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Application of Artificial Intelligence in Healthcare: The Need for More Interpretable Artificial Intelligence

Aplicação de Inteligência Artificial em Cuidados de Saúde: A Necessidade de Mais Inteligência Artificial que Seja Interpretável

Jorge TAVARES✉[1]
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Keywords: Artificial Intelligence; Delivery of Health Care; Machine Learning
Palavras-chave: Aprendizagem Automática; Inteligência Artificial; Prestação de Cuidados de Saúde

INTRODUCTION

Understanding artificial intelligence (AI) and its different types is of the utmost importance for the application of this technology in healthcare.[1,2] Artificial intelligence is a field of knowledge which combines computer science and advanced statistics to support problem-solving.[3] It is divided in two sub-fields: machine learning (ML) and deep learning.[1] The ML concept resides in the ability of using computer algorithms that have the capability to recognize patterns and efficiently learn to train the model to predict, make recommendations or find data patterns.[1,3] After a sufficient number of repetitions and algorithm adjustments, the machine becomes capable to accurately predict an output.[1,3] Deep learning is a newer and more complex approach of AI that uses deep neural networks. The neural network starts with an input layer that then progresses to a variable number of hidden layers.[1] Since the algorithm uses multiple layers with deep neural networks, it can successively refine itself, without explicitly programmed directions.[1] It is a fact that, by using deep learning, the models usually achieve higher accuracy compared with ML. Still, when using ML, it is frequently possible to better understand which are the input variables that have more influence on the output variables.[4]

In both medical and clinical practices, it is often particularly relevant to understand why an AI technique is suggesting a certain classification or direction for a certain action.[1] Not only in healthcare but also in other fields of knowledge, explainable AI (also called XAI) is growing its influence.[4] The current European legal regulation, specifically the General Data Protection Regulation (GDPR), requires that automated models provide meaningful information about the rationale on how the algorithm operates.[4]

The goal of this article is not to provide an exhaustive view about all existing AI models and explainable AI, but instead to provide a summarized and easy to understand view of what should be considered when implementing AI in healthcare and in clinical practice.

Definition of explainable artificial intelligence

Most likely, the best way to start describing the goal of explainable AI is to use an example from the literature. The case that is described here is about the classification of patients with pneumonia.[5] When a patient was first diagnosed with pneumonia, the hospital (located in the USA) needed to make one critical decision early on: whether to treat the patient as an inpatient or an outpatient.[5] An AI/ML group of experts was tasked with building models to predict patient survival rates and identify which patients were at greatest risk, which could help the hospital triage new patients.[5] The result was a head-to-head of traditional ML models (logistic regression, rule-learning model, decision tree) and a neural network.[5] Among all the models tested, the neural network achieved the best accuracy at identifying and classifying the patients with the lowest survival rates.[5] The most obvious decision would be to use the neural network, but in the end it was not. Another researcher had been training a rule-based model on the same dataset. Rule based models are among the most easily interpreted ML models. They typically take the form of a list of 'if x, then y' rules, that are easier to be interpreted by humans.[5] During the verification of the rules a strange rule was identified. The rule read that if a patient had a history of asthma, then they had a lower risk of death and should be treated as an outpatient.[5]

Based on this strange and contradictory rule, the researchers decided to approach the physicians. The physicians said that the fact that the asthma patients had better survival rates was most likely because they immediately received high standards of care, and not only stayed immediately in the hospital but were also transferred to the intensive care unit.[5] Another issue was that the neural network model was also classifying the asthma patients as outpatients.[5] A major classification issue with serious consequences was therefore avoided because it was possible to comprehend the rule-based model. The same ability to

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comprehend how the neural network was classifying the patients was not available.[5] Explainable AI/ML should be accurate and robust and the models need to be transparent and comprehensible.[4] This means that it has to be possible to explain how the algorithm works, starting from the inputs, how the data is processed and what is the rationale on how the outputs are generated.[4]

Types of artificial intelligence and machine learning models concerning explainability.

Broadly, AI/ML models can be defined as being transparent or opaque/black box models.[4] For a model to be considered transparent it should follow into one or more of the three categories. The first category is simulatability, and it refers to the ability to be simulated by a human.[4] A good example of this type of models is the rule-based model explained in the previous section.[4] The second category is decomposability, and it denotes the ability to break down a model into parts.[4] Decision trees fall into this category.[3,4] The last category is the algorithmic transparency, and it is the ability to understand the way the model generates its output.[4] It is often only possible to inspect it through a mathematical analysis, which is still sufficient to validate it as transparent.[4] Some examples of the models that fall into this category are linear/logistic regression, and k-means clustering.[3,4] Opaque models lack these categories of transparency, and newer techniques are now being studied to provide explainability to them, which are still in their early stages of development.[4,5] Deep learning models are the most well-known example of this type of models.[3,4] Figure 1 shows the different types of models and their graphical outputs.

How to decide which models to implement

Healthcare deals with very specific and sensitive types of data and approaches topics of high complexity. An AI/ML model should not be implemented without the participation of a group of experts composed of healthcare

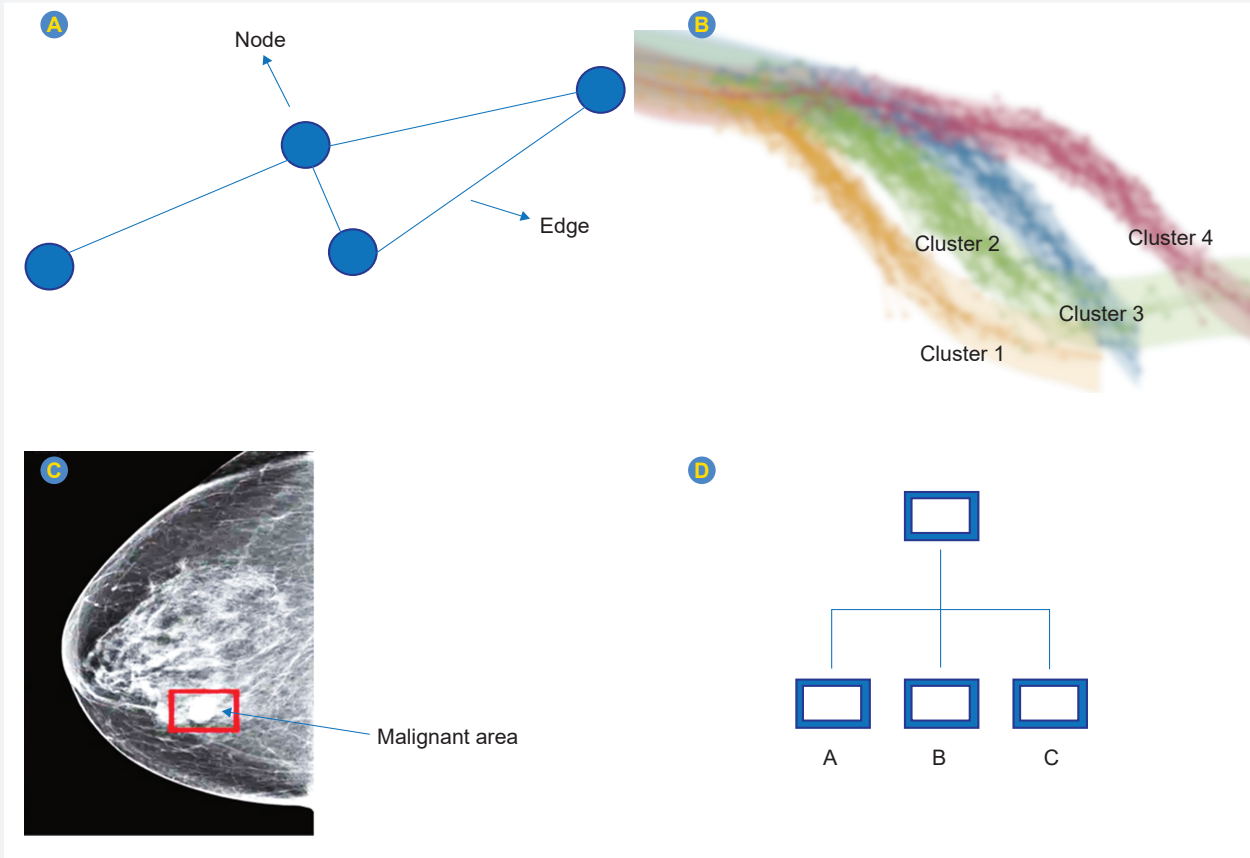

Figure 1 – AI/ML models with graphical capabilities that allow interpretation of results. ML graph, the model learns to make predictions based on the graph's structure and the attributes of nodes and edges (A). Mixture of Gaussian processes, that in this case aggregates patient disease progression trajectories into clusters using a non-parametric approach (B). AI computer vision models supported by attention plots that identify the relevant areas for disease diagnosis (C). Simple decision tree that following certain rules, can visually help to interpret the relevant parameters for class classification (D).

professionals, biostatisticians, data scientists, regulators and/or members of an ethics committee.[6-8] The European Union (EU) is working on specific legislation for AI: the EU AI Act.[4] It emphasizes that AI systems used in the EU should be transparent, safe, protect confidentiality, traceable, non-discriminatory and should be overseen by humans, rather than by automation, to prevent harmful outcomes.[4] Recent studies showed cases of risk of biased AI connected to specific ethnic groups, particularly the ones with lower socioeconomic strata.[8] This should be managed by including diverse groups in clinical studies and controlling the model outputs via interpretability.[8] The new EU AI legislation emphasizes the need of having explainable AI/ML models and using them as a first choice.[7] Still, it is important to understand how to choose which type of models to implement. In applications where explainability is relevant, it is of the utmost importance to use a transparent model (e.g.: treatment decision algorithm, algorithm to decide patient inclusion in a clinical trial).[2,4] But it is not always possible to solve problems using the simpler and/or more transparent approaches.[5,7,8] A second layer of options is to use models that may be more complex but still retain some ability to be understood. These models are called semi-opaque models, because they can provide feature importance (which variables are more important in our model to explain the problem we want to understand) and/or allow the extraction of rules or decision paths that explain how the model arrived at a particular prediction.[4,5,8] Examples of these valuable approaches are random forests, ML graphs with visual interpretation, gradient-boosted trees and Mixture of Gaussian processes in combination with a clustering approach.[4,5,8,9] A recently published article using the Mixture of Gaussian process with a clustering approach, which is a method sustained by a robust statistical approach, showed potential superiority to analyze disease progression in patients with amyotrophic lateral sclerosis compared with more traditional parametrical approaches like Kaplan-Meier curves.[9] In cases where high accuracy is required and other alternatives do not show good results, the use of an opaque model may be justified (e.g.: tumor detection in MRI using deep learning networks).[4] The European Medicines Agency (EMA) published on July 10, 2023, a reflection paper on the use of AI/ML in drug development.[7] Fig. 2 provides an overview on how the EMA approaches the application of AI in healthcare and clinical practice.

CONCLUSION

The increase in the usage of AI in healthcare poses questions about how these algorithms work and how transparent they are. Therefore, it is of the utmost importance to develop explainable AI/ML in healthcare. The EU is developing new AI legislation that emphasizes the need of having transparent models. The decision to implement a certain type of AI/ML model should take into consideration not only the need of being able to explain what the model does, but it should also consider specific legislation and ethical concerns. Explainable AI/ML frequently relies on statistical models, and there is an opportunity to bridge it

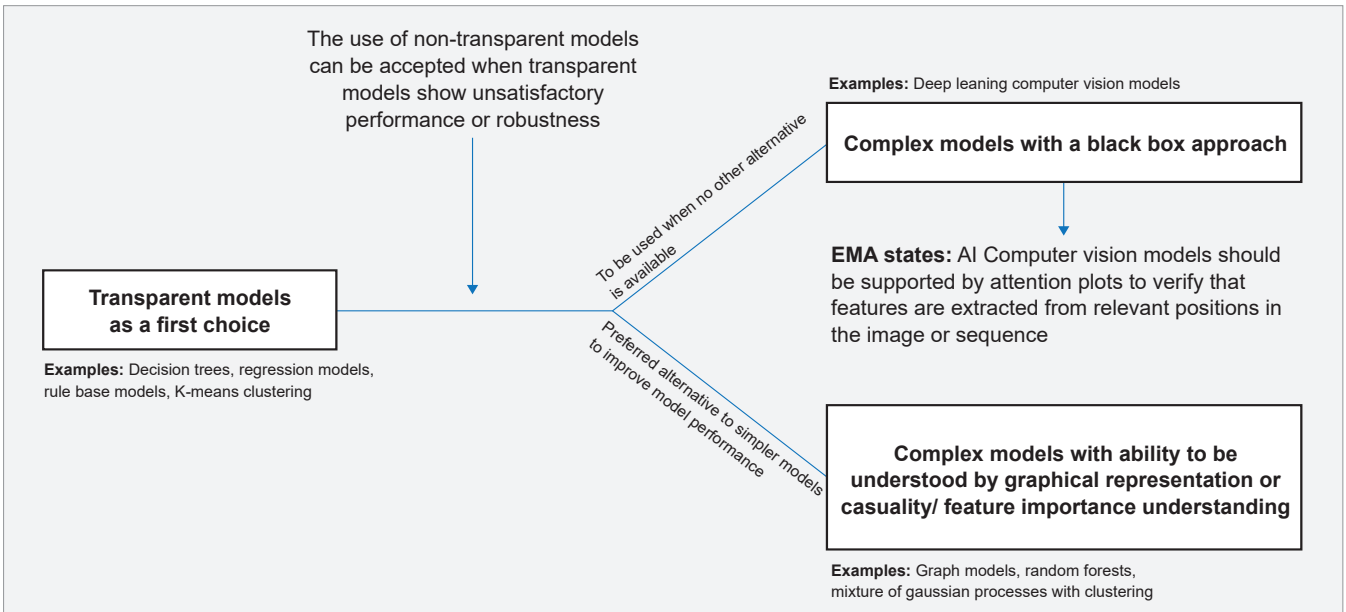

Figure 2 – Decision flow about selecting AI/ML models following the latest guidance from EMA that favors interpretable models as the first approach. SHAP and/or LIME analyses are also recommended by EMA.

with Biostatistics in order to increase the knowledge that we can obtain from research studies. The new EMA reflection paper requires that AI should be implemented considering the principles of Biostatistics guidelines.[7] Due to the high complexity of AI/ML in healthcare, multidisciplinary teams should include healthcare professionals during the development stage of the AI model algorithm, to ensure that the model meets the clinical and ethical requirements.

COMPETING INTERESTS

The author has declared that no competing interests exist.

