]

Diagnosis of AIP, VP and HCP requires the presence of increased urinary PBG levels, often many orders of magnitude above normal, which do not occur in any other medical condition (Table 1).[6,48] This high degree of specificity enables prompt identification and treatment. Exceptionally in the ultra-rare ADP, PBG levels are normal, but ALA levels are typically elevated.[17,46,47]

Measurement of urine porphyrins is important to ensure that VP or HCP are

Table 1 – Diagnostic test outcomes for each subtype of acute porphyria. Adapted from[47]

Acute porphyria subtype	Clinical presentation	First-line testing			Second-line testing		Third-line testing
		Urinary PBG	Urinary ALA	Urinary porphyrins	Plasma porphyrins with fluorescence scan	Fecal porphyrins	Genetic testing
ADP	Acute attacks	Normal or slight ↑	↑↑	↑ COPRO III	No peak or ~619 nm	Normal or slight ↑	*ALAD*
AIP	Acute attacks	↑↑	↑	↑ URO, COPRO III	No peak or ~619 nm	Normal or slight ↑	*PBGD*
HCP	Acute attacks and/or cutaneous symptoms	↑	↑	↑ or normal URO, COPRO III	No peak or ~619 nm	↑↑ COPRO III COPRO III/COPRO I > 2	*CPOX*
VP	Acute attacks and/or cutaneous symptoms	↑	↑	↑ or normal URO, COPRO III	~626 nm	↑ PROTO >> COPRO III	*PPOX*

ADP: ALA dehydratase deficiency porphyria; AIP: acute intermittent porphyria; ALA: aminolevulinic acid; COPRO III: coproporphyrin III; HCP: hereditary coproporphyria; PBG: porphobilinogen; PROTO: protoporphyrin; URO: uroporphyrin; VP: variegate porphyria; ↑ increased.

not misdiagnosed, because urinary PBG levels are often less elevated and return to normal more rapidly in VP and HCP than in AIP.[6] General increases in porphyrins are not specific to porphyrias and can be found in hepatic disease of all causes; nevertheless, a specific pattern of porphyrins exists for each subtype of acute porphyria (Table 1).[17,46,47]

Second-line testing

Measurement of plasma and fecal porphyrins and plasma fluorescence scanning are useful second-line diagnostic tests to confirm or exclude porphyrias or to determine the subtype of acute porphyria (Table 1). In HCP, coproporphyrin (COPRO) III isomer is more elevated in feces than in urine, and the ratio of COPROIII/COPRO I is usually greater than two; in VP there is a distinct plasma porphyrin fluorescence emission peak at 624 - 628 nm and, in feces, the level of protoporphyrin (PROTO) is higher compared to COPRO III isomer.[17,46,47]

Third-line testing

Genetic testing of the acute porphyria genes can identify the pathogenic familial mutation and is useful to fully characterize the index case and to prevent acute attacks in at-risk patients with a pathogenic mutation (Table 1).[49,50] Demonstration of an acute porphyria mutation identifies a genetic trait for porphyria, but, by itself, is insufficient to establish a diagnosis or determine a biochemically active acute porphyria, due to the low clinical penetrance of acute porphyrias.[13,14,46,47]

Differential diagnosis

The symptoms of acute porphyria often resemble those of other gastrointestinal, neurological or neuropsychiatric diseases (Table 2).[21,51-55]

Table 2 – Common clinical conditions mimicked by an acute attack of acute porphyria[21,51-55]

Gastrointestinal conditions	Acute gastroenteritis
	Appendicitis
	Biliary colic/ acute cholecystitis
	Intestinal occlusion
	Pancreatitis
	Peptic ulcer disease
	Peritonitis
Genitourinary conditions	Nephrolithiasis
	Urinary tract infection
	Pelvic inflammatory disease
	Pregnancy complications
Metabolic/endocrine conditions	Acute hypoadrenalism (Addisonian crisis)
	Acute hypoparathyroidism and hypocalcemic crisis
	Pheocromocytoma
Neuropsychiatric conditions	Acute myopathies
	Acute psychotic episode
	Delirium
	Epilepsy
	Hemicrania
	Guillain–Barré syndrome
	Panic attack/ anxiety
Cardiovascular conditions	Hypertensive crisis
	Tachyarrhythmia
Hematological conditions	Acute drepanocytic crisis
	Acute hemolytic crisis
Other conditions	Lead poisoning
	Pseudoporphyria
	Tyrosinemia

Acute porphyria should be suspected when severe abdominal pain of unknown cause is accompanied by other symptoms that suggest central, peripheral, or autonomic nervous system involvement (Fig. 1). In addition, acute porphyria should be considered when factors often associated with attacks are present, such as female sex, luteal phase of the menstrual cycle, weight loss, alcohol abuse, stress, infection, or porphyrinogenic drugs which can induce porphyria attacks (the database for porphyrinogenic drugs can be accessed on www.drugs-porphyria.org).[11,17,51]