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Processos de Apreciação Ética como Barreira à Investigação nos Cuidados de Saúde Primários: Reflexão sobre a Submissão de um Estudo Multicêntrico

Ethical Review Processes as a Barrier to Research in Primary Healthcare: Reflection on the Submission of a Multicenter Study

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Palavras-chave: Comissão de Ética; Cuidados de Saúde Primários; Investigação Biomédica; Medicina Geral e Familiar
Keywords: Biomedical Research; Ethics Committees; General Practice; Primary Health Care

INTRODUÇÃO

A apreciação ética de projetos de investigação desempenha um papel fundamental na salvaguarda dos princípios morais, jurídicos e científicos, bem como no respeito pelos direitos humanos no contexto da investigação em saúde. Esta prática assegura que os projetos de investigação sejam realizados de acordo com padrões éticos rigorosos, evitando danos físicos, psicológicos ou sociais aos participantes envolvidos. Além disso, a avaliação ética garante a validade e a integridade dos resultados dos estudos, pois ajuda a evitar vieses ou distorções que poderiam surgir de práticas antiéticas. A confiança pública na comunidade científica também é fortalecida quando os projetos de investigação são conduzidos de maneira ética, promovendo a transparência, a responsabilidade e a credibilidade das descobertas científicas.[1]

A produção científica desempenha um papel fundamental no avanço do conhecimento médico e na melhoria da qualidade dos cuidados de saúde sendo importante a criação de estruturas capazes de se adequarem à necessidade de apoiar, criticamente, estudos que, em última análise permitam a melhoria dos resultados em saúde quando se tratam doentes do mundo real.[1,2]

As Comissões de Ética desempenham papel fundamental neste âmbito, sendo para tal necessário, segundo a regulamentação portuguesa vigente, a sua aprovação, para homologação pelas entidades diretivas, existindo, à data do caso presente, uma por administração regional de saúde (ARS), unidade local de saúde (ULS) e serviço regional de saúde.[1,2]

As comissões de ética para a saúde (CES) das ARS têm-se desenvolvido no sentido de promover a investigação com qualidade nos Cuidados de Saúde Primários (CSP) e estão regulamentadas.[1,3] No entanto, a submissão de protocolos de projetos de investigação multicêntricos a várias CES pode representar uma barreira à investigação nos CSP em Portugal.[4,5]

O Decreto-Lei n.º 21/2014, prevê a criação de uma plataforma informática nacional para facilitar o processo de submissão e a formação da Rede Nacional de Comissões de Ética para a Saúde (RNCES),[1,6] uma medida para promover a padronização e a simplificação das submissões, otimizando a colaboração entre as CES e os investigadores, mas que apesar de regulamentada,[3] nunca chegou a ser implementada. O artigo 4.º do decreto-Lei n.º 80/2018 vem enfatizar o papel e importância da RNCES. Esta legislação prevê ainda a emissão de parecer pelas CES em 30 dias.[1]

A 1 de janeiro de 2024, foi implementada uma nova organização no Serviço Nacional de Saúde com a divisão em unidades locais de saúde, que congregam as unidades de CSP e as diversas unidades hospitalares públicas. Neste processo, com a extinção programada das diferentes ARS, é ainda incerto (à data de redação deste artigo) o destino das diferentes CES destas estruturas. Ainda mais desconhecido é o modo de atuação e articulação entre as diferentes CES, que se antevê que tenham o âmbito de ULS.

No presente trabalho procede-se à análise dos desafios enfrentados pelos investigadores no processo de submissão de um protocolo de estudo de âmbito nacional às diferentes CES. Este artigo reflete a perspetiva dos autores

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quanto às dificuldades sentidas e às propostas que realizam para a otimização das condições logísticas e organizacionais, sem desmerecer o esforço dos profissionais das distintas comissões de ética para a saúde em Cuidados de Saúde Primários. Os investigadores enfrentaram desafios ao submeter o seu protocolo a múltiplas CES, em diferentes regiões e ULS. Destacam-se a burocratização, a falta de padronização dos diversos modos de submissão, os diferentes documentos necessários com diferentes solicitações de informação e os tempos de apreciação desconformes, que dificultam e atrasam o processo de aprovação.

O suscitar de possíveis soluções para melhorar o processo de submissão de protocolos de investigação nos CSP em Portugal é importante, pelo que os autores apresentam uma descrição reflexiva sobre o tema.

Relato de submissão às CES de um protocolo de estudo de âmbito nacional

Descreve-se o processo de submissão de um protocolo de um estudo observacional, transversal, que envolveu a aplicação de um inquérito a nível nacional cujo objetivo principal era a caracterização da investigação em CSP, em Portugal. Visto tratar-se de um estudo a nível nacional e com todos os profissionais de saúde a exercer funções em CSP como público-alvo, a amostra pretendida previa a obtenção de, pelo menos, 200 respostas por grupo profissional e por região. Na Tabela 1 encontra-se detalhado o processo de submissão às diferentes CES.

Tabela 1 – Processo de submissão às diferentes Comissões de Ética para a Saúde (anonimizadas) (secção inicial)

CES (Submissão inicial)	Contactos subsequentes	Parecer final
1 (26 de julho 2022)	28 de julho: Contacto a solicitar a submissão das declarações dos diferentes Diretores Executivos, foi também solicitado que fossem retificados os anexos e que fosse anexado um documento PDF com o inquérito, e documentos separados com cronograma e orçamento. (incluídos no documento do protocolo) 2 de agosto: Resposta da equipa a solicitar escusa de autorização prévia por inviabilidade do pedido e submissão dos documentos requeridos. 29 de agosto: Contacto a informar que o estudo estava incluído na Ordem de Trabalhos da reunião do dia 13 de setembro e que faltava a declaração do Orientador do Estudo. - Apesar de o projeto ter iniciado de forma integrada com um projeto de doutoramento, o trabalho em questão conta com uma equipa alargada, sem relação com o projeto de doutoramento. Além do exposto, a declaração de Orientação é solicitada no sentido de garantir a exequibilidade do projeto. A formação em metodologias de investigação apresentada nos CV dos Investigadores Principais pressupõe capacidade metodológica para a realização de um estudo da natureza proposta (observacional, transversal, analítico), contando ambos com experiência clínica e de investigação na área que suportam. Ainda assim a ARS não prescindiu desta declaração, pelo que o documento solicitado foi remetido no dia 14 de setembro, embora com atraso por estar dependente de terceiros ao projeto, tendo contribuído para um atraso de um mês na apreciação do projeto.	13 de outubro
2 (26 de julho 2022)	Necessário reformular a informação enviada de acordo com o formulário próprio da CES;	28 de outubro
3	16 de setembro: Parecer intermédio favorável condicionado a esclarecimentos sobre o processo de confidencialidade de dados.	4 de novembro
4 (26 de julho 2022)	2 de agosto: Necessário reformular a informação constante na declaração de Investigador Principal de acordo com o formulário próprio da CES; - Indicação para submeter a documentação a outras CES existentes no na região 13 de outubro: Contacto telefónico a informar que para a realização do estudo será necessário o parecer prévio da diretora executiva e a solicitar esclarecimento de questões éticas relativamente ao estudo. Os esclarecimentos e pedido de autorização para a Diretora Executiva seguiram no mesmo dia e a autorização pela Diretora Executiva foi enviada no dia 26 de outubro.	Não emitiu parecer até ao momento

(continua)

Tabela 1 – Processo de submissão às diferentes Comissões de Ética para a Saúde (anonimizadas) (secção final)

CES (Submissão inicial)	Contactos subsequentes	Parecer final
5 (26 de julho 2022)	29 de julho: Necessário reformular a informação enviada de acordo com o formulário próprio da CES e dois CV que estavam em falta; 2 de agosto: A equipa enviou o formulário preenchido, embora desformatado, por incompatibilidade de versões do *software* Microsoft Word utilizadas; 23 de agosto: A ARS informou que o acesso ao *link* com o inquérito apresentava um erro e que tinham recriado o inquérito a partir das variáveis, tendo sido necessário reformatar o formulário de submissão. Informou também que não existia possibilidade de prescindir da autorização das diferentes direções executivas dos ACeS, visto que os profissionais trabalham nos ACeS e serão contactados através dos mesmos. Mais informou que o pedido de autorização para os diferentes ACeS seguiria diretamente através da CES. Neste processo, o relator informou a IP que tinha perdido meio dia a reformatar o formulário (algo que já tinha custado várias horas à equipa de investigação).	4 de outubro Parecer favorável com autorização dos diferentes Diretores Executivos para divulgação internamente
6 (2 de agosto)	4 de agosto: Email a informar que bastaria aprovação da CES da ARS para que o estudo fosse aplicado na região.	
7 (2 de agosto)	1 de setembro: Deliberação da Comissão de Ética de 22/08/2022: "Apreciada a documentação a CE deliberou por unanimidade de voto de todos os membros presentes, convidar a requerente a submeter para apreciação toda a documentação em falta, Mais deliberou: informar a requerente que o estudo carece ainda de autorização por parte do Conselho de Administraçãoda ULS." Deliberação do Conselho de Administração de 31/08/2022 "Deverá a requerente ser informada do teor do parecer da CE. Posteriormente o CA poderá autorizar, devendo ser os resultados depois apresentados na ULS." Na sequência desta informação a IP reencaminhou, no mesmo dia, os documentos enviados e adicionou declaração de Orientador através do formulário constante na página da ARS e solicitou informação relativamente a quais documentos estariam em falta. A equipa de investigação não obteve resposta até à data.	
8 (2 de agosto)	Parecer favorável a 8 de setembro	
Documentação enviada na submissão inicial: - Requerimento à CES para apreciação; - Termo de responsabilidade do Investigador Principal de acordo com a declaração de Helsínquia; - Protocolo de Investigação completo; - Declaração de Conflitos de Interesse da equipa; - Curricula da equipa (CV); - Declaração de propriedade de dados e compromisso de entrega de relatório final à CES; - Formulário para o inquérito.		

Constrangimentos regionais na implementação e disseminação do estudo

Posteriormente, surgiram barreiras adicionais relacionadas com a distribuição do convite para resposta ao inquérito pelas diferentes ARS e ACeS, com muitos agrupamentos a exigir o preenchimento de formulários próprios para avaliação local. Devido a essas variações no protocolo e nos formulários, a equipa teve de adaptar a informação em 32 ocasiões para concretizar a submissão a nível nacional.

Discussão e conclusão

A heterogeneidade dos requisitos e procedimentos das CES em CSP, incluindo as de ULS, representa um desafio importante de trabalho, quando se pretende realizar um estudo multicêntrico e com representatividade nas várias regiões do país.

A falta de padronização e uniformidade nas submissões dificulta a aprovação em tempo oportuno dos protocolos, resultando em trabalho adicional tanto para as CES como para as equipas de investigação. A burocracia excessiva e os atrasos no processo de aprovação dificultam a realização de investigação e, em última análise, a promoção da inovação e melhoria dos serviços de saúde.

Este caso exemplifica as dificuldades encontradas durante o processo de submissão do protocolo de um estudo observacional transversal a nível nacional, destacando as diferentes exigências e obstáculos impostos pelas diferentes CES, resultando em atrasos e incertezas na aprovação.

O processo de submissão às CES em CSP em Portugal e mesmo nas Regiões Autónomas deve ser repensado e aprimorado, especialmente tendo em conta o paradigma atual que contempla a subdivisão das administrações regionais de saúde em múltiplas ULS. Embora a criação da plataforma informática nacional proposta pelo Decreto-Lei n.º 21/2014 e a formação da Rede Nacional de CES sejam passos positivos, é necessário avançar para a sua operacionalização efetiva, melhorando procedimentos. Compreende-se que a presença de CES em ARS, ULS e Regiões Autónomas pode dar origem a particularidades de observação, mas limita, contudo, os estudos multicêntricos. A criação de uma entidade centralizada poderia resolver essa questão, mas potencialmente implicaria atrasos significativos devido ao extenso volume de trabalho e aos custos associados ao trabalho profissional centralizado, incluindo reuniões regulares envolvendo muitos elementos que precisariam de se deslocar. Alternativamente, seria necessário alocar tempo para essa função, que não se limita apenas à reunião, mas também envolve o estudo dos processos. Além disso, é importante considerar a profissionalização e a compensação adequada dos membros das CES, a fim de garantir a eficiência e agilidade na aprovação dos protocolos de investigação. Simplificar e padronizar esse processo beneficiará tanto os investigadores quanto a qualidade da investigação realizada nos CSP.

Um modelo possível de articulação pode/deve contemplar o reconhecimento tácito de parecer positivo por parte de uma CES, pelas estruturas homólogas das outras instituições, nomeadamente para prossecução de trabalhos de âmbito nacional, obviando-se assim a necessidade de submissão de um protocolo individualmente a cada CES.

Propomos o aproveitamento da reforma da organização dos cuidados de saúde para a reorganização das CES no sentido de simplificar procedimentos e facilitar a investigação multicêntrica em CSP em Portugal.

CONTRIBUTO DOS AUTORES

MGC, RR, GC: Redação do rascunho, revisão de literatura, revisão crítica do manuscrito.

LMS: Revisão de literatura, redação e revisão crítica do manuscrito.

Todos autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFLITOS DE INTERESSE

MGC e LMS são membros de uma Comissão de Ética em Saúde (CES).

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

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Ophthalmology Census 2021: A Demographic Characterisation of Ophthalmologists in Portugal

Estudo Demográfico da População de Oftalmologistas em Portugal: Censo de Oftalmologia 2021

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ABSTRACT

Introduction: Human resources in ophthalmology have recently received particular attention, and it has been questioned whether there is a sufficient number of workers. The aim of this study was to analyze and characterize Portugal's ophthalmologist population.

Methods: In this descriptive, cross-sectional study, an online questionnaire was sent to all ophthalmologists registered with the Portuguese College of Ophthalmology in December 2021. Information on the following variables was collected and analyzed: demographic factors, professional qualifications, professional activity, weekly professional activity and medium-term plans.

Results: Among the 910 registered ophthalmologists, a response rate of 64.7% was achieved. There were 0.9 ophthalmologists for every 10 000 inhabitants, 0.45:10 000 working in the public sector (0.35:10 000 full-time equivalent). Among the respondents, 57.6% were over 50 years old (59.6% male), 97.3% were Portuguese, 46.7% completed their residency in the Lisbon region, 27.3% complemented their programme with additional training, 9.5% had a PhD and approximately 58% lived and worked in large urban centres. Regarding professional activity, 58.5% of the respondents worked in the public sector (4.2% exclusively), while 67.9% worked in different economic sectors. The median number of weekly working hours reported was 45 hours, with those in the public sector reporting 35 hours. Private/social sector work and public sector work accounted for 12 926 hours/week and 10 808 hours/week, respectively. It was found that 31.4% of the respondents provided emergency medical services and that 52.8% performed surgical procedures more than once a week. Looking ahead, 38.7% of the ophthalmologists intended to reduce their workload within the next five years due to family reasons, fatigue and demotivation. The projected rate of retirement or cessation of activity in the next five years was estimated to be 1.7%, while an average of 20 new ophthalmologists are expected to enter the profession annually, resulting in a generational balance of 0.8%.

Conclusion: While the number of ophthalmologists in Portugal meets the international recommendations, there is a shortage in the public sector and most ophthalmologists work in large urban centres. The number of ophthalmologists in Portugal is expected to be stable for the next five years.

Keywords: Ophthalmologists/statistics & numerical data; Ophthalmology; Portugal; Surveys and Questionnaires

RESUMO

Introdução: Tem sido dada particular atenção aos recursos humanos na oftalmologia, questionando a sua adequação à realidade. O objetivo do estudo foi caracterizar a população de oftalmologistas em Portugal.

Métodos: Estudo descritivo e transversal realizado com recurso a um questionário aplicado *online*, à data de dezembro de 2021. O questionário desenhado analisou as seguintes variáveis: demografia, habilitações profissionais, atividade profissional ativa, atividade profissional semanal e planos a médio prazo.

Resultados: A taxa de resposta foi de 64,7% (de um total de 910 oftalmologistas inscritos). Existem 0,9 oftalmologistas para 10 000 habitantes; 0,45 colaboram com o sector público (0,35 para equivalente de tempo completo). Há 57,6% de oftalmologistas com mais de 50 anos (59,6% do sexo masculino) e 97,3% têm nacionalidade portuguesa. A formação específica em oftalmologia foi realizada na região de Lisboa em 46,7% dos casos, 27,3% complementaram o internato com formação adicional e 9,5% fizeram um doutoramento. Aproximadamente 58,5% residiam e trabalhavam nos grandes centros urbanos. A colaboração com o sector público acontecia em 58,5% (4,2% em exclusividade) e 67,9% acumulavam funções em diferentes setores económicos. A mediana global do horário de trabalho semanal é de 45 horas, sendo de 35 horas no público. Foram exercidas um total de 12 926 horas/semana e 10 808 horas/semana no setor privado/social e público, respetivamente. A atividade de urgência é desempenhada por 31,4% dos profissionais que responderam. A atividade cirúrgica é realizada mais do que uma vez por semana para 52,8%. No que aos planos a médio prazo (cinco anos) diz respeito, 38,7% dos inquiridos pretende reduzir o seu horário, sendo os principais motivos relacionados com a família, fadiga e/ou desmotivação. Estima-se, a cinco anos, que a taxa de saída por reforma/cessação de atividade seja de 1,7%, a taxa de entrada seja de 20 titulações/ano e o balanço geracional de 0,8%.

Conclusão: O número de oftalmologistas em Portugal está de acordo com as recomendações internacionais, no entanto, existe uma carência destes profissionais de saúde no setor público. A maioria dos oftalmologistas reside e exerce a sua atividade nos grandes centros urbanos. Prevê-se, a cinco anos, uma população de oftalmologistas estável.

Palavras-chave: Inquéritos e Questionários; Oftalmologia; Oftalmologistas/estatísticas e dados numéricos; Portugal

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INTRODUCTION

The sustainability and proper functioning of a healthcare system depend on there being an adequate number of professionals available to meet the population's needs over a given period.[1,2] To successfully manage the differentiated human resources within a healthcare system, it is essential to implement a training and (re)allocation strategy designed to deliver suitable medium- and long-term results. As such, the development of such a strategy requires a thorough understanding and analysis of existing resources and future needs.[3]

Recently released data indicates that Portugal ranks third among all Organization for Economic Co-operation and Development (OECD) countries in terms of doctors *per capita*.[4] However, when we look at the data for ophthalmologists *per capita*, Portugal (0.9:10 000) sits in ninth place in Europe, above Spain (0.89:10 000), France (0.88:10 000) and the United Kingdom (0.22:10 000).[5] Greece (2.8:10 000) and Cyprus (1.4:10 000) occupy the top spots on the list.[5]

In Portugal, the healthcare workforce, particularly in ophthalmology, is poorly characterized. Two studies were published about a decade ago that aimed to anticipate the demand for professionals. The studies were based on data from the Portuguese National Health Service (PNHS) and Statistics Portugal (SP) and primarily focused on the PNHS.[6,7]

In the National Strategy for Eye Care 2018, which was developed under the leadership of the Directorate General of Health, a ratio of 0.5 ophthalmologists per 10 000 inhabitants was recommended, based on current international guidelines.[8] Official data from the Central Administration of the Health System (CAHS) indicates that, in 2017, 471 ophthalmologists were working in the PNHS, and they accounted for 44% of all ophthalmologists registered in the Portuguese Medical Association (PMA). However, according to the National Strategy for Eye Care 2018, a deficit of 114 ophthalmologists in the PNHS was identified, assuming a standard 40-hour work week.[6]

It is important to note that healthcare systems and policies can vary significantly from country to country, as well as the practices of healthcare professionals and their employment models. Additionally, inconsistency in the monitoring and evaluation of human resources and the associated strategies makes it difficult to accurately compare human resources and strategic outcomes across nations.[1,3,9]

To reduce the obstacles preventing country-level comparisons, the World Health Organization has been taking steps to implement internationally standardized classifications.[9] The overall plan for assessing the human resources in healthcare involves obtaining reliable information on the size and composition of the healthcare workforce and identifying variations across spatial units (e.g., administrative districts, states, provinces or regions), demographic characteristics (e.g., age, sex, migration status) and other socioeconomic factors (e.g., educational attainment, income level, sector of activity).[3,9-15]

Therefore, it is vital to conduct in-depth studies that not only assess the number of ophthalmologists in the public and/or private/social sectors but also thoroughly characterize the existing resources. Hence, the purpose of this study is to fully characterize the existing human resources in terms of productive capacity, age segmentation, geographical distribution and areas of specific differentiation. The goal is to collect rigorous and standardized information, which, in turn, will allow accurate analysis of the current situation and estimation of future needs.[1,3,9,16]

The main goals of this study can be summarized as follows:

1. To characterize the population of Portuguese ophthalmologists in terms of demographics and professional differentiation.
2. To determine the professional activities of Portugal's ophthalmologist population, including the workload and employment status of ophthalmologists, as well as the economic sector(s) in which they work.
3. To gain insight into potential changes in Portuguese ophthalmologists' employment/retirement status and working hours within the next five years.

METHODS

The Portuguese College of Ophthalmologists (PCO) conducted a census in partnership with the Santarém Higher School of Management and Technology (SHSMT) to gather information about all the ophthalmologists working in Portugal.

Study design

A descriptive, cross-sectional study was conducted.

Study population

The study population consisted of all ophthalmologists who were registered with the PCO (N = 910) and whose fee payments were up to date at the time the questionnaire was administered (November 30, 2021).

Data collection instrument

The data collection instrument consisted of a well-structured questionnaire that could be self-completed by the respondents. The questionnaire was generated using the Survey Monkey tool [available through the Life Quality Research Center (CIEQV)], funded by the Foundation for Science and Technology, project no. UID/CED/04748/2020.

Variables

The questionnaire items were designed to collect information on the following variables:

- Demographics: age, sex, place of residence (Nomenclature of Territorial Units for Statistics 3), nationality.
- Professional qualifications: academic training, residency, differentiated training within the specialty, hospital medical career degree.
- Active professional activity: workplaces (Nomenclature of Territorial Units for Statistics 3), sectors in which professional activity is carried out (public, private/for-profit or social/non-profit), weekly workload, practice of emergency services, contractual regime.
- Weekly professional activity: schedule, clinical/surgical/non-clinical activity, areas of differentiation within the specialty (medical and surgical).
- Medium-term plans: intention to leave the public sector, retirement or cessation of activity.

Data protection and formal procedures

All formal procedures inherent to research of this nature were followed, with meticulous respect for data protection principles. The PMA's National Council approved the study protocol. The data were appropriately anonymized, and informed consent was obtained before data collection. The data will be stored for five years and then destroyed. Only those designated by the PCO's Board of Directors and SHSMT team will have access to the data.

Pre-test and data collection procedures

a) Pre-test: A pre-test was conducted with eight PCO members to assess the questionnaire's effectiveness. Subsequently, a focus group of six ophthalmologists (with similar characteristics to the subjects under study) provided feedback. Overall, the participants found the questions to be pertinent, the questionnaire concise and the number of items suitable. However, two questions required adjustment: 1) the options for training obtained after residency were clarified to mitigate different interpretations of the term fellowship and 2) redundancies in the questions about plans for the future were addressed.

b) Dissemination of the questionnaire: Various measures were taken to disseminate the questionnaire and encourage participation in the study. An initial email, sent in advance to all ophthalmologists on the PMA mailing list, explained the study's purpose and emphasized the importance of participation. The study was further promoted through emails from the PMA and the newsletter of the Portuguese Society of Ophthalmology (PSO). Additionally, the project was presented at the 64th Portuguese Congress of Ophthalmology in December 2021.

c) Application procedures: The questionnaire was made available on December 1st, 2021, through the Survey Monkey platform, and the link was sent via email from the PMA to all ophthalmologists on the PMA mailing list. To maximize reach, the link was also included on printed cards handed out at the aforementioned congress. To encourage a high response rate, reminders were sent via the PMA, PSO and PSO newsletter on three separate occasions. Furthermore, a text message was sent by the PMA close to the questionnaire submission deadline (February 14th, 2022).

Data treatment and analysis

Only fully completed questionnaires were considered eligible for analysis. Exploratory analysis was performed using descriptive analysis techniques (absolute and relative frequencies, means and standard deviations). SPSS software (version 21.0) was used for this purpose. The following pre-defined parameters were used in the analysis: age at the beginning of the activity = 27 years, age of retirement = 70 years and medium-term = five years. The SP 2021, PORDATA 2021, OECD 2021 and Statista 2021 databases were consulted to complement and contextualize the obtained information.[4,5,17,18]

RESULTS

From the 910 ophthalmologists who were registered with the PCO, we received 856 responses; hence, the response rate was 94.1%. However, only completed questionnaires were considered for analysis; this led to 29.2% being rejected, as per the pre-defined criteria. The final sample was composed of 589 individuals, resulting in a response rate of 64.7% and a maximum margin of error of ± 2.4% for a 95% confidence level.

Demographic factors

The number of ophthalmologists has increased by 161% over the 30 years prior to the time of the data collection; our results indicated that there were 0.9 per 10 000 inhabitants at the time of the data collection (Table 1). The average age of the ophthalmologists was 53.4 years (range = 27 - 86 years; aged over 50 years: 37.3% in the public healthcare system), and most were male (Table 1). The retirement/cessation of activity rate was estimated to be 1.7% over the next five years, and an average of 20 new professionals are expected to begin working per year. Therefore, the generational balance was calculated to be 0.8%. The majority (97.3%) of the ophthalmologists were Portuguese, and the geographical distribution of the respondents is shown in Fig. 1.

Table 1 – Demographic data

a) Portugal[1]	1991 N	1991 N/10 000 inhab	1991 M:F	2021 N	2021 N/10 000 inhab	2021 M:F	Increase 1991 - 2021 (%)
Doctors	28,326	56.7	1.5:1	58,735	113.7	0.8:1	107
Ophthalmologists	446	0.4	-	1140	1.1	-	161

b) Ophthalmologists (2021)	Statistics Portugal[2]	PCO[3]	PNHS[4]	PNHS FTE 40h[4]
N	1140	910	471	390
N/10,000 hab	1.1	0.9	0.45	0.35

c) Age (years range)[5]	≤ 30	31 ≤ 40	41 ≤ 50	51 ≤ 60	60 ≤ 70	> 70	Total
N	15	138	97	123	156	60	589
%	2.5	23.4	16.5	20.9	26.5	10.2	-
M:F	0.5:1	0.8:1	1.1:1	1.6:1	2.5:1	3.6:1	1.5:1
M:F (2027)	0.9:1	0.9:1	1:1	1:1	1.7:1	3:1	1.5:1

d) Nacionality	Portuguese	Spanish	Italian	Brasilian	French	American	Total
N	**573** (97.30%)	**7** (1.20%)	**3** (0.51%)	**3** (0.51%)	**2** (0.34%)	**1** (0.17%)	**589**

e) Residents[5]	Total	Average/year (2011 - 2021)	In 5 years	% of the ophthalmologists
N	83	23	80	2.5

f) Five-year projection for generational balance	New professionals	Retirement/cessation	Balance
	2.5%	1.7%	0.8%

a) Evolution of the number of doctors and ophthalmologists in Portugal (1991-2021), evolution per 10,000 inhabitants and the male:female ratio; **b)** Number of ophthalmologists in Portugal (2021) and number per 10,000 inhabitants according to National Statistics and the PCO records; the number of ophthalmologists working with the PNHS and corresponding FTE 40 hours; **c)** Distribution of the population by age and sex; **d)** Distribution of the population by nationality; **e)** Residents: absolute number; average of graduation per year over a 10 year; 5 years estimated predicted number; **f)** 5-year ophthalmologists balance projection [CI0.95 (0.37%, 1.23%)].
[1]: PORTATA 2021; [2]: Statistics Portugal, 2021; [3]: Portuguese College of Ophthalmologist 2021; [4]: Central Administration of the Health System 2021; [5]: Census 2021;
N: number; inhab: inhabitants; M: male; F: female, PCO: Portuguese College of Ophthalmology; PNHS: Portuguese National Health Service; FTE; Full Time Equivalent.

Academic background and specific training in ophthalmology

Most (82.3%) of the ophthalmologists had a degree in medicine and/or an integrated master's degree, and 9.5% had a doctoral degree. In terms of where they completed their ophthalmology residency, 95% of the respondents

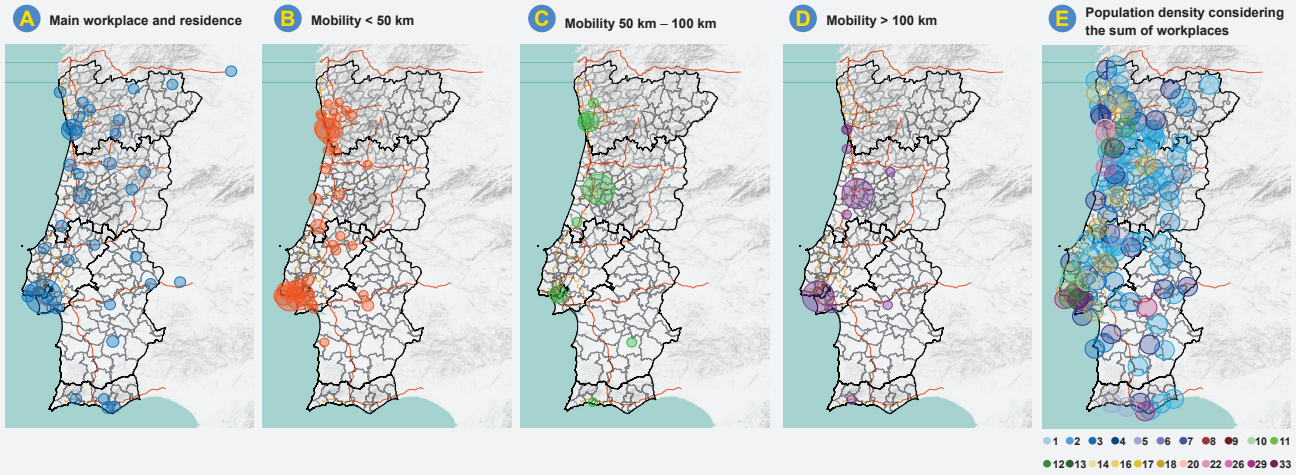

Figure 1 – Geographic distribution of the ophthalmologists by Nomenclature of Territorial Units III: (A) Places of residence and main places of work; (B - D) Reported travelling distance to work < 50 km, 50 - 100 km and > 100 km, respectively; (E) Population density considering the sum of the workplaces.

completed their residency in Portugal, with 46.69% undertaking their training at the Central Lisbon University Hospital Center (formerly Lisbon Civil Hospitals) (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20321/15334). After their residency, 27.3% pursued further training, primarily in clinical areas. More than half (51%) had attended clinical internships for over three months. Since 2015, there has been a trend towards taking the European Board of Ophthalmology examination (13%/year).

Professional activity

The Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20321/15334) summarizes the information collected from the respondents on their medical career degrees, professional activity, sectors of work and contractual regimes. Among the respondents, 76.3% were professionally active, 20.2% were retired but continued to practice and 3.6% had ceased professional activity. Table 2 outlines the workload distribution of the respondents according to economic sector. It was found that 39.1% of the ophthalmologists provided emergency services and that 21% were working more than 12 hours/week. Within the PNHS subgroup, 61.8% of the respondents were providing emergency services (Table 2). This activity was mainly located in the Lisbon, Oporto and Coimbra regions. Information on the respondents' age, sex and medical career grade according to activity type is shown in Table 3.

Distribution of weekly activity

Clinical activity was found to dominate the respondents' weekly activity, accounting for 84.4% of their workload. Around 50% of the ophthalmologists had been working in differentiated clinics for more than 10 years, except for those who specialized in neuro-ophthalmology, ergo-ophthalmology and oncology and oculoplastics. The reported surgical activity did not vary with age. The most frequently performed surgery was cataract surgery (80%), followed by intravitreal injections (48%). The remaining areas of differentiated surgical practice were performed by approximately 15% of the ophthalmologists. The distribution of the respondents' weekly hours of work is shown in Table 2.