In acute porphyria, the most important differential feature is the presence of markedly elevated levels of urine PBG and/or ALA (Fig. 1). Lead intoxication and hereditary tyrosinemia can also present with elevated ALA levels (but normal PBG), and symptoms that are indistinguishable from acute ADP attacks.[56,57] In case of lead intoxication, measuring the blood lead level is definitive for diagnosis. In the case of hereditary tyrosinemia, it usually manifests during infancy or early childhood, whereas acute porphyria is rarely active before puberty.[58]

TREATMENT

Porphyrinogenic drugs can potentially trigger an attack of acute porphyria.[11] Therefore, before initiating any pharmacological treatment in patients with acute porphyria, the Norwegian-IPNET drugs database (www.drugs-porphyria.org) should be consulted to assess the porphyrinogenic potential of the different medications.[59]

Treatment of acute attacks

Acute attacks may progress into severe and potential life-threatening outcomes, if not properly treated. The treatment should be initiated immediately after the manifestation of typical symptoms and detection of increased urinary PBG.[7,60,61]

Hospitalization is usually required, particularly when intravenous therapies and close observation are necessary. When the vital capacity is compromised, admission to an intensive care unit is mandatory. In case of well-characterized patients with a similar pattern of recurrent attacks, and which respond promptly to treatment, management can be performed in outpatient settings.[17]

Treatment should be primarily focused on the suppression of ALAS1 activity, and symptomatic management (Fig. 2). All the potential precipitating factors should be identified and eliminated. For early symptoms of an attack (e.g., mild pain, no paresis), a high carbohydrate diet should be started, if oral intake is tolerated. If not tolerated, carbohydrates can be provided as intravenous 5% dextrose in normal saline up to 2 L per day. Patients should be under regular clinical monitoring, including the evaluation of pain score, neurological function, and plasma sodium levels. If symptoms do not improve or escalate into severe pain, with significant hyponatremia, peripheral neuropathy, urinary retention or incontinence, central nervous system involvement, or arrhythmias, hemin 3 mg/kg daily (up to 250 mg/day) should be intravenously administered for four consecutive days. When hemin is not available, intravenous 10% - 20% glucose in normal saline in up to 2 L daily is indicated.[7,60-66]

Symptomatic treatment should be started as needed (Fig. 2). For mild pain, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are first-line analgesic agents, whereas for severe and unbearable pain, parenteral opioid medications should be administrated. Benzodiazepines, such as lorazepam, can be used to potentiate the analgesic effect and to decrease the concomitant anxiety. Gabapentin and pregabalin should be used when clear neuropathic features are present.[18]

Nausea and vomiting can be effectively managed with ondansetron, chlorpromazine or promethazine, and constipation can be treated with lactulose or repeated enemas. Control of tachycardia and systemic arterial hypertension can be achieved with beta blockers, angiotensin-converting enzyme inhibitors, or calcium channel blockers.[7,61]

Seizures should be treated with benzodiazepines, gabapentin, or levetiracetam; status epilepticus requires sedation with propofol. Careful correction of hyponatremia is necessary, particularly when associated with seizures. In acute porphyria, hyponatremia is commonly linked to SIADH, and its correction should be performed according to the specific guidelines.[67,68] Even though fluid restriction is the best option to treat SIADH, it is poorly tolerated. Infusion with saline solution and loop diuretics are second- and third-line options for SIADH, respectively.[7,61]

Anxiety and insomnia can be managed with low-dose benzodiazepines and hypnotics. Agitation and psychosis should be treated with olanzapine, clozapine, or haloperidol. For depression, fluoxetine, venlafaxine, or duloxetine can be safely prescribed for patients with acute porphyria.[19,61,69]

Long-term treatment

Patient education is a critical aspect of long-term management. Patients should be counseled to avoid or minimize triggering factors and to maintain a balanced diet with an appropriate carbohydrate and caloric intake.[61,64,66] Alongside, management of persistent symptoms and/or the administration of disease-modifying therapies should be individually considered for each patient.

Symptomatic treatment

First-line options for chronic neuropathic pain include the antidepressants duloxetine, fluoxetine, and amitriptyline, and the antiepileptics pregabalin and gabapentin.

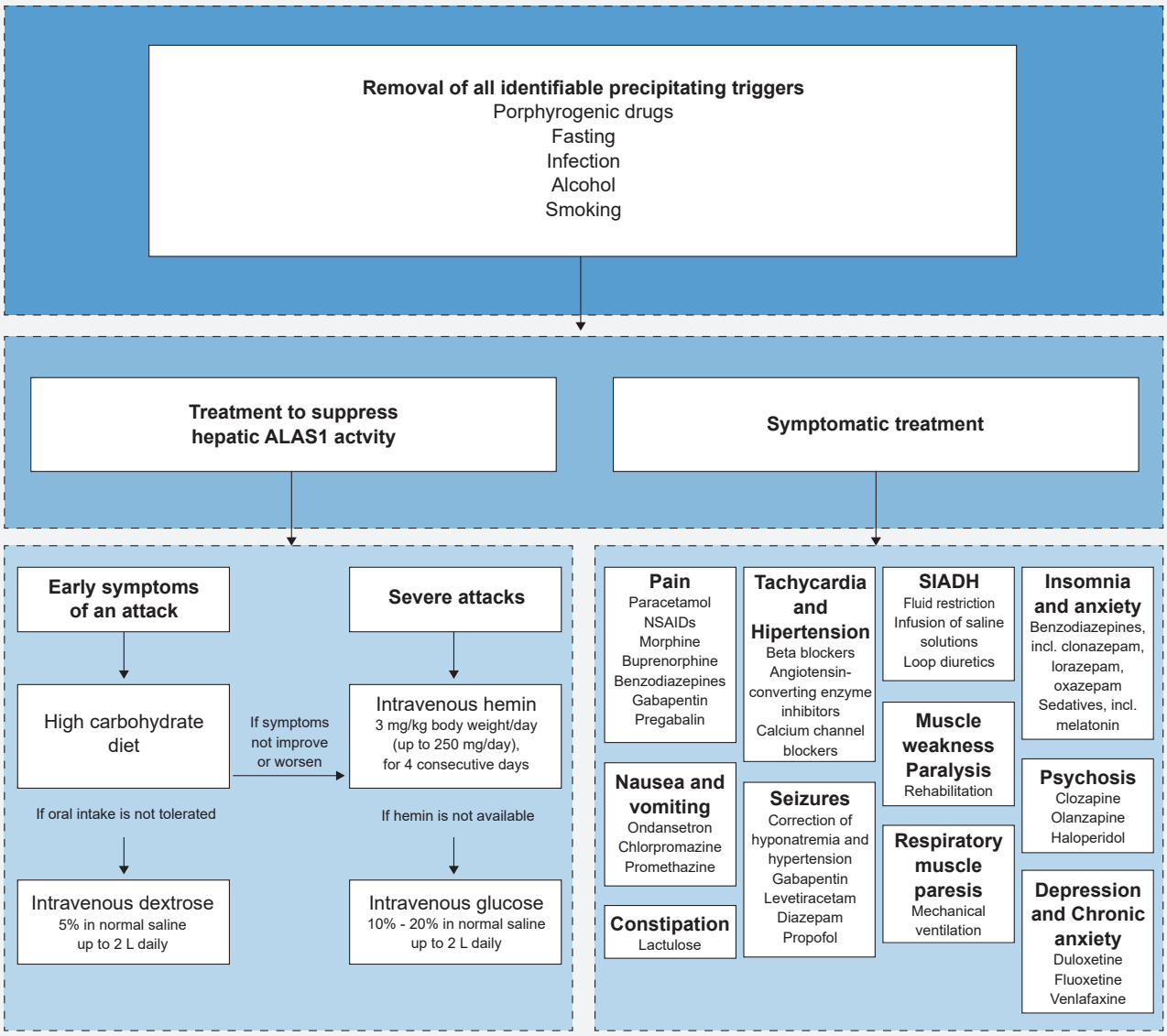

Figure 2 – Treatment algorithm for acute porphyria

Second- and third-line options include tramadol and stronger opioids, like oxycodone and hydrocodone, respectively; but these should be prescribed after evaluating the addiction risk. NSAIDs and paracetamol are only recommended for mild musculoskeletal pain.[18]

Patients with muscular weakness and/or paralysis will need regular intensive physiotherapy for recovery of function, which typically takes six to 12 months. In case of respiratory muscle paresis or failure, artificial ventilation may be needed for a period of several months.[7,61] Other chronic symptoms can be treated with the pharmacological options presented in Fig. 2.

Disease-modifying treatment

Givosiran is a small interfering RNA therapy which decreases the expression of ALAS1 in hepatocytes, resulting in reduced circulating levels of the neurotoxic intermediates ALA and PBG. Givosiran is approved for the treatment of acute porphyrias in patients aged ≥ 12 years, with a recommended dose of 2.5 mg/kg once monthly, subcutaneously.[70-72]

The six-month phase 3 study (givosiran 2.5 mg/kg *versus* placebo),[73] and the 24-month data from the open label extension (givosiran 2.5 mg/kg or 1.25 mg/kg)[74] demonstrated that AIP patients with recurrent attacks treated with givosiran had a significant reduction in acute attacks

number and sustained reduction in urinary ALA and PBG levels, as well as decreased daily pain and improved quality of life.[70,75,76] Real-world experience demonstrated that givosiran prevented recurrent attacks in patients with severe AIP and it is most effective when given early in the disease course.[77] Of note, efficacy and safety data of givosiran in VP, HCP and ADP are limited.