Table 2 – Workload and weekly professional activity

a) Professional Status (N/%)				
In the exercise of the professional activity	**Retired and working**	**Retired and not working**		
449 (76.2)	119 (20.2)	21 (5.6)		
b) Hours assigned to each Activity Sector (hours/week)				
Statistics	**Sum**	**Mean**	**Median**	**Std. Deviation**
Public	10 809	32.2	35	9.4
Private	12 926	24.0	20	13.5
Social	786	14.3	12	10.2
c) Emergency Service assigned to each Activity Sector (hours/month)				
Statistics	**N Sum**	**Mean**	**Median**	**Std. Deviation**
Public	209 10 136	48	40	42
Private	198 9 897	50	40	44
Social	18 930	52	35	55
d) Weekly Clinical Activity - average hours dedicated to:		**e) Population distribution by regularity of surgical activity** (%)		
General Ophthalmology	16.8	**1x/month**	4.4	
Retina, Glaucoma and Pediatric Ophthalmology	9.4 - 1.4	**2x/month**	12.3	
Immunopathology, Cornea, RI, Oculoplastic and Ergophthalmology	6.2 - 8.0	**1x/week**	30.5	
Contactology, Neuroophthalmology and Oncology	3.9 - 5.3	**≥ 2x/week**	52.8	

Distribution of the population according to: **a)** Exercise of professional activity; **b)** Working hours assigned to each activity sector; **c)** Emergency service workload; **d)** and **e)** Clinical and Surgical activity.

Table 3 – Activity sector analysis

	Public		Private		Social	
	N	%	N	%	N	%
a) Sex						
Female	168	49.7%	191	42.3%	9	33.3%
Male	170	50.3%	261	57.7%	18	66.7%
Total	338	100.0%	452	100.0%	27	100.0%
b) Age range						
31 - 40	144	42.6%	138	30.5%	11	40.7%
41 - 50	68	20.1%	80	17.7%	7	25.9%
51 - 60	73	21.6%	95	21.0%	4	14.8%
61 - 70	49	14.5%	103	22.8%	4	14.8%
> 70 years	4	1.2%	36	8.0%	1	3.7%
Total	338	100.0%	452	100.0%	27	100.0%
c) Hospital Medical Career Grade						
Hospital Assistant	141	43.9%	159	38.6%	13	48.1%
Graduated Hospital Assistant	153	47.7%	194	47.1%	13	48.1%
Senior Hospital Assistant	27	8.4%	59	14.3%	1	3.7%
Total	321	100.0%	412	100.0%	27	100.0%

Distribution of the population according by Activity Sector according to age, sex and Medical Career Degree.

Table 4 – Future scenarios

a) Changes in working hours in the next 5 years (N/%)									
Reduce			**Mantain**			**Increase**			
220 (38.7)			335 (59.0)			13 (2.3)			
b) Reason to reduce working hours (N/%) **(Total = 220)**									
Family	**Fatigue**	**Lack of motivation**	**Health**	**Burnout**	**Lack of recognition**	**Another professional orientation**	**Search for better salary**	**Carreer progression**	**Another reason**
74 (33.8)	48 (21.8)	21 (9.5)	13 (6.0)	12 (5.4)	5 (2.3)	7 (3.2)	4 (1.8)	2 (0.9)	31 (14.0)

c) Highlight (N)					
Sectors	**Exclusivity 1 private institution**	**Exclusivity 1 social institution**	**Exclusivity 1 public institution**	**Work in the Public Sector**	**Not working in the Public Sector**
Intend to work exclusively in the private sector	83	0	2	13	5
Intend to work in various private sector institutions	27	0	0	76	50
Abandon/Reduce Public	0	0	0	7	0

Distribution of the population according to: **a)** Plans for changes in working hours in 5 years; **b)** Reasons for working hours reduction; **c)** Intention to change the professional activity profile concerning the activity sector.

Future plans

Among the respondents, 59% intended to maintain their current workload without any changes and 38.7% intended to reduce their workload. The main reasons the respondents gave for intending to reduce their workload were family and fatigue (Table 4).

DISCUSSION

To the best of our knowledge, this is the first comprehensive characterization of Portugal's ophthalmologist population, whose members work across the public, private and social sectors. By conducting a census, we were able to gather precise, detailed and standardized information and produce a comprehensive overview of the ophthalmologists working in Portugal.[19,20] The methodology we applied in this study allowed us to surpass the limitations typically encountered in survey-based studies; namely, that sample sizes are often too small to allow precise estimations. To promote cross-national comparisons in the future, we have diligently used internationally standardized variables to generate this comprehensive overview of the human resources in ophthalmology. It is important to note that the list of studied variables is not exhaustive and may be used in other human resource assessments.

The response rate of this census was 64.7%, which is higher than the 54% usually obtained in this type of study.[19,21-23]

When we compared the data on the respondents who were working in the PNHS with the data provided by CAHS,[6] we found that our results aligned. The two data sets showed a similar percentage of ophthalmologists working in the PNHS (CAHS, 51.8% *vs* CENSUS 2021, 58.5%), as well as an equivalent age distribution (aged over 50 years: CAHS, 39.4% *vs* CENSUS 2021, 37,3%). Ophthalmologists working in the PNHS and younger ophthalmologists were found to have participated in the Ophthalmology Census 2021 at a slightly higher rate.

The number of ophthalmologists, in Portugal, has increased over the past few years, following an increase in the number of doctors.[4,5] Between 1991 and 2021, the number of doctors increased by 107% and the number of ophthalmologists by 161%.[18] The number of ophthalmologists per 10 000 inhabitants went from 0.4 to 1.1 in the same period.[18] Currently, Portugal has the ninth highest number of ophthalmologists in Europe,[5] with 0.9 PCO-enrolled ophthalmologists per 10 000 inhabitants. This figure drops to 0.6 if we only consider the ophthalmologists under 70 years old. The figure in the PNHS is 0.45, and it drops to 0.35 when only full-time equivalent (FTE) workers, who work 40 hours/week, are considered. Therefore, considering the international recommendation (1:10 000)[8] and the current Portuguese population (10 344 066), it can be concluded that the number of ophthalmologists in Portugal is in line with the recommendations. However, if we focus on the number working in the PNHS, there is a deficit of 127 professionals.[8] These findings reflect the problem of retaining qualified professionals in the PNHS.

The current number of ophthalmologists is expected to remain stable for the next five years, as shown by the generational pyramid (balance of 0.8%). However, it is essential to undertake an in-depth analysis of the future needs of the ageing and growing population to determine whether having 20 - 21 new ophthalmology residents per year will be sufficient.

In 2011, Correia *et al*[1] analyzed the population of ophthalmologists and concluded that 65.5% were over 50 years old and that 32% were female. Our results showed that 57.6% were over 50 years old and that 40.4% were female, indicating that the average age decreased by 10 years and that the number of female ophthalmologists increased. Detailed examination of the age distribution data showed that there was a stable pyramid with a slight predominance of doctors over 60 years old and a slight deficit of professionals in their forties. This variation is in line with the fluctuation in the total number of physicians and can be explained by the variance in both medical school and residency admissions. The observed increase in the number of females in ophthalmology follows the general trend in medicine. Although female (56.1%) outnumbered male in the 40 - 50-year age group, men remained the majority across all age groups. This may need to be taken into account when predicting the need for professionals since women tend to work fewer hours in the earlier stages of their careers and may take maternity leave.[24-26]

The proportion of ophthalmologists who are foreign nationals was found to be low (2.7%), as was the proportion of ophthalmologists who completed their residency abroad (4.9%). The former was a consequence of working in Portugal and of our healthcare services not being attractive, possibly due to low salaries and poor working conditions.

The geographical distribution of the respondents was asymmetrical. Most of the respondents (58.1%) lived and worked in the Lisbon, Oporto and Coimbra regions. The respondents tended to live and work in the regions where they graduated until they entered the job market as specialists. Few respondents reported travelling more than 50 km to work (3%), and this low workforce mobility accentuates the gaps in the healthcare services experienced in Portugal, especially for primary healthcare services. Our analysis measured only mobility, not the hours spent in each location. This means that the national coverage may be even less than what a brief analysis of the data presented in Fig. 1 may indicate.

The distribution according to graduation and residency training regions reflects the country's situation prior to the 1960s and 1970s when there was no *numerus clausus* and most medical graduates in Portugal studied at the University of Lisbon. Focusing on the ophthalmology residency data, it can be seen that 49.7% of the respondents completed their training program in the Lisbon region; this cohort included most doctors over 50 years old and reflects the fact that

training was offered at the former Lisbon Civilian Hospitals (now the CHULC). As new generations enter the job market, we will continue to witness a decentralization of the training programs. Currently, there are programs available outside the leading hospitals in Lisbon, Oporto and Coimbra.

Regarding the development of professional skills, the respondents favored training and differentiation: 17.6% had a master's degree (pre-Bologna) or PhD, and 27.3% complemented their training in ophthalmology. Among the younger cohorts (under 40 years old), there was a demand for international certification, presumably to create opportunities to work abroad. Analyzing the postgraduate training data was a complex task because there was significant heterogeneity and a lack of standardization in the reported training. This was one of the variables that we had difficulty analyzing and that needs to be reviewed in the future.

Our analysis did, however, reveal that some of the ophthalmologists continued to practice even after retiring: 20.2% were retired but still working (10% were over 70 years old).

The respondents reported working in three economic sectors: the public, private and social sectors. A wide variety of employment contracts were also used. This heterogeneity made it difficult to draw conclusions. Nevertheless, the results showed that the respondents' work was distributed between the public and private sectors, with a residual collaboration with the social sector. More ophthalmologists were found to work exclusively in a single institution in the private sector (25%) than in the public sector (4.2%). Just over half (58.5%) collaborated with the public sector, regardless of the contractual relationship. According to Correia *et al*, the percentage was lower in 2011, at 45.1%.[1] The large number of retired doctors at the time may help explain these numbers.[1] In comparison to the 30 - 40-year age group, the 40 - 50-year age group showed a significant reduction in the percentage of ophthalmologists working in the public sector; the 40 - 50-year age group had fewer ophthalmologists. A premature withdrawal from the public system could explain this finding.

As mentioned above, there was considerable variation found in the types of employment contracts that governed the labor activities of the ophthalmologists: 20% were under a public service contract (25% in the subgroup of professionals collaborating with the public sector). The most frequent type of contract used in the public sector was the individual employment contract, but there were also individual and corporate service contracts in use. In the private and social sectors, most of the contracts were freelance contracts. The variation in the types of contractual agreements that were found to be in place in the public sector amplifies the instability observed in the delivery of healthcare services and training capacities.

The limited career progression of the respondents was reflected in the reduced number of Senior Hospital Attendings, particularly among those working in the PNHS and in the 50 - 60-year age group (1.9%). The progression of this group of professionals is vital to the functioning of specialized services and the provision of training capacities.

We next analyzed the weekly activity data of the respondents and found that the median number of reported work hours was 45 hours, with 35 hours dedicated to the public sector. In the subgroup of respondents who collaborated with the public sector, the median number of hours dedicated to the private/social economic sector was still considerable at 20 hours. There were 471 ophthalmologists working in the public sector, and this figure was reduced to 390 when only FTE workers (working 40 hours/week) were considered. These findings reflect the work done in different economic sectors and the existence of reduced hours in the public sector, which allows an additional 20 hours/week of work in other economic sectors.

The total number of hours assigned to the private/social sector (12 926 hours) was higher than those assigned to the public sector (10 809 hours). Analysis of this data must take into account the differentiated clinical care provided in each economic sector. Nevertheless, this finding revealed that the provision of ophthalmological healthcare outside the scope of the public sector is significant and should be acknowledged.

When we examined the weekly activity data in greater depth, we found that the respondents mainly undertook clinical work (> 80%) and surgical activity (52.8% reported undertaking this activity more than twice a week). We also noticed that general ophthalmology was practiced twice as much (average 16.8 hours) as differentiated care (average 7.6 hours). Of those who practiced differentiated care, 50% had done so for over 10 years. Almost all of the ophthalmologists performed surgeries (91.7%): 80% performed cataract surgeries and 48% performed intravitreal injections. Further analysis of this data must include productivity data from the different departments to identify where the training capacity lies.

Regarding the respondents' future plans, 59% intended to maintain their level of activity as it is, 38.7% wanted to reduce their level of activity and 2.3% wanted to cease their activity. The main reasons for reducing activity were personal, family-related issues, fatigue and demotivation or other health issues.

The issue of healthcare worker retention is critical and demands immediate attention. It is a concern that extends beyond Europe and affects countries worldwide. Factors that influence the retention of healthcare workers include professional and career growth, organizational aspects, and personal considerations. Developing effective human

resource strategies requires the leadership of established institutions and collaboration with educational institutions and professional associations.

This study is limited due to self-reported questionnaires, with greater participation by younger ophthalmologists and those working in the PNHS. Some responses on training after specialization were complex to analyze and should be reviewed in future studies. Moreover, we have not performed a comparative analysis to examine our findings in the European or international context or addressed Portugal's specific needs in visual healthcare. Both are complex tasks that we cannot handle at this time.

The dynamics of human resources in healthcare are complex and depend on multiple variables, including politics. However, characterizing the human resources in healthcare is the first step in the process of designing, planning, and implementing successful interventions. In the next step in our project, we will study the existing capacity, predict the population's needs and repeat the process every five years. The collected data will be used to plan training needs, and it is also vital to take into account that the number of specialized professionals must meet the population's needs for a given period and that the quality of the provided services is affected by the excess or lack of professionals.

By projecting the future needs, it is possible to create training strategies and to prioritize and recommend sustainable policies for the health programs of the successive Constitutional Governments that ensure access, equity and proximity, as stated in the Constitution of the Portuguese Republic, the Basic Health Law, the National Health Plan and the National Strategy for Eye Care 2018.

CONCLUSION

In Portugal, the ratio of ophthalmologists to inhabitants is higher than the European average and in line with the OECD's recommendations. However, the ratio drops when the public sector is considered alone, and even further when an FTE workload of 40 hours/week is considered. This highlights the disparity between the public and private/social sectors in terms of the distribution and workload of ophthalmologists. Geographically, the ophthalmologists in our study were concentrated in the urban areas of Lisbon, Oporto and Coimbra, indicating an asymmetry in the distribution of resources across the country. Furthermore, our findings revealed that the workload in the private/social sector was more significant than in the public sector, emphasizing the role of private practice in the provision of ophthalmological healthcare. Looking forward, the generational balance for the ophthalmologist workforce is expected to remain stable, with an annual increase of 0.8% ophthalmologists per year. The valuable knowledge generated in this study will be used to develop effective strategies for training new specialists and address the challenges in ensuring the sustainability of the ophthalmological healthcare system in Portugal.

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PREVIOUS AWARDS AND PRESENTATIONS

The study results were formally presented at the 65th Portuguese Congress of Ophthalmology in 2022.

AUTHOR CONTRIBUTIONS

PML, SO, AM: Study design, data collection, analysis and interpretation, writing and critical review of the manuscript, supervision.

AM, CV, JTF: Study design, data collection, analysis and interpretation, writing and critical review of the manuscript.

JN, SL: Study design, data collection, analysis and interpretation.