Givosiran has potential adverse effects, especially risk of hepatic, renal and cutaneous adverse effects and of hyperhomocysteinemia.[70,78,79] In the clinical trials, alanine aminotransferase (ALT) elevations were observed between three and six months after starting givosiran; most of these elevations were transient and/or resolved with decreased monthly doses.[70] Givosiran is also associated with an early and reversible decline of renal function; however, it is difficult to distinguish the long-term effects of givosiran from the natural progression of acute porphyria-associated renal disease.[78] The clinical significance of givosiran-associated hyperhomocysteinemia is not completely understood, but can potentially lead to cardiovascular diseases, and pancreatitis. An optimal strategy to minimize hyperhomocysteinemia is being debated, and currently 80 mg/day vitamin B6 seems to be the best available regimen.[79]

Prevention of attacks

Appropriate education of patients to avoid precipitating factors and potential porphyrinogenic drugs is fundamental to preventing acute attacks.[10,58]

Additionally, off-label prophylactic hemin preparations are used in many countries to prevent recurrent attacks. Weekly prophylaxis with hemin (3 - 4 mg/kg) decreased acute attacks and increased quality of life in patients with recurrent attacks.[80,81] Nevertheless, long-term use of hemin may be associated with hepatic iron overload, thrombocytopenia, phlebitis, and tachyphylaxis.[66,80]

In women suffering from catamenial-associated attacks, the use of gonadotropin-releasing hormone agonists to suppress ovulation may provide relief, but most patients experience severe estrogen deficiency side effects.[82] Progestins are identified as triggering agents; therefore, hormonal contraceptives should generally be avoided.[7,10]

For cutaneous manifestations, the treatment should be centered on avoiding sunlight exposure and wearing protective clothing. Dietary supplementation with vitamins C and E may mitigate oxidative damage in VP, although evidence for its benefit is scarce.[83-85]

In extreme cases of recurrent attacks not responding to other therapies, liver transplant could be an option. Liver transplant effectively restores the heme biosynthesis pathway in the liver and is curative. In a study reviewing the European experience with liver transplantation, the one-year and five-year survival rates were similar between AIP patients and patients who received transplants for other metabolic diseases for an equal period. Improved porphyria-related neuropathy was observed, but severe neuropathy and advanced pretransplant renal impairment increased the risk of poor outcomes.[86] Overall, given the shortage of donors and the high risks associated with the procedure, this option should be reserved as the final option.[7,65]

MONITORING

Monitoring of patients with acute porphyria must be individualized, and it is paramount to prevent acute attacks, hospitalization, and long-term complications.

Patients should receive proper information about their disease, potential porphyrinogenic drugs, and precipitating factors. Signs and symptoms during and between attacks, medications, and potential precipitants should be thoroughly documented in the electronic health records of the patient. In addition, symptomatic patients should be routinely monitored for acute porphyria activity, long-term complications, and treatment safety through laboratory and other diagnostic tests (Table 3). Asymptomatic patients should be monitored annually.

Pregnancy increases the susceptibility of women to acute attacks, although most patients have completely normal pregnancies.[87] A pre-conception evaluation is recommended, and patients should be followed by an obstetrician during pregnancy and during the postpartum period.[7,87]

RECOMMENDATIONS FOR FAMILY STUDY

Patients with acute porphyrias are likely to have genetically affected relatives, who are often asymptomatic. Family screening to identify those with latent disease is essential to minimize their risk of acute attacks.[7,8,32]

DNA analysis is the method of choice; once the familial mutation is identified, first-degree family members should undergo reliable targeted mutation analysis.[17,50] Relatives who have inherited a pathogenic mutation are at risk for developing symptoms, and therefore they should be properly educated on how to recognize disease symptoms early on and avoid precipitants. At-risk patients with an acute porphyria mutation should be evaluated clinically and undergo biochemical testing to assess disease activity annually.[47]

PATIENT REFERRAL

In Portugal, patients with a diagnosis or suspicion of acute porphyria should be referred to the reference centers for inherited metabolic disorders (RC-IMD; Centros de Referência de Doenças Hereditárias do Metabolismo). There are 5 RC-IMDs, namely Centro Hospitalar e Universitário de Coimbra, Centro Hospitalar e Universitário de Lisboa Central, Centro Hospitalar e Universitário de Lisboa Norte, Centro Hospitalar e Universitário de São João, and

Table 3 – Monitoring of patients with acute porphyrias[5-7,10,17,20,38,41,58,61,70]

Parameter	Frequency	
	Symptomatic patients (≥ 1 attack within the last 2 years)	
	Sporadic attacks (1 - 3 attacks/year)	Recurrent attacks (≥ 4 attacks/year)
Clinical monitoring		
Clinical history of acute porphyria manifestations	Every 6 months	Every 3 months
Physical examination	Every 6 months	Every 3 months
Medication review	Every 6 months	Every 3 months
Quality of life	Every 6 months	Every 3 months
Laboratory monitoring		
Biomarkers for acute porphyria Urine ALA and PBG	Every 6 months and as clinically indicated	
Exosomal ALAS1 mRNA	As clinically indicated – investigational biomarker (still not available in clinical routine)	
Standard blood and urine tests Complete blood count Comprehensive metabolic panel Renal function panel Hepatic function panel	Every 6 months and in acute attacks	
Plasma homocysteine*	Annually	
Alpha-fetoprotein	Annually	
If receiving treatment with givosiran Total plasma homocysteine Vitamin B6, B9, B12 Liver function tests Renal function tests	Monthly for the first 3 months Then, every 3 - 6 months	
If receiving prophylactic hemin therapy Ferritin with iron studies	Every 3 months	
Monitoring by complementary methods of diagnosis and therapy		
Brain magnetic resonance imaging	If clinically indicated or annually in symptomatic patients or with recurrent attacks	
Electromyography	Annually or if clinically indicated	
Holter monitoring	Annually	
TILT test	Annually	
Abdominal ultrasound	Annually	
Renal ultrasound	Annually	
Ambulatory Blood Pressure Monitoring	Annually	
Echocardiogram	Annually	
If receiving GnRH analogue Dual-energy X-ray absorptiometry Gynecological screening	 Annually Annually	
Asymptomatic patients (no attacks within the last 2 years) should be monitored annually		

* If homocysteine persistently elevated perform genetic test for homocystinuria

Centro Hospitalar e Universitário do Porto.[88] The RC-IMDs provide an initial porphyria screening, which includes assessment of PBG, ALA, and urinary porphyrins. For complete and accurate biochemical and genetic testing, the samples should be sent to Unidade de Rastreio Neonatal, Metabolismo e Genética (URN) - Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA, Porto).

Patients with acute porphyria should be followed by a core multidisciplinary team with an internist or pediatrician, neurologist, psychiatrist, and dermatologist. Additional

support may be required from a nephrologist, cardiologist, gastroenterologist, geneticist, gynecologist and/or hematologist. Social care support, a psychologist, and a nutritionist should also be involved in patient care. All healthcare team members should have a solid background in porphyria.

An online database is currently being developed for the epidemiological registry of patients with acute porphyrias in Portugal. For additional information on this database and how to register acute porphyria patients, use the following email address: registonacionaldasporfirias@outlook.pt.

CONCLUSION

Given the rarity of acute porphyrias and their heterogeneous and often non-specific presentation, patients remain undiagnosed or misdiagnosed with other medical conditions. A delay of several years usually occurs between symptom onset and the diagnosis. Therefore, increasing awareness of acute porphyrias among healthcare professionals is essential for making an earlier diagnosis and initiating rapid and accurate treatment. In addition, new evidence on breakthrough therapies is emerging. In this consensus paper, guidance is provided for a timely diagnosis of acute porphyrias, as well as evidence-based recommendations for the treatment and monitoring of patients and their families.

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AUTHOR CONTRIBUTIONS

LBA: Coordination of the project, study design, and writing of the manuscript.

LP, AO, FiF, PF, ICR, EC, FaF, AAP, PM, SM: Study design and writing 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.

COMPETING INTERESTS

All authors declared that Alnylam Pharmaceuticals provided financial support to Sociedade Portuguesa de Medicina Interna (SPMI) for the medical writing of this manuscript.

LBA received honoraria for lectures, presentations, and for acting as a speaker, and support for attending meetings and/or travel from Alnylam Pharmaceuticals, Sanofi and Takeda. LP received honoraria for acting as speaker and moderator at events sponsored by Sanofi Genzyme, Eusa Pharma, and SPMI; received support for attending meetings and/or travel from Sanofi Genzyme; participated in an advisory board for Eusa Pharma; has non-profitable positions as a coordinator of Núcleo de Estudos de Doenças Raras (NEDR) of SPMI and as a director of the Rare Awareness Program, NEDR.

AO received grants or contracts, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events, and support for attending meetings and/or travel from Amicus and Sanofi; participated in an advisory board for Gilead.

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Carta ao Editor Referente a "Atitudes, Conhecimentos e Perspetivas dos Médicos Portugueses acerca das Terapêuticas Não Convencionais: Um Estudo Transversal"

Letter to the Editor Concerning "Attitudes, Knowledge and Views of Portuguese Physicians Regarding Complementary and Alternative Medicine: A Cross-Sectional Study"

Palavras-chave: Médicos; Portugal; Terapias Complementares
Keywords: Complementary Therapies; Physicians; Portugal

Caro Editor,

Nogueira *et al*, no artigo "Atitudes, Conhecimentos e Perspetivas dos Médicos Portugueses acerca das Terapêuticas Não Convencionais: Um Estudo Transversal"[1] publicado em maio de 2022 na Acta Médica Portuguesa, onde foram analisadas as respostas de 4334 médicos em Portugal, observaram que quase metade da amostra não se sente confortável em abordar as terapêuticas não convencionais com os doentes.

Na minha perspetiva, este resultado pode indicar não apenas uma lacuna de conhecimento e treino dos médicos nas terapêuticas não convencionais, conforme referido por Nogueira *et al* na discussão do seu artigo,[1] mas também pode ser interpretado como sinal de falta de confiança ou de incerteza nas terapêuticas não convencionais, pois a maioria da amostra (72,4%) acredita que estas não deviam ser incluídas no Serviço Nacional de Saúde português.

Os médicos portugueses estudados podem ter adotado esta abordagem cautelosa devido à perceção da limitada evidência científica robusta sobre a eficácia e segurança das terapêuticas não convencionais, e cujas recomendações algo inconsistentes do National Institute for Clinical Excellence (NICE), entidade conhecida pela sua independência e rigor, não tornam mais claro.[2] Consequentemente, os médicos podem sentir que existe a necessidade de estudos mais robustos sobre as terapêuticas não convencionais antes de as abordarem com os doentes.