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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Neurological Involvement in a Portuguese Cohort of IgG4-Related Disease

Envolvimento Neurológico numa Coorte Portuguesa de Doentes com Hiper-IgG4

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ABSTRACT

Introduction: Neurological involvement in immunoglobulin G4-related disease (IgG4-RD) is increasingly recognized. Its diagnosis can be challenging due to clinical mimics and difficulty in obtaining nervous system biopsies. The aim of this study was to describe a cohort of neurological IgG4-RD patients.
Methods: Patients were recruited from a neuroimmunology tertiary center. Clinical, laboratory, neuroimaging and histological data were reviewed.
Results: Fifteen patients (60% women), with a median age of 53 years (48.5 – 65.0) were included: 13 (86.7%) classified as possible IgG4-RD, one (6.7%) as probable and one (6.7%) as definitive. The most common neurological phenotypes were meningoencephalitis (26.7%), orbital pseudotumor (13.3%), cranial neuropathies (13.3%), peripheral neuropathy (13.3%), and longitudinally extensive transverse myelitis (LTEM) (13.3%). Median serum IgG4 concentration was 191.5 (145.0 – 212.0) mg/dL. Seven in 14 patients had CSF pleocytosis (50.0%) and oligoclonal bands restricted to the intrathecal compartment, while most cases presented elevated CSF proteins (64.3%). Magnetic resonance imaging abnormalities included white matter lesions in four (26.7%), hypertrophic pachymeningitis in two (13.3%), and LETM in two (13.3%). Two patients had biopsy-proven IgG4-RD in extra-neurological sites.
Conclusion: This study highlights the phenotypical variability of the neurological IgG4-RD. Biopsy inaccessibility reinforces the importance of new criteria for the diagnosis of this subset of patients.
Keywords: Immunoglobulin G; Immunoglobulin G4-Related Disease/diagnosis; Nervous System Diseases

RESUMO

Introdução: O envolvimento neurológico na doença associada a imunoglobulina G4 é cada vez mais reconhecido. O seu diagnóstico pode ser desafiante por poder mimetizar outras doenças e ser difícil obter amostras de tecido nervoso. O objetivo deste estudo é descrever uma coorte de doentes com doença neurológica associada a IgG4 (IgG4-RD).
Métodos: Os doentes foram recrutados a partir de um hospital terciário com consulta de Neuroimunologia. Os dados clínicos, laboratoriais, neuroimagiológicos e histológicos foram obtidos retrospetivamente.
Resultados: Foram incluídos 15 doentes (60% mulheres) com uma idade mediada de 53 anos (48,5 – 65,0): 13 (86,7%) classificados como IgG4-RD possível, um (6,7%) como provável e um (6,7%) como definitivo. Os fenótipos neurológicos mais frequentes foram a meningoencefalite (26,7%), pseudotumor orbitário (13,3%), neuropatias cranianas (13,3%), neuropatia periférica (13,3%), e mielite transversa longitudinalmente extensa (13,3%). A concentração sérica mediana de IgG4 foi de 191,5 (145,0 – 212,0) mg/dL. Sete em 14 doentes tinham pleocitose no líquido cefalorraquidiano (50,0%) e bandas oligoclonais sem espelho sérico, enquanto a maioria dos casos apresentava proteinorráquia elevada (64,3%). As alterações na RM incluíram lesões na substância branca em quatro doentes (26,7%), paquimeningite hipertrófica em dois (13.3%) e LETM em dois (13,3%). Dois doentes tinham confirmação histológica da doença.
Conclusão: Este estudo destaca a variabilidade fenotípica da IgG4-RD neurológica. A inacessibilidade da biópsia reforça a importância de atualizar os critérios de diagnóstico para o subgrupo de doentes neurológicos.
Palavras-chave: Doença Relacionada a Imunoglobulina G4/diagnóstico; Doenças do Sistema Nervoso; Imunoglobulina G

INTRODUCTION

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a fibro-inflammatory disease characterized by tumefactive lesions involving multiple organs, with typical histopathological features and a rapid clinical response to glucocorticosteroids.[1,2]

Neurological involvement is a recognized feature of IgG4-RD, mainly in the form of diffuse inflammation of the dura mater (hypertrophic pachymeningitis), hypophysitis, and cranial neuropathies (usually associated with orbitopathy).[3] Furthermore, peripheral neuropathy, carotid/ intracerebral vasculopathy, and brain/ spinal cord parenchymal lesions have been rarely described.[4]

The diagnosis of IgG4-RD can be challenging due to several clinical mimics, histological intra- and inter-organ variability and absence of elevated IgG4 serum concentration in 30% - 50% of patients with biopsy proven IgG4-RD.[1,5] In the nervous system, the diagnosis is even more complex given the lack of organ-specific diagnostic criteria (only

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available for head and neck glands, eye, chest, pancreas and biliary tree, kidney, and retroperitoneum) and biopsy inaccessibility in some circumstances.[6,7]

The available evidence regarding the neurological phenotype in IgG4-RD is even rarer, consisting of case reports and a few case series focusing on specific phenotypes like pachymeningeal involvement.[8-12]

In this study, we provide a clinical, neuroradiological, and biochemical description of an IgG4-RD cohort from our centre.

METHODS

Patient selection

We retrospectively reviewed all patients with suspected IgG4-RD based on an electronic search of the neuroimmunology outpatient clinical database from a tertiary referral centre. Patients were diagnosed between 2015 and 2022. IgG4-RD was defined according to the 2020 Revised Comprehensive Diagnostic Criteria of the Japanese College of Rheumatology, and further classified in possible, probable and definite.[6] All the included cases had been sufficiently investigated that alternative diagnoses that were set as exclusion criteria had been excluded. These comprised the following: serological findings of positive antibodies (ANCA, Ro, La, dsDNA, RNP, and Sm) or clinical diagnosis of similar conditions [Sjögren disease, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, sarcoidosis, Castleman disease, primary sclerosing cholangitis, secondary retroperitoneal fibrosis, inflammatory bowel disease (if pancreaticobiliary disease present), Hashimoto thyroiditis (if the thyroid is the only organ involved), tumors].[6,7]

Serum IgG4 quantifications were obtained using enzyme-linked immunosorbent assay (ELISA) with a cutoff value adapted using the reference value set by our laboratory (14 - 74 mg/dL). Neurological manifestations comprised clinical or radiological evidence suggestive of involvement of the following structures: extra-ocular muscles and levator palpebrae; cranial nerves; meninges; brain or spinal cord parenchyma; pituitary gland; peripheral nerves; plexuses; nerve roots; ganglia; and intracranial or neck vasculature.

Data collection

Demographic, clinical, laboratory, imaging and histological data were collected from medical records, using a structured protocol.

Demographic data included the date of birth and gender, while clinical data was divided in neurological and systemic features. Neurological characterization comprised age at presentation, onset pattern (acute, ≲ seven days; subacute, > seven days and ≲ three months; and chronic, > three months), and description of symptoms and signs (based on interview and neurological examination at first observation). Patients were further divided as having a common or uncommon neurological IgG4-RD syndrome, according to the predominant neurological features. Regarding systemic features, all patients were assessed by a specialist in autoimmune disorders.

Analytical measurements (obtained during active disease or during the first neurological evaluation) comprised serum IgG4, and other Ig populations, presence of hypocomplementemia, eosinophilia and other paraclinical autoantibodies (autoimmune and/or paraneoplastic autoantibodies depending on the clinical presentation). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were analyzed according to the reference values of 0 - 19 mm and 0 - 5 mg/L, respectively. Cerebrospinal fluid (CSF) characteristics of interest included pleocytosis, cell differentiation, protein, presence of CSF specific oligoclonal bands, and IgG and IgG4 measurements from the first lumbar puncture (LP). Serum IgG4 concentration was also re-assessed after treatment, and during a relapse. Spinal cord and brain magnetic resonance imaging (MRI) were reviewed by a neuroradiologist blinded to the clinic, with a focus placed on T1, T2, FLAIR and T1 with gadolinium enhancement sequences at first hospital admission, after treatment and during a relapse. Neurophysiological study results were also retrospectively collected. Histological features were retrieved from written pathology reports, when available.

Data on pharmacological treatments (oral and intravenous corticosteroids, corticosteroid-sparing agents, and respective response) was additionally detailed. Time to treatment was defined as time (months) from initial neurological manifestations to initiation of corticosteroids. Response to treatment included an unequivocal improvement of neurological symptoms and/or radiological findings.

Lastly, outcome information involved follow-up duration, disease progression and number of relapses (defined as new IgG4-related clinical or imaging manifestations).

Descriptive statistics

Qualitative variables were studied using absolute and relative frequencies. For quantitative variables, the median and interquartile range (p25 - p75) (IQR) were used.

Ethics

This study was approved by Centro Hospitalar Universitário de Santo António Ethics Committee. Written informed consent was obtained from each patient.

RESULTS

Fifteen patients (60% women), with a median age of 53 years (48.5 - 65.0) were included in this study. Thirteen patients were classified as possible IgG4-RD, one as

Table 1 – Histological features in biopsy specimens

Pt	Organ	Findings
3	Lacrimal gland	Lymphoplasmocytic infiltration, IgG4/IgG cell > 40% and IgG4 cell/HPF > 10 and < 100.
4	Skin nodule	Plexiform neurofibroma, no IgG4 staining.
8	Pulmonary nodule, parotid gland, pancreatic cyst, sural nerve	Pulmonary nodule – lymphoplasmocytic infiltration, IgG4/IgG cell > 40% and IgG4 cell/HPF > 10; Parotid gland – few plasmocytes, no IgG4 staining; Pancreas cyst – few plasmocytes, IH NP; Sural nerve – chronic neuropathy, no plasmocytes, no IgG4 staining.
10	Skin	Lymphoplasmacytic infiltration, epidermal necrosis, hypodermal proliferation of myofibroblasts, no IgG4 staining.
11	Conjunctiva	No lymphoplasmacytic infiltration nor IgG4 staining.
12	Liver	Cirrhotic steatohepatitis, lymphoplasmacytic infiltration, biliary duct lesions, Mallory bodies, IH NP.
13	Nasopharynx	Lymphoplasmocytic infiltration, IgG4/IgG cell < 20%.
14	Thyroid	Adenomatous hyperplasia, IH NP.

probable and one as definitive. The Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397) summarizes the clinical and paraclinical findings from our cohort. Elevated serum IgG4 was present in all patients except for Patient 8, which was diagnosed based on supporting histological features (Table 1). Median serum IgG4 concentration was 191.5 (145.0 - 212.0) mg/dL. Serum IgG4 measurement was performed during active disease in seven patients (46.7%).

Neurological manifestations were the presenting symptom of the disease in 80% of our cohort (n = 12/15). The median age at first neurological manifestation was 49.0 (34.5 - 57.5) years. Median time to diagnosis was three years (0.0 - 4.5). Onset was subacute in seven (46.7%), acute in five (33.3%) and chronic in two (13.3%). The most common neurological phenotypes were meningoencephalitis in four patients (26.7%) (two with classical features of hypertrophic pachymeningitis), orbital pseudotumor in two (13.3%), and cranial neuropathies in two (13.3%, multiple in one). Peripheral nerve involvement was present in two individuals (13.3%), in the form of radiculopathy in one (which also presented a tonically dilated pupil – Adie's Pupil) and sensitive polyneuropathy in one. One patient (6.7%) presented with cavernous sinus syndrome and one (6.7%) with brain parenchymal lesions. Two patients (13.3%) presented with longitudinally extensive transverse myelitis (LTEM); extensive investigation ruled out other potential causes for myelitis. Additionally, in one patient with asymmetrical parkinsonism, a brain MRI was performed due to initial poor levodopa response, disclosing mild pachymeningitis (Fig. 1C). For this reason, this patient was considered asymptomatic for IgG4-RD. Three patients presented extra-neurological symptoms: xerostomia (Patient 8, with unilateral parotid enlargement), dacryoadenitis (Patient 3, with unilateral lacrimal gland enlargement) and panniculitis and orchiepididymitis (Patient 10). All patients performed thoracic-abdominal-pelvic CT, of which only one was deemed as normal. Mediastinal-hilar-axillary lymphadenopathies were the most common finding, being present in seven patients (46.7%). Other features are

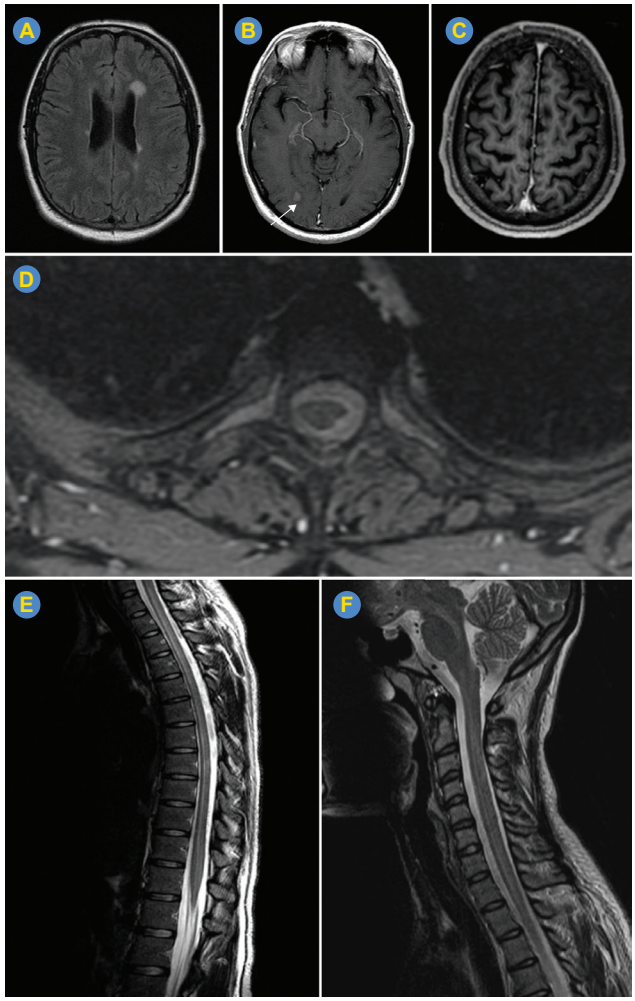

Figure 1 – MRI at disease onset. Oval, periventricular white matter lesions in FLAIR-WI, and one gadolinium-enhancing lesion (arrow) (A, B, Patient 15). Sagittal T1-WI after gadolinium administration displays mild pachymeningitis at left parasagittal parietal dura (C, Patient 14). Patient 7 features circumferential thickening of the dura (hypertrophic pachymeningitis), from C6-D12, with marked gadolinium-enhancement as shown in axial T1-WI at lower dorsal level (D). Extensive hyperintensity of spinal cord on T2-WI between T2 and conus medullaris (LETM) (E, F, Patient 13).

summarized in the Appendix.

In fourteen patients a CSF analysis was performed. Seven patients had pleocytosis (50.0%), with a median cell count of 8.5 (1.0 - 180.0) cells/mm^3, all lymphocytic-predominant. Elevated CSF proteins were present in 64.3%, with a median protein count of 74.0 (32.0 - 104.0) mg/dL. Oligoclonal bands restricted to the intrathecal compartment were present in seven patients (50.0%). One case had hypereosinophilia and none had hypocomplementemia. Erythrocyte sedimentation rate was above reference level in 33.3% (range 25.0 - 94.0 mm/h) and elevated CRP in 20.0% (range 11.1 – 63.3 mg/L, respectively). Other autoantibodies found included ANA in four patients, and peroxidase and thyroglobulin in one. Four patients had elevated total IgG and two had hyper-IgE, while another two cases had IgA and IgM deficiencies. Anti-aquaporin 4 (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) were negative in the patients with LETM.

Concerning brain and/or spinal cord MRI at first hospital admission (Fig. 1), the observed abnormalities were the following: white matter lesions (n = 4), hypertrophic pachymeningitis (n = 3), myelitis (n = 3, two LETM), orbital pseudotumor (n = 1), multiple cranial nerve hyperintensity (n = 1), middle cerebellar peduncle hyperintensity (n = 1), and diffuse leptomeningeal enhancement (n = 1). Three patients had normal brain and spinal MRI (Patients 6, 9, 10).

Histopathological data was available in seven (46.7%) patients (Table 1). Two patients fulfilled the histopathological criteria for IgG4-RD with specimens taken from a lung nodule (Patient 8) and lacrimal gland (Patient 3). A peripheral nerve biopsy from patient 8 showed no specific features suggestive of IgG4-RD (Fig. 2.) In the remaining five patients, two skin biopsies (corresponding to one case of panniculitis and one of hypermetabolic subcutaneous lesion on PET scan), one conjunctival biopsy (asymptomatic), one liver biopsy (cytocholestasis) and one nasopharynx biopsy (nasopharyngeal thickening) did not find IgG4-related pathological features.