A literatura recente aconselha que para além das evidências de segurança, eficácia e relação custo-efetividade, se considerem fatores como o impacto da doença, magnitude do efeito, utilização atual, bem como a procura, equidade e facilidade de integração antes de se emitirem recomendações clínicas sobre terapêuticas não convencionais.[3] A atual ausência destes fatores nas recomendações também pode ter sido um motivo para os médicos se sentirem desconfortáveis ou evitarem abordar as terapêuticas não convencionais com os doentes, seguindo os princípios da medicina baseada na evidência (MBE). Outra causa possível poderá ser a presença na amostra de uma visão mais conservadora em relação aos cuidados de saúde, que prefere as terapêuticas convencionais em detrimento das não convencionais. As crenças individuais dos médicos sobre a eficácia de cada uma das terapêuticas não convencionais e a distinta evidência científica entre estas também podem ter influenciado a sua abordagem, pois no estudo de Nogueira *et al*[1] foi observado algum nível de apoio em relação a uma das terapêuticas, a acupuntura.

Por último, é conhecida a escassez de tempo de consulta que os médicos têm para cuidar dos seus doentes,[4] situação que pode desencorajar os médicos a envolverem-se em extensas discussões sobre terapêuticas não convencionais.

Nogueira *et al* finalizam o seu artigo[1] preconizando que se continue a estudar a visão dos médicos e dos doentes sobre as terapêuticas não convencionais, opinião que partilho.

Futuros estudos qualitativos serão necessários para examinar as razões subjacentes às atitudes em relação às terapêuticas não convencionais em Portugal.

CONFLITOS DE INTERESSE

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

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Determinantes Comerciais da Saúde: Um Desafio a Considerar no Contexto Nacional em Portugal

Commercial Determinants of Health: A Challenge to Consider at the National Level in Portugal

Palavras-chave: Comércio; Determinantes Sociais da Saúde; Saúde Pública
Keywords: Commerce; Public Health; Social Determinants of Health

Os determinantes comerciais da saúde são definidos, num artigo publicado na revista *The Lancet* que integra um conjunto de artigos sobre o mesmo tema, como os "sistemas, práticas e vias através dos quais os atores comerciais influenciam a saúde e a igualdade".[1] Essa influência pode ser exercida diretamente, através da venda e consumo de produtos nocivos, como o tabaco, ou, indiretamente, através de, por exemplo, técnicas de influência em políticas regulatórias da indústria do tabaco, que têm sido extensamente estudadas.

Internacionalmente, tem havido um aumento do reconhecimento da importância de explorar como os determinantes comerciais afetam a saúde e o aumento das desigualdades, e de como melhor proteger a saúde das populações e do planeta neste contexto. Este reconhecimento vem também espelhado em várias iniciativas da Organização Mundial da Saúde (OMS). Em 1981 foi instituído o Código Internacional do Marketing para substitutos do leite materno[2] e em 2010 a OMS coproduziu um guia para profissionais de saúde sobre o *marketing* da indústria farmacêutica.[3] Em 2003, a Convenção-Quadro da OMS para o Controlo do Tabaco foi introduzida, cobrindo agora 90% da população mundial.[4]

Os determinantes comerciais da saúde têm sido pouco investigados na área académica e científica em Portugal. Existem publicações sobre as indústrias do álcool[5] e tabaco,[6] mas destaca-se a necessidade de aprofundar esta evidência e expandi-la para outras indústrias.

Em novembro de 2022, com vista a contribuir para a discussão a nível nacional, teve lugar o *workshop* "Determinantes comerciais - do contexto internacional à intervenção local" no âmbito do III Congresso Nacional dos Médicos de Saúde Pública, organizado pela Associação Nacional dos Médicos de Saúde Pública (ANMSP). O *workshop* teve como objetivo a introdução à temática, partindo da evidência internacional e nacional para a identificação e debate dos exemplos observados a nível profissional. Os participantes debateram estratégias e boas práticas a adotar, bem como os principais desafios que se colocam à sua implementação.

Face à importância do tema, propôs-se que a temática dos determinantes comerciais de saúde fosse aprofundada pela ANMSP, com o intuito de produzir recomendações específicas para a ação institucional e profissional. Este trabalho encontra-se em desenvolvimento. Contudo, destacam-se as recomendações já emanadas do trabalho conduzido pela série temática de artigos publicadas na revista *The Lancet*, nomeadamente: 1) chamar a atenção para o assunto; 2) encorajar a ação; 3) envolver os profissionais de saúde; 4) investir e desenvolver investigação, e construir capacidade na área dos determinantes comerciais da saúde.[7] Com este artigo pretendemos dar resposta ao primeiro ponto, estando em curso iniciativas para também dar resposta aos restantes.

CONTRIBUTO DOS AUTORES

MP: Conceptualização e redação do manuscrito.

ABN, AL, SC, MM: Conceptualização e revisão crítica do manuscrito.

CONFLITOS DE INTERESSE

ABN é vice-presidente da Associação Nacional dos Médicos de Saúde Pública.