Ten patients (66.7%) received high-dose IV methylprednisolone pulse therapy during active disease, six later switched to oral prednisolone taper. The median time from diagnosis to treatment was 1.5 (0.0 - 72.0) months. Steroid-sparing immunosuppressors were also used, most frequently azathioprine (40.0%) and rituximab (13.3%) (Appendix 1:

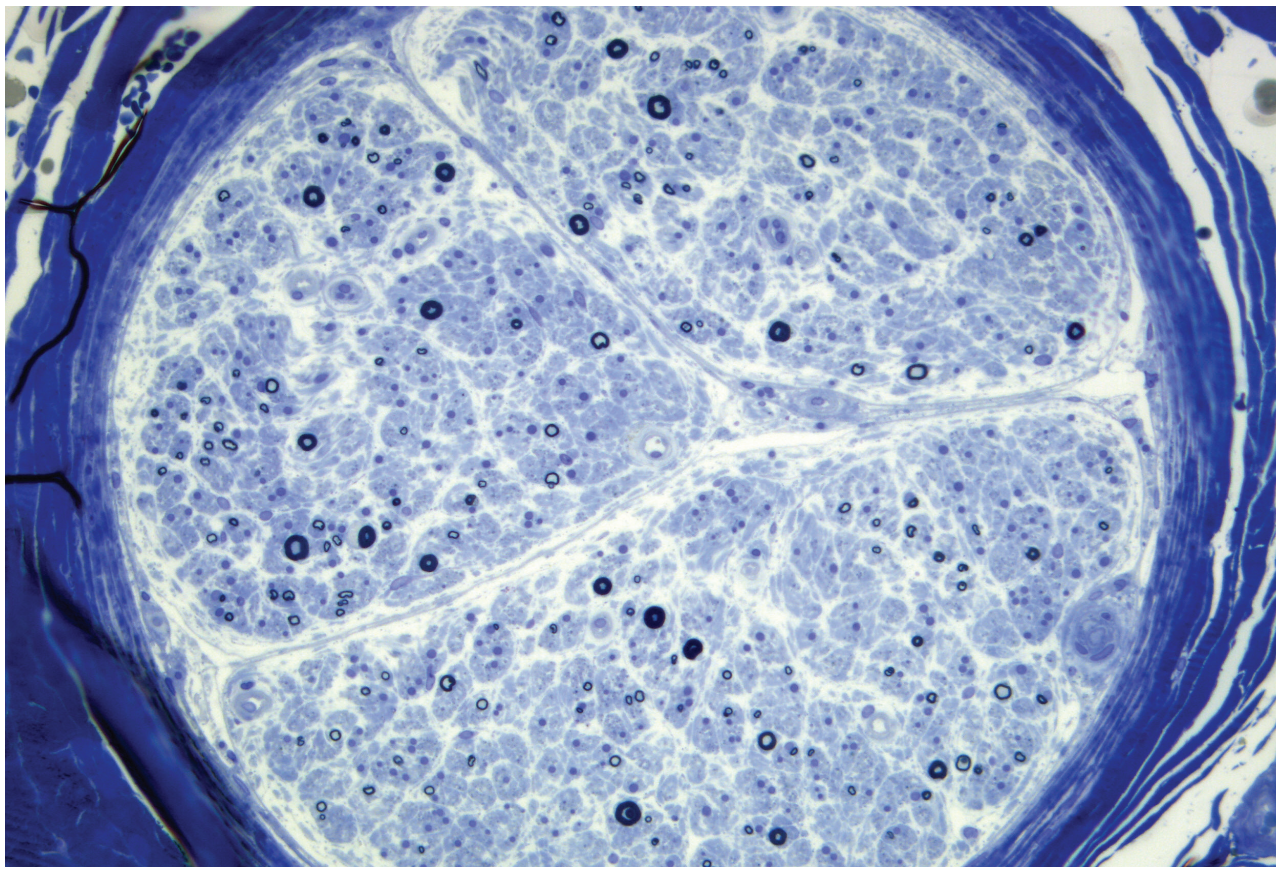

Figure 2 – Sural nerve biopsy of Patient 8. Chronic and severe neuropathy, with loss of large and small myelinated fibres, and moderate endoneurial fibrosis. There are no regeneration clusters, or onion bulbs. Absence of lymphoplasmacytic infiltration or deposition of abnormal substances precludes immunohistochemistry performance. Toluidine blue, scale bar: 100 µm.

https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397). All treated patients had improvement under corticosteroids (oral and/or IV), and neuroimaging improvement was documented in five (Fig. 3.). Serum IgG4 concentration decreased after corticotherapy in 80.0% (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20767/15397). Two patients remained free from neurological manifestations after treatment (Patients 2 and 4). Relapses were identified in four patients (cranial nerve neuropathy, paroxysmal vertigo, and meningoencephalitis in two), albeit new brain MRIs did not show additional lesions. Serum IgG4 concentration upon relapse increased in 75.0%, and two relapses were temporally related to steroid tapering. After a median follow-up time of 45.5 (1.0 - 143.0) months, four patients (26.7%) were asymptomatic and had a normal neurological examination.

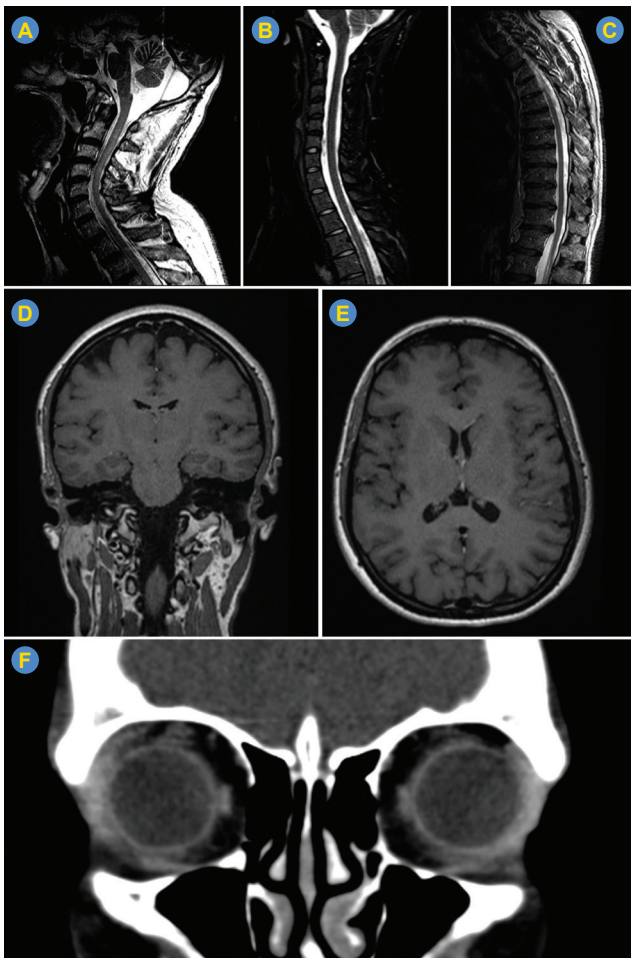

Figure 3 – MRI after corticosteroids. Regression of the extensive spinal cord T2 hyperintensity (A, B, C, Patients 11 and 13). Regression of leptomeningeal and pachymeningeal enhancement (D, E, Patient 13). Orbital CT in Patient 3 showing reduction of right lacrimal gland enlargement (F).

DISCUSSION

We describe a cohort of patients with IgG4-RD that illustrates the high variability in clinical expression associated with this disorder, with both central and peripheral nerve involvement.[1]

Meningoencephalitis with or without associated hypertrophic pachymeningitis is a classical manifestation of IG-RD and was the most common presentation in our cohort.[11] The variety in clinical features at presentation reflects mechanical compression of vascular or nerve structures in these cases.[9,13] Gait instability has previously been described in cases of IgG4-RD with meningeal involvement, in agreement with our findings.[14] Interestingly, we described one case with asymptomatic hypertrophic pachymeningitis and two cases with meningoencephalitis lacking meningeal enhancement on brain MRI. These findings suggest that a continuous inflammatory process in IgG4-RD may go unnoticed on routine imaging studies and may even be subclinical.[15]

Brain parenchyma involvement was present in four patients. While being considered non-specific in three, one patient had a clear inflammatory periventricular lesion. This was considered a clinically isolated syndrome for many years, but persistently elevated IgG4 serum concentration together with radio-labelling of thyroid, lung and lymph node tissue in PET-scan favored the diagnosis of IgG4-RD. Brain parenchyma involvement is considered a rare finding in IgG4-RD.[16]

Classical IgG4-related neurological manifestations were less frequently found in our cohort and included orbital pseudotumor and cranial neuropathies. Most of the cohort had isolated neurological IgG4-RD, and this is in line with the literature.[1] Investigation directed at systemic involvement revealed minor abnormalities in different organs, in spite of not fulfilling the organ-specific diagnosis criteria for the disorder.

Interestingly, we identified two patients presenting with involvement of the spinal cord parenchyma, which is atypical for IgG4-RD.[1,3] To the best of our knowledge, there are only two previous descriptions of parenchymal spinal cord involvement.[17,18] Patient 11 has previously been described as a case report by our group.[19]

Other atypical findings were present in our cohort, including a patient with sensory ganglionopathy (Patient 8). This patient had parotid gland obstruction and lung biopsy-proven IgG4-RD.*K.* Ohyama *et al* (2015)[20] found IgG4-positive plasma cells in sural nerve biopsies of patients with idiopathic peripheral neuropathies, although dorsal root ganglion involvement has never previously been described. The finding of bilateral Adie pupil in Patient 9 further raises the possibility of lymph node involvement.

Overall, IgG4 concentration appeared to decrease after

treatment with corticosteroids. CSF analysis showed elevated protein levels and intrathecal production of oligoclonal bands in most cases, which is consistent with previous studies.[1] The brain MRI evaluation showed that, although the pachymeninges are the most common meningeal component involved, the inflammation may extend diffusely to the leptomeninges, which has been previously reported in four cases.[10,21-23] Three of the cases that presented pachymeningeal involvement have previously been described.[8]

The main strength of this work is the well-documented patient history and the descriptive imaging findings that it provides. However, this study has several limitations that should be accounted for. A relevant limitation of this study is the limited number of IgG4-RD histopathological confirmations. Possible explanations for the some of the biopsies being negative include: (1) performance of biopsies in anatomical locations normally associated with findings of poor specificity (lymph nodes, skin, conjunctiva), (2) use of needle aspiration biopsy, in the case of pancreatic lesion, (3) absence of immunohistochemistry in five biopsy samples, and (4) histological evaluation not being directed towards the organ of disease activity, with only one patient having a biopsy sample of the nervous system (sural nerve).[5,7] The two biopsy-proven IgG4-RD did not show a swirling, 'cartwheel' pattern of fibrosis (storiform fibrosis) or obliterative phlebitis. However, the consensus pathologic criteria contemplate the absence of these features in the specific cases of lacrimal and lung specimens. Second, the upper limit cutoff for the serum IgG4 concentration was different from the one set by the Japanese College,[6] even if in the three patients presenting values below 135 mg/dL they were consistently above 100 mg/dL in further measurements and other mimics were extensively searched for and excluded. Third, this is a retrospective study from a single centre, with a relatively small sample size, which limits generalizability.

CONCLUSION

This study highlights the phenotypical variability of the neurological IgG4-RD and underscores the importance of considering IgG4-RD in the differential diagnosis of recurrent aseptic meningitis, cranial neuropathies with atypical features, sensory ganglionopathies, and longitudinally extensive myelitis. The absence of non-neurological manifestations and biopsy inaccessibility hampers the diagnosis of neurological IgG4-RD. In the future, additional neurological and neuroimaging descriptions as well as nervous system-specific criteria are needed.

AUTHOR CONTRIBUTIONS

JM, MJM: Study design, data collection and analysis, drafting of the manuscript.

FJ, EP, AS, IL, VO, APS, JD, LM, NVC, RS, RT, AMS: Data analysis, critical review of the article.

ES: Study design, data analysis, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

LM received payments from Alnylan for consulting services and giving lectures in symposia.

All other authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Contributions for the Validation of the European Portuguese Version of the Vascular Quality of Life-6 Questionnaire for Peripheral Artery Disease

Contribuições para a Validação da Versão em Português Europeu do Questionário Vascular Quality Of Life-6 para Doença Arterial Periférica

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ABSTRACT

Introduction: Peripheral arterial disease (PAD) is an occlusive atherosclerotic disease of the arteries of the extremities of the body that affects more than 230 million people worldwide. The most common symptom is intermittent claudication, described as leg pain which occurs mainly while walking. The symptoms impair the ambulation and functional capacity of patients, leading to loss of mobility, disease deterioration, increased risk of other cardiovascular diseases, and lower quality of life (QoL). Therefore, the aim of this study was to perform a cross-cultural adaptation and validation of the VascuQol-6 questionnaire for the Portuguese population to obtain a quick, sensitive, and easy-to-use way to assess the QoL of Portuguese patients diagnosed with PAD.

Methods: The Vascular Quality of Life-6 Questionnaire (VascuQoL-6) was adapted and translated into European Portuguese using standard validation methodology, including 115 patients with a mean age of 64.67 (7.23) years, with PAD with IC stable for more than three months; and ABI < 0.9 at rest. VascuQoL-6, SF-36, International Physical Activity Questionnaire (IPAQ), and the PAD Knowledge Questionnaire (PADKQ) were used. Reliability, construct validity analysis through convergent and discriminant validity, known-group validity, and responsiveness analysis were tested.

Results: The Cronbach's alpha was 0.64 and the average inter-item correlation was 0.27, indicating acceptable internal consistency. VascuQoL-6 was positively associated with SF-36 Physical Component Summary and Mental Component Summary scores (r = 0.64, $p < 0.01$ and r = 0.42, $p < 0.01$, respectively). In turn, there was no significant correlation between VascuQoL-6 scores and the PADKQ or IPAQ. A statistically significant difference between groups according to IC severity [$F(2.47) = 8.35$, $p < 0.001$] was found. A paired samples *t*-test showed differences between VascuQol-6 scores before a walking program (M = 15.65, SD = 3.09), and after a walking program (M = 17.41, SD = 2.71), $t(67) = 3.94$, $p \leq 0.001$.

Conclusion: The VascuQoL-6 is a six-item instrument to assess the QoL associated with PAD with good psychometric properties, convergent and discriminant validity with SF-36, PADKQ and IPAQ. The instrument proved to have known group validity and responsiveness.

Keywords: Peripheral Arterial Disease; Portugal; Quality of Life; Reproducibility of Results; Surveys and Questionnaires; Translating

RESUMO

Introdução: A doença arterial periférica (DAP) é uma doença aterosclerótica oclusiva das artérias das extremidades do corpo que afeta mais de 230 milhões de pessoas em todo o mundo. O sintoma mais comum é a claudicação intermitente (CI), descrita como dor nas pernas que ocorre principalmente durante a marcha. Os sintomas prejudicam a deambulação e a capacidade funcional dos doentes, levando à perda de mobilidade, deterioração da doença, aumento do risco de outras doenças cardiovasculares e diminuição da qualidade de vida (QV). Assim, este estudo teve como objetivo realizar uma adaptação e validação transcultural do questionário *Vascular Quality Of Life-6* (VascuQol-6) para a população portuguesa, de forma a obter uma forma rápida, sensível e de fácil utilização para avaliar a QV dos doentes portugueses com diagnóstico de DAP.

Métodos: O VascuQoL-6 foi adaptado e traduzido para o português europeu através de metodologia de validação *standard*, incluindo 115 doentes com idade média de 64,67 (7,23) anos, com DAP com CI estável há mais de três meses; e ITB < 0,9 em repouso. Foram utilizados o VascuQoL-6, o SF-36, o Questionário Internacional de Atividade Física (IPAQ) e o Questionário de Conhecimento sobre DAP (PADKQ). Foram testadas a fiabilidade, a análise da validade através da validade convergente e discriminante, a validade do grupo-conhecido (*known-group validity*) e a análise da capacidade de resposta (*responsiveness*).

Resultados: O alfa de Cronbach foi de 0,64 e a correlação média inter-itens foi de 0,27, indicando uma consistência interna aceitável. O VascuQoL-6 foi positivamente associado aos *scores* da Componente Física e da Componente Mental do SF-36 (r = 0,64, $p < 0,01$ e r = 0,42, $p < 0,01$, respetivamente). Por outro lado, não houve correlação significativa entre os *scores* do VascuQoL-6 e o PADKQ ou IPAQ. Foi encontrada uma diferença estatisticamente significativa entre grupos de acordo com a gravidade da CI [$F(2,47) = 8,35$, $p < 0,001$]. Um teste *t* para amostras emparelhadas mostrou diferenças estatisticamente significativas entre os *scores* do VascuQol-6 antes de um programa de caminhada (M = 15,65, DP = 3,09) e depois de um programa de caminhada (M = 17,41, DP = 2,71), $t(67) = 3,94$, $p \leq 0,001$.

Conclusão: O VascuQoL-6 é um instrumento de seis itens para avaliar a QV associada à DAP com boas propriedades psicométricas, validade convergente e discriminante com o SF-36, PADKQ e IPAQ. O instrumento demonstrou ter validade de grupo-conhecido e responsividade.

Palavras-chave: Doença Arterial Periférica; Inquéritos e Questionários; Portugal; Reprodutibilidade dos Resultados; Tradução

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INTRODUCTION

Peripheral arterial disease (PAD) is an occlusive atherosclerotic disease of the arteries of the extremities of the body that affects more than 230 million people worldwide.[1,2] Intermittent claudication (IC) is the most common symptom of PAD and is described as leg pain that occurs mainly while walking.[3] The symptoms impair the ambulation and functional capacity of patients, leading to loss of mobility, disease deterioration, increased risk of other cardiovascular diseases, and lower quality of life (QoL).[4]

Disease severity and functional impairment in patients with IC are usually quantified by the ankle-brachial index (ABI) at rest and after exercise and walking distance by standardized walking tests.[5,6] However, the exclusive use of these parameters requires specialized equipment and professionals, is costly, time-consuming, and does not adequately reflect the patient's day-to-day walking ability and perception of their functional impairment.[7] In addition, these parameters do not assess the impact of the disease concerning the social and emotional consequences of living with PAD. Therefore, it has been suggested that traditional measures should be complemented with patient-reported outcome measures, such as health-related QoL instruments.[8]

Health-Related Quality of Life (HRQoL) questionnaires have been used as an essential tool in the evaluation of clinical outcomes and are aimed at assessing the impact of the disease and treatment on the biopsychosocial scope of the patient. In addition, they are of great relevance in improving knowledge about different conditions and in analyzing the economic cost of an intervention.[9]

In a systematic review by Poku *et al*,[10] different tools used for psychometric evaluation were analyzed and the Vascular Quality of Life Questionnaire (VascuQol) was recommended as the preferred questionnaire to measure HRQoL outcomes in patients with PAD.[9,11]

The VascuQoL is a 25-item specific measure of HRQoL for patients with PAD. A shorter version, VascuQoL-6, was developed to facilitate the use of the instrument, consisting of six items with different response scales, and is now widely used to assess QoL in patients with PAD.[12,13] The validation study by Larsen *et al*[13] demonstrated improved accuracy and discriminating power for measuring QoL compared to the original 25-item questionnaire in a group of 21 patients with IC.

This instrument was translated and validated in different countries, including in the Portuguese language for the Brazilian population.[9,11,13,14] The Brazilian version of the VascuQoL-6 showed adequate valid and reliable indicators, allowing its use in patients with PAD and with IC symptoms.[14]

Although the VascuQol-6 questionnaire has already been translated into Portuguese, it has only been validated in the Brazilian population, making its application in the Portuguese population difficult due to their sociocultural differences. Thus, the aim of study was to perform a cross-cultural adaptation and validation of the VascuQol-6 questionnaire for the Portuguese population in order to develop a fast, sensitive, and easily applicable way to assess QoL in Portuguese patients diagnosed with PAD.

METHODS

A cross-sectional study of cultural adaptation and validation of the European-Portuguese version of the VascuQoL-6 questionnaire was conducted. All the patients provided written informed consent to participate in the study. This study was approved by the Department of Education, Training, and Research of Centro Hospitalar Universitário Santo António, on October 22nd, 2019 (reference no. 184/2020, of May 7th, 2020, and reference 069-DEFI/068-CES, respectively).

The first phase of the study concerned the translation, cultural adaptation, and assessment of the semantic equivalence of the questionnaire following the principles of good practice for the translation and cultural adaptation process of patient-reported outcomes.[15,16]

The questionnaire was originally provided by the author in the target language (European Portuguese). As such, a direct translation of the questionnaire was not necessary. Instead, the focus was on cultural adaptation, which involved ensuring that the items of the questionnaire were clear, relevant, and appropriate for the study population. To this end, an expert committee including vascular surgeons and nurses was set up to assess and evaluate the content of the items, i.e., if the items were adequate and adjusted to the population, to identify any potential cultural differences or ambiguities that could affect the interpretation of the questions.[17] After the revision of each item, the expert committee concluded that no modifications were necessary, as the questionnaire items were deemed clear and relevant for the study population.

The second phase of the study concerned evaluation of reliability and validity of the translated version of the scale. This included the internal consistency analysis, construct validity analysis through convergent and discriminant validity, known-group validity, and responsiveness analysis.

Participants

The VascuQoL-6 questionnaire was applied to voluntary participants whose native language was European Portuguese. These participants were PAD patients followed in an Angiology and Vascular Surgery Department of a Central Hospital. Inclusion criteria were (a) Symptomatic PAD; (b)

IC stable for more than three months; (c) Ankle-brachial index (ABI) < 0.9 at rest; and (d) age between 50 and 80 years old. Patients with cognitive impairment (evaluated with the Mini Mental State Examination), and asymptomatic PAD were excluded from the study.

Data collection and procedures

All data collection was performed during 2021 at Centro Hospitalar Universitário Santo António and was divided in two different evaluation sessions. The sessions were performed by a multidisciplinary team comprising a vascular surgeon, a psychologist, a physical exercise technician and a clinical physiologist. The assessment was performed face-to-face in an interview format. In an initial session, the ABI was measured using a handheld Doppler device [LifeDop 150 Doppler (8 MHz), USA], according to the AHA/ACC guidelines.[18]

A treadmill test was conducted to provide an objective assessment of performance since it is an accepted method used in patients with IC to evaluate walking ability. Severity is generally described in terms of claudication distance, and it can be objectively measured by a treadmill test with the assessment of pain-free walking distance (PFWD).[19,20] This way, the modified Gardner-Skinner Treadmill Protocol was used, where participants begin to walk on the treadmill at 1 km/h with a 0% slope. After two minutes, the speed is increased to 1.6 km/h, at 0% slope. Then, the speed is increased by 0.8 km/h every two minutes until reaching 3.2 km/h. After reaching 3.2 km/h, the speed is kept constant, and the slope is increased by 2% every two minutes.[21] The PFWD was recorded as the first sign of claudication pain.

To assess reliability and validity of the scale, patients were asked to answer the VascuQoL-6, Short-Form Health Survey (SF-36), International Physical Activity Questionnaire for elderly-Short Form (IPAQ), and the Peripheral Arterial Disease Knowledge Questionnaire (PADKQ) questionnaires.

Participants that met the inclusion criteria received a prescription of a physical exercise program, that included walking three times a week for a minimum of 30 minutes for the duration of three months, which is the first-line therapeutic measure recommended by clinical practice guidelines.[18]

In a second session, after three months, the participants completed the VascuQoL-6 questionnaire again to enable the assessment of the degree to which the VascuQoL-6 questionnaire was sensitive to change in response to an intervention (physical exercise program).

Questionnaires

Sociodemographic and clinical data questionnaire

The sociodemographic questionnaire included questions on sex, age, employment status, and education level, and the clinical data questionnaire included information about risk factors and lifestyle habits.

VascuQoL-6 questionnaire

The VascuQol-6 questionnaire is composed of six items that reflect the five dimensions of the original VascuQoL and assess the QoL of patients with PAD. These six items relate to limitations in performing activities (activity), tiredness in the legs (symptom), walking ability (activity), concern about poor circulation in the legs (emotional aspect), ability to participate in social activities (social aspect), and discomfort from pain in the legs (pain).[11] Each item has a four-point response scale ranging from 1 (worst patient-perceived QoL) to 4 (best patient-perceived QoL). The responses to the items are added to generate an overall score ranging from 6 to 24 points. Higher values indicate a better health status.[14]

Short-Form Health Survey

The Short-Form Health Survey (SF-36) is a widely used generic HRQoL measure that encompasses multiple dimensions of physical and mental health. This instrument consists of 36 items with different response scales assessing eight health concepts: bodily pain, physical functioning, role limitations due to physical problems, mental health, vitality, social functioning, role limitations due to emotional problems and general health. Two summary components can be calculated: physical component score (PSC) and mental component score (MCS). The scores for each domain were converted into a 0 - 100 scale, with higher scores indicating better HRQoL.[8,22] In this sample, Cronbach alpha for PSC was 0.73 and for MCS was 0.84.

International Physical Activity Questionnaire for elderly-Short Form

The International Physical Activity Questionnaire for elderly-Short Form (IPAQ) version adapted for the elderly was used. This version consists of four self-reported moderate-to-vigorous physical activity and sedentary behavior (sitting) items. The items encompass the following behaviors, in the last seven days: the time spent sitting, the days and time spent walking, the days and time spent in moderate-intensity activities, and the days and time spent in vigorous-intensity activities. Scores range from 0 to indefinite minutes of physical activity per week and higher results correspond to a greater amount of physical activity performed. Results are reported in categories (low, moderate, or high activity levels).[23]

Peripheral Arterial Disease Knowledge Questionnaire

The Peripheral Arterial Disease Knowledge Questionnaire (PADKQ) is a 16-item questionnaire that assesses patients' level of knowledge about PAD risk factors, symptoms, treatment options, and self-management strategies. The total score ranges from 0 to 16 with higher scores on the PADKQ indicating greater knowledge about PAD.[24] In this sample, Cronbach alpha was 0.77.

Statistical analysis

Descriptive statistics were used for the sociodemographic characterization of the sample and summarization of the VascuQoL-6, SF-36, IPAQ, and PADKQ scores. The distribution analysis of the quantitative variables was performed using the Shapiro-Wilk test, and all variables had a normal distribution. This way, parametric tests were used for the statistical analysis. The statistical analysis was performed with SPSS Version 28.0.

In terms of reliability, internal consistency reflects the extent to which the questionnaire items are inter correlated, or whether they are consistent in the measurement of the same construct.[17] Internal consistency of the VascuQol-6 items was assessed using the Cronbach's alpha, which is the most used internal consistency measure.[25] Values above 0.60 can indicate an acceptable level of internal consistency, but 0.70 is the most commonly used threshold for questionnaires intended for clinical use.[26,27]

McDonald's omega and average inter-item correlation were also calculated since these are alternative measures to Cronbach's alpha. McDonald's omega is based on a factor analytic approach and some authors defend that it has been proven to be more robust that Cronbach's alpha. Values of 0.70 or higher are considered acceptable.[28] Average inter-item correlation involves calculating the correlation coefficients between each pair of items within the questionnaire and then computing the average of these correlations. Some authors defend that this measure is better for scales that have a small number of items (less than 10) which may invoke low Cronbach's alpha values. Optimal average inter-item correlation values range from 0.20 to 0.40.[29]

Convergent and discriminant validity are integral aspects of assessing the construct validity of a questionnaire, ensuring that it accurately measures what it is intended to measure.[17,30] Pearson correlation coefficients were computed to evaluate (a) the relationship between the score obtained in the VascuQoL-6 questionnaire and the SF-36 questionnaire to assess convergent validity and (b) evaluate the relationship between the score obtained in the VascuQoL-6 questionnaire and the IPAQ and PADKQ to assess discriminant validity.

Known-groups validity is another way of assessing the validity of an instrument.[31] For this, one-way analysis of variance (ANOVA) was conducted to compare the mean VascuQoL-6 scores among the PAD clinical presentation of participants. Patient treadmill PFWD was categorized based on the Fontaine classification where patients with PFWD ≥ 200 m were classified with Mild IC (stage IIa), 50 - 200 with Moderate IC (stage IIb) and < 50 with Severe IC (stage III).[32]

The Tukey's Post-hoc test was performed to identify specific group differences. A *p*-value of < 0.05 was considered statistically significant. The known-group validity of the VascuQoL-6 questionnaire was determined based on the ability of the questionnaire to differentiate between different clinical presentations of PAD (Mild IC, Moderate IC, and Severe IC) as indicated by significant differences in mean scores across Treadmill PFWD categories.

Responsiveness is considered the longitudinal aspect of validity.[33] To assess the responsiveness of the VascuQoL-6 questionnaire, change scores were calculated by subtracting the baseline scores from the scores obtained after the three-month physical exercise program. The statistical analysis included paired *t*-tests to determine the significance of changes in VascuQoL-6 scores following the intervention consisting in a physical exercise prescription. A *p*-value of < 0.05 was considered statistically significant. Effect sizes (Cohen's criteria) were also calculated to quantify the

Table 1 – Demographic and risk factor characteristics in the patient population (n = 115)

Variables		Mean (SD) or n (%)
Sociodemographic		
Sex	Male	98 (85.2)
	Female	17 (14.8)
Age (years)		64.67 (7.23)
Education level (years)		6.41 (3.77)
Risk factors		
Hypertension	No	16 (13.9)
	Yes	99 (86.1)
High cholesterol	No	14 (12.2)
	Yes	101 (87.8)
Obesity (BMI > 30)	No	85 (73.9)
	Yes	30 (26.1)
Type 2 diabetes *mellitus*	No	65 (56.5)
	Yes	50 (43.5)
Smoking history (active or former)	No	10 (8.7)
	Yes	105 (91.3)
Ankle-brachial index (ABI)		
Right ABI		0.71 (0.19)
Left ABI		0.71 (0.18)

magnitude of change. These effect sizes were evaluated based on established benchmarks: a small effect size was indicated by d = 0.2, medium by d = 0.5, and a large by d ≥ 0.8.[34] The responsiveness of the VascuQoL-6 questionnaire to the physical exercise program was evaluated based on the magnitude and significance of changes in scores over time.

RESULTS

From the 115 participants that answered the VascuQoL-6, 85.2% were male and the mean age was 64.67 (7.23) years. Most the patients had hypertension (86.1%), dyslipidemia (87.8%), and were current or previous smokers (91.3%). Detailed demographic and risk factor characteristics can be found in Table 1. Table 2 provides a comprehensive characterization of the evaluation instruments employed in our study.

To gain a deeper understanding of the QoL within this cohort, an analysis examining potential differences related to sex, age, and education in relation to the VascuQoL-6 total scores was conducted. Our analysis did not reveal significant differences in VascuQoL-6 scores among different demographic subgroups. The results of this analysis are presented in Table 3.