AL é membro suplente da direção da Associação Nacional dos Médicos de Saúde Pública, membro efetivo da Comissão Técnica de Vacinação, e recebeu pagamentos ou honorários da Pfizer para palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educativos.

MM recebeu uma bolsa de investigação (ARPP-2020-002) do Health Research Board, Irlanda; recebe direitos de autor do livro *Big Food & Cie* publicado pela Editions Thierry Souccar; recebeu honorários de consultoria da Pan American Health Organization (PAHO)/ Regional Office of the WHO, Global NCD Platform, Office of the Deputy Director-General, World Health Organization (WHO), Global Health Advocacy Incubator (GHAI)/ The University Of North Carolina at Chapel Hill (UNC), USA, da Universidade do Ghana, financiada pelo International Development Research Centre (IDRC), Vital Strategies, The Nutrition Coalition, USA, US Right to Know, USA; recebeu pagamentos por palestras da UniLaSalle Beauvais, França.

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Disfluências e Gaguez: Uma Perspetiva dos Cuidados de Saúde Primários

Stuttering in Children: A Primary Health Care Perspective

Palavras-chave: Criança; Cuidados de Saúde Primários Gaguez; Intervenção Educacional Precoce; Perturbações da Linguagem
Keywords: Child; Early Intervention, Educational; Primary Health Care; Speech Disorders; Stuttering

Caro Editor,

Foi com grande interesse que lemos o artigo publicado na Acta Médica Portuguesa intitulado "Disfluências e Gaguez: Revisão e Critérios de Referenciação".[1]

Durante o desenvolvimento do discurso podem surgir dificuldades no controlo preciso do sistema motor da fala, o que pode causar variações da fluência, tais como a gaguez, que pode a longo prazo influenciar negativamente a aquisição de competências sociais, académicas e emocionais da criança,[2] com consequente impacto na família.[3] De acordo com o trabalho de Yairi e Ambrose,[4] a prevalência desta condição na população em geral é de 1%. Na unidade de saúde em que trabalhamos, a prevalência total da rubrica 'P10 Gaguejar, balbuciar, tiques' (de acordo com o sistema de classificação ICPC-2, usado pelos médicos de família no Serviço Nacional de Saúde) é de 0,21%.

O médico de família (MF), como primeiro ponto de contacto com o sistema de saúde, desempenha um papel importante na identificação e diagnóstico precoce das perturbações da comunicação e linguagem (PCL), bem como na orientação do doente e na referenciação para profissionais especializados sempre que for necessário.[5] Além disso, a sua posição de proximidade com os seus doentes permite-lhe monitorizar, acompanhar e participar no plano terapêutico, tendo por base uma abordagem holística centrada na criança e nos seus contextos.

Este artigo constitui uma ferramenta para a prática clínica do MF, apresentando de forma clara as diferenças entre gaguez e disfluência, fatores de risco para o desenvolvimento de PCL, meios complementares de diagnóstico e conselhos a fornecer aos pais destas crianças.[1]

Gostaríamos de destacar uma problemática de grande importância: o reduzido número de referenciações aos serviços de intervenção precoce, nomeadamente o Sistema Nacional de Intervenção Precoce na Infância (SNIPI).[3] Tal poderá dever-se a barreiras na avaliação formal das PCL nas consultas de saúde infantil e juvenil, ao reduzido tempo das mesmas, a lacunas de conhecimento do diagnóstico e processo de referenciação, lentidão do processo, falta de recursos humanos e a atitude dos próprios pais ou tutores.[3] Por outro lado, é frequente, na prática, que os critérios de referenciação locais variem, o que poderá levar a diferentes abordagens das PCL. Assim, cremos que seria relevante uma avaliação crítica das limitações da orientação precoce, com vista à sua resolução e à uniformização dos critérios de referenciação mencionados neste artigo.[1]

O diagnóstico precoce e a intervenção adequada nas PCL são essenciais para fornecer suporte às crianças e respetivas famílias. Consideramos que este artigo constitui um ponto de partida para futura investigação, adequação de estratégias institucionais e implementação de práticas que otimizem o processo de referenciação de crianças com PCL a partir dos cuidados de saúde primários.

CONTRIBUTO DOS AUTORES

CP, SN: Conceptualização, pesquisa, redação, e aprovação final do manuscrito.

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O Envolvimento do Público e dos Doentes na Investigação nos Cuidados de Saúde Primários em Portugal é a 17.ª Estratégia

The Involvement of the Public and Patients in Research in Primary Health Care in Portugal is the 17th Strategy

Palavras-chave: Avaliação de Programas; Cuidados de Saúde Primários; Investigação; Investigação em Serviços de Saúde; Portugal
Keywords: Health Services Research; Portugal; Primary Health Care; Program Evaluation; Research

Caro Editor,

No artigo "Estratégias para a Promoção da Investigação nos Cuidados de Saúde Primários em Portugal: Um Estudo Qualitativo"[1] publicado *ahead of print* na Acta Médica Portuguesa, Morgado *et al* nomearam 16 estratégias para promover a investigação nos Cuidados de Saúde Primários (CSP) em Portugal, com base nas opiniões de 12 médicos e dois decisores. Esta lista de estratégias abrange um vasto leque de aspetos importantes para promover a investigação nos CSP portugueses.

Como médico de família, investigador nos CSP e pertencente à área geográfica da Administração Regional de Saúde do Centro, região pouco representada no estudo, da qual só um elemento entrevistado foi incluído, gostaria de acrescentar uma 17.ª estratégia, que não foi identificada no trabalho de Morgado *et al*[1]: o envolvimento do público e dos doentes nos estudos clínicos nos CSP, em todas as suas fases (desenho, condução e disseminação),[2] tal como previamente defendido por investigadores, comunidades, agências reguladoras e entidades financiadoras.[3] Este envolvimento pode ajudar a criar um maior apoio para as iniciativas de pesquisa e conduzir ao seu sucesso (e.g., através da identificação e recrutamento de participantes elegíveis para a amostra),[4] promover uma cultura de valorização da pesquisa nos CSP na sociedade, e deste modo contribuir para a diminuição da hesitação da população em participar em investigação, com a construção de parcerias e confiança entre os investigadores e a sociedade.[4] O envolvimento do público e dos doentes na investigação também será importante para aumentar a consciencialização da sociedade sobre a importância da realização de investigação em ambiente de CSP e sobre o impacto desta na melhoria das unidades de saúde e nos resultados em saúde.

Além da importância de incentivar o envolvimento da comunidade na investigação, não deve ser esquecida a igual importância da comunicação dos resultados da pesquisa de uma forma acessível e compreensível para o público em geral, para que estes se traduzam num real benefício para a comunidade estudada.

É ainda relevante reconhecer que, embora a estratégia de envolver o público e os doentes nos estudos clínicos nos Cuidados de Saúde Primários (em todas as suas fases) seja importante, a sua implementação exigirá a superação de vários desafios, tais como obstáculos burocráticos, recursos limitados e barreiras socioculturais. Como tal, só uma abordagem proativa destes obstáculos (e daqueles enunciados na discussão dos resultados no estudo de Morgado *et al*[1]) promoverá efetivamente a investigação nos Cuidados de Saúde Primários em Portugal.

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Transforming Healthcare: Prioritizing Psychological Trauma through Trauma-Informed Care

Transformar os Cuidados de Saúde: Priorizar o Trauma Psicológico através de Cuidados Informados sobre o Trauma

Keywords: Adult Survivors of Child Abuse; Adverse Childhood Experiences; Mental Disorders
Palavras-chave: Experiências Adversas da Infância; Perturbações Mentais; Sobreviventes Adultos de Maus-Tratos Infantis

Psychological trauma is a significant public health concern with long-lasting effects on physical and mental well-being. According to the Substance Abuse and Mental Health Administration, a public agency within the U.S. Department of Health, trauma refers to the impact of harmful or life-threatening events on an individual's overall health and functioning. This concept includes personal, interpersonal (such as childhood abuse, neglect, and household dysfunction), and collective trauma (such as racism, stigma, oppression, and genocide).[1]

Trauma-informed care (TIC) is an approach to healthcare that acknowledges the prevalence and impact of trauma in society. Research shows a strong correlation between adverse childhood experiences and various health risks in adulthood, including alcoholism, drug abuse, depression, and chronic diseases.[2] Trauma-informed care seeks to understand how past trauma and social contexts influence patients' health and behavior. It acknowledges that extreme behaviors often stem from coping adaptations to traumatic experiences, and it aims to actively prevent re-traumatization by anticipating and avoiding practices that could cause distress or resemble traumatic experiences.[3]

Healthcare providers should recognize not only personal trauma but also the interpersonal, cultural, historical, social, political, and structural trauma affecting individuals and communities across generations. This recognition is particularly important in social and health services to prevent re-traumatization, especially among minority and vulnerable communities, such as the elderly. Examples of potential re-traumatization in healthcare settings include lack of empathy and sensitivity during medical encounters, inadequate communication and privacy during physical examination, invasive procedures without proper informed consent or sensitivity to the patient's needs, disregard for the patient's boundaries and preferences, and substandard hospital facilities, such as lack of quiet rooms or access to natural light. Trauma-uninformed practices also increase staff distress and can lead to vicarious trauma, which includes compassion fatigue, countertransference, and burnout.[4,5]

Trauma-informed care involves six key principles: safety, trustworthiness, peer support, collaboration, empowerment, and cultural considerations. Safety implies the need for a consistent, predictable, and supportive environment in the delivery of healthcare while trustworthiness emphasizes open communication and transparency between staff and patients. Peer support and collaboration involve creating opportunities for deeper mutual connections among staff and seeing patients as partners in developing treatment plans. Empowerment emphasizes patient's autonomy and choices, while cultural considerations recognize diverse

backgrounds and identities.[1]

These principles guide healthcare providers in creating an environment that fosters healing, safety, and empowerment. Implementing trauma-informed care requires training and ongoing commitment from healthcare organizations and professionals to ensure that these principles are consistently applied in practice.

PROTECTION OF HUMANS AND ANIMALS

The author 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.

COMPETING INTERESTS

The author has declared that no competing interests exist.

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