Table 2 – Characterization of evaluation instruments (n = 115)

Variables		Mean (SD) or n (%)
Treadmill test[a]		
Pain free walking distance (PFWD) (meters)		125.31 (118.31)
Fontaine classification based on PFWD	Mild claudication - stage IIa (≥ 200 m)	26 (24.3)
	Moderate claudication - stage IIb (50 - 200 m)	45 (42.1)
	Severe claudication- stage III (< 50 m)	36 (33.6)
VascuQoL-6		
Item 1: Activity		3.17 (0.89)
Item 2: Symptoms		2.25 (1.22)
Item 3: Activity (walking)		2.59 (0.67)
Item 4: Emotional		1.96 (1.05)
Item 5: Social activities		3.50 (0.82)
Item 6: Pain		1.81 (0.70)
Total Score		15.28 (3.28)
SF-36[b]		
Physical functioning		18.69 (5.48)
Physical role limitations		11.55 (5.80)
Emotional role limitations		12.06 (3.84)
Mental health		17.57 (4.92)
Social functioning		7.98 (2.37)
Energy/vitality		14.29 (3.74)
General health perceptions		14.70 (3.50)
Bodily pain		5.75 (2.42)
Physical component score (PCS)		50.70 (13.43)
Mental component score (MCS)		51.90 (12.56)
IPAQ		
IPAQ categories	Insufficiently active	80 (69.6)
	Moderately active	29 (25.2)
	Vigorously active	6 (5.2)
Disease knowledge (PADKQ)[c]		11.07 (3.26)

[a]: n = 107; [b]: n = 49; [c]: n = 111

Table 3 – Quality of life differences among demographic subgroups

	n	Mean (SD)	*p*-value
Male	98	15.50 (3.325)	0.082
Female	17	14.00 (2.784)	
Age ≤ 65	64	15.11 (3.019)	0.539
Age < 65	51	15.49 (3.608)	
Education level ≤ 4 years	63	15.09 (3.627)	0.513
Education level > 4 years	52	15.50 (2.832)	

Table 4 – Correlation coefficients (r) for physical and mental components of SF-36, IPAQ, and PADKQ scores and individual items of VascuQoL-6 at baseline

		Item 1: Activity	Item 2: Symptoms	Item 3: Walking activity	Item 4: Emotional	Item 5: Social activities	Item 6: Pain	Total score
SF-36	Physical component score (PCS)	0.380*	0.274	0.441*	0.366*	0.303*	0.518**	**0.635****
	Mental component score (MCS)	0.255	0.180	0.272	0.288*	0.106	0.397*	**0.419***
IPAQ		0.067	0.306	0.083	-0.144	-0.109	-0.073	**0.065**
PADKQ		-0.172	0.199	0.062	-0.369	0.014	0.022	**-0.078**

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

Internal consistency

The value obtained for the Cronbach's alpha was 0.64, indicating an acceptable internal consistency.[35] McDonald's Omega was also measured, and the value obtained was 0.64.

Analyzing the internal consistency coefficients of Cronbach's alpha and McDonald's Omega presented above, it is possible to see that this scale is below the value of 0.70, a particularly commonly used threshold for questionnaires intended for clinical use.[36-38] In this sense, the average inter-item correlation was calculated and revealed an average inter-item correlation of 0.27, suggesting an acceptable level of inter-item correlation, reflecting a reasonable degree of homogeneity among the items.[29,39]

Construct validity

Convergent validity

To assess the convergent validity, the correlation between the VascuQoL-6 questionnaire and the SF-36 questionnaire was examined. The sample comprised 49 participants with PAD who completed both questionnaires. Pearson correlation coefficients were computed between the two measures. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the SF-36 correlated with the VascuQoL-6 scores (r = 0.64, $p < 0.01$ and r = 0.42, $p < 0.01$, respectively). Table 4 shows the correlation between the VascuQoL-6 score and SF-36 domains.

Discriminant validity

To assess discriminant validity, the correlation between VascuQoL-6 scores and two other measures (PADKQ and the IPAQ questionnaire) was examined. Results indicated that there was no significant correlation between VascuQoL-6 scores and scores on either the PADKQ questionnaire or the IPAQ questionnaire. Table 4 shows the correlation between VascuQoL-6 score and PADKQ and IPAQ.

Known-group validity

To assess Known-group validity, a one-way ANOVA was conducted to compare the mean VascuQoL-6 scores among the patients with PAD (Mild IC, Moderate IC, and Severe IC). There was a statistically significant difference between groups [$F(2.47) = 8.35$, $p < 0.001$].

A Tukey post hoc test showed that the Mild IC group was able to walk without pain further than the Moderate IC group ($p = 0.005$) and Severe IC group ($p < 0.001$) and these differences were statistically significantly. There was no statistically significant difference between the Moderate IC and Severe IC groups ($p = 0.691$).

Responsiveness

A paired samples *t*-test was performed to evaluate whether there was a difference between VascuQol-6 scores before the walking program and after the walking program. The results indicated that the VascuQoL-6 summary score after the physical exercise program (M = 17.41, SD = 2.71) was significantly higher than the VascuQoL-6 summary score before the physical exercise program (M = 15.65, SD = 3.09), $t(67) = 3.94$, $p = < 0.001$. There was also a statistically significant improvement in the symptoms, walking ability and pain items (item 2, 3 and 6).

Effect sizes of SF-36 domains and component summary scores and all items and summary score of VascuQoL-6 are shown in Table 5. According to Cohen's criteria, there was a

Table 5 – Responsiveness to change. Effect size of SF-36, domains and component summary scores, and VQ6, all items and summary score.

		Effect Score
VascuQoL-6	Activity	0.1
	Symptoms	0.5
	Walking activity	1.6
	Emotional aspects	0.1
	Social aspects	0.2
	Pain	0.3
	VascuQoL-6 summary score	0.5
SF-36	Physical functioning	1.0
	Physical role limitations	0.5
	Emotional role limitations	0.3
	Mental health	0.8
	Social functioning	0.3
	Energy/vitality	0.7
	General health perceptions	0.2
	Bodily pain	1.1
	Physical component summary score (PCS)	0.9
	Mental component summary score (MCS)	0.7

small effect size for Activity, Emotional, and Social aspects, a small to moderate effect size for Pain, a moderate effect size for Symptoms, and a large effect size for Walking activity. The VascuQoL-6 summary score showed a moderate effect size (d = 0.5).[34]

DISCUSSION

In this study of the psychometric properties of the HRQoL questionnaire VascuQoL-6 revealed an acceptable internal consistency, suggesting that the items within the questionnaire are sufficiently interrelated in measuring the construct of interest.[35] The observed internal consistency, while deemed satisfactory, also revealed that other validation studies conducted on the VascuQoL-6 reported higher alpha values, indicating stronger inter-item reliability in those investigations.[9,11,13,14] One plausible explanation for the differences might be the variations in the study populations across different validation studies. In our study, we deliberately excluded patients with critical ischemia, which represents the most severe form of PAD. By excluding this subset of patients, who often face unique challenges and significant impact on their QoL, we may have inadvertently influenced the internal consistency results of the VascuQoL-6.

In this sense, the average inter-item correlation was calculated and revealed a moderate level of inter-item correlation, reflecting a reasonable degree of homogeneity among the items. The average inter-item correlation provides valuable insights into the internal consistency of the VascuQoL-6 questionnaire, indicating that the items collectively contribute to a coherent measurement of peripheral artery disease-specific QoL.[29,39]

A good correlation between the physical domains and the PCS of the SF-36 and the VascuQoL-6 score was found, providing evidence of convergent validity, although the correlation between the VascuQoL-6 and the MCS was low (0.42), which may be due to the fact that VascuQoL-6 includes only one item that assesses emotional aspects. These results suggest that the VascuQoL-6 questionnaire is measuring a construct similar to the SF-36 and that it is a valid measure of QoL in individuals with vascular disease. Similar results were demonstrated in previous validation studies of the VascuQoL-6 instrument, where correlations between the dimensions of SF-36 and the items in the VascuQol-6 were somewhat stronger for the items representing physical components.[9,11,13]

No significant correlation between VascuQoL-6 scores and scores on either the PADKQ questionnaire or the IPAQ questionnaire was found. These findings suggest that the VascuQoL-6 is measuring a distinct construct from disease knowledge and physical activity, providing evidence for discriminant validity of the questionnaire.

In the present study, we aimed to assess the known-group validity of the VascuQoL-6 questionnaire by comparing its scores among three groups of patients with varying degrees of IC severity: mild, moderate, and severe. Our findings revealed that the VascuQoL-6 questionnaire demonstrated significant discriminative ability in distinguishing between patients with mild and moderate IC, as well as between those with mild and severe IC. These results suggest that the questionnaire is effective in capturing meaningful differences in vascular-related QoL between these two pairs of groups, indicating its sensitivity to varying degrees of disease impact on patients' daily lives.

When comparing patients with moderate and severe claudication, the known-group validity analysis did not yield significant differences in VascuQoL-6 scores between these two groups. This unexpected finding warrants further exploration and consideration. One possible explanation could be the overlapping symptomatology and functional limitations experienced by patients in the moderate and severe claudication groups. It is plausible that patients in both groups may experience comparable levels of impairment, leading to similar VascuQoL-6 scores. Additionally, the VascuQoL-6 questionnaire may have limitations in distinguishing the subtle differences in QoL experienced by patients with moderate versus severe claudication, particularly if the impact of the disease becomes more profound in both groups.

Despite the non-significant result in the comparison between moderate and severe IC groups, the overall findings provide valuable insights into the known-group validity of the VascuQoL-6 questionnaire. The significant differences observed between mild and moderate IC, as well as between mild and severe IC, indicate that the questionnaire is capable of capturing clinically meaningful distinctions in QoL in relation to disease severity. As such, the VascuQoL-6 remains a valuable tool for assessing the impact of PAD on patients' QoL, particularly in distinguishing between patients with mild disease and those with more pronounced impairment.

In the present study, we aimed to evaluate the responsiveness of the VascuQoL-6 questionnaire to an intervention involving the prescription of physical exercise for patients with PAD. Our results demonstrated promising evidence of the questionnaire's sensitivity to changes in vascular-related QoL following the physical exercise program.

Specifically, the overall responsiveness analysis revealed a moderate effect size for the VascuQoL-6 summary score, indicating a meaningful and noticeable improvement in patients' overall QoL after engaging in the prescribed physical exercise program. This finding suggests that the VascuQoL-6 can detect clinically important changes in vascular-related QoL, highlighting its relevance as a valuable outcome measure in the context of interventions targeting PAD. Larsen *et al*, and Soria-Juan *et al*, also had similar findings where excellent responsiveness to change was demonstrated.[9,13]

Some limitations were found with this study. The fact that the sample was collected in only one hospital in the north of the country does not allow us to generalize the results to other geographic areas. Moreover, the study cohort consisted primarily of male participants, potentially introducing a sex-related bias that may impact the generalizability of results. Another limitation is the variation in sample size, particularly the fact that only 49 patients completed the SF-36 questionnaire.

One significant limitation to acknowledge is the absence of a test-retest analysis. Ideally, such an analysis would have been valuable to assess the stability of responses over time. However, due to the three-month interval between assessments and the concurrent implementation of a physical exercise intervention, conducting a reliable test-retest analysis was not feasible within the constraints of the study. This extended interval and intervention may have introduced variability in participants' responses, potentially affecting the reliability of the instrument.

Additionally, the exclusion of patients with critical ischemia from the sample limits the generalizability of the results to this specific subgroup of individuals with PAD.

To address these limitations in future research, it is recommended that studies aim to recruit a more diverse and larger sample to enhance the external validity of the findings. While conducting a traditional test-retest analysis may not have been feasible in our study contexts, researchers can explore this method to assess the stability of responses over time. Additionally, investigating the instrument's performance in a broader range of PAD severity levels, including patients with critical ischemia, will provide a more comprehensive understanding of its utility in clinical practice.

CONCLUSION

This study presents the Portuguese version of the VascuQoL-6 questionnaire and contributes to its validation as an instrument to assess the QoL of Portuguese patients with PAD. This tool can be especially valuable in follow-up evaluations, to measure the result of the physical exercise prescription, more invasive surgical interventions, as well as to compare the results with the international literature.

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AUTHOR CONTRIBUTIONS

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

RP: Data acquisition, analysis, and interpretation, writing and critical review of the manuscript.

IS: Study design, writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Assessment of the Impact of Home-Based Hospitalization on Health Outcomes: An Observational Study

Avaliação do Impacto da Hospitalização Domiciliária nos Resultados em Saúde: Um Estudo Observacional

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ABSTRACT

Introduction: In Portugal, evidence of clinical outcomes within home-based hospitalization programs remains limited. Despite the adoption of home-based hospitalization services, it is still unclear whether these services represent an effective way to manage patients compared with inpatient hospital care. Therefore, the aim of this study was to evaluate the outcomes of home-based hospitalization compared with conventional hospitalization in a group of patients with a primary diagnosis of infectious, cardiovascular, oncological, or 'other' diseases.

Methods: An observational retrospective study using anonymized administrative data to investigate the outcomes of home-based hospitalization (n = 209) and conventional hospitalization (n = 192) for 401 Portuguese patients admitted to CUF hospitals (Tejo, Cascais, Sintra, Descobertas, and the Unidade de Hospitalização Domiciliária CUF Lisboa). Data on demographics and clinical outcomes, including Barthel index, Braden scale, Morse scale, mortality, and length of hospital stay, were collected. The statistical analysis included comparison tests and logistic regression.

Results: The study found no statistically significant differences between patients' admission and discharge for the Barthel index, Braden scale, and Morse scale scores, for both conventional and home-based hospitalizations. In addition, no statistically significant differences were found in the length of stay between conventional and home-based hospitalization, although patients diagnosed with infectious diseases had a longer stay than patients with other conditions. Although the mortality rate was higher in home-based hospitalization compared to conventional hospitalization, the mortality risk index (higher in home-based hospitalization) assessed at admission was a more important predictor of death than the type of hospitalization.

Conclusion: The study found that there were no significant differences in outcomes between conventional and home-based hospitalization. Home-based hospitalization was found to be a valuable aspect of patient- and family-centered care. However, it is noteworthy that patients with infectious diseases experienced longer hospital stays.

Keywords: Home Care Services, Hospital-Based; Hospitalization; Patient-Centered Care; Patient Safety

RESUMO

Introdução: Em Portugal, a evidência dos resultados clínicos dos programas de Hospitalização Domiciliária tem sido limitada. Apesar da adoção de serviços de hospitalização domiciliária, ainda não se sabe se estes representam uma forma eficaz de gerir os doentes em comparação com os cuidados hospitalares em regime de internamento. Por conseguinte, este estudo avaliou o impacto da hospitalização domiciliária em comparação com a hospitalização convencional em doentes que receberam um diagnóstico primário de doença infecciosa, cardiovascular, oncológica ou 'outro'.

Métodos: Foi realizado um estudo observacional retrospetivo com recurso a dados administrativos anonimizados para investigar os resultados da hospitalização domiciliária (n = 209) e da hospitalização convencional (n = 192) em 401 doentes portugueses internados em hospitais CUF (Tejo, Cascais, Sintra, Descobertas e Unidade de Hospitalização Domiciliária CUF Lisboa). Foram recolhidos dados demográficos e de resultados clínicos, nomeadamente índice de Barthel, escala de Braden, escala de Morse, mortalidade e tempo de internamento. A análise estatística incluiu testes de comparação e regressão logística.

Resultados: Neste estudo não foram encontradas diferenças estatisticamente significativas na variação no índice de Barthel, na escala de Braden e na escala de Morse entre a admissão e a alta hospitalar, tanto nos doentes em hospitalização domiciliária como hospitalização convencional. Não foram encontradas diferenças estatisticamente significativas no tempo de internamento entre a hospitalização domiciliária e hospitalização convencional, mas os doentes diagnosticados com doenças infeciosas apresentaram um tempo de internamento maior do que os restantes doentes. Embora a taxa de mortalidade tenha sido maior na hospitalização domiciliária do que na hospitalização convencional, o índice de risco de mortalidade (elevado na hospitalização domiciliária) avaliado na admissão revelou-se um preditor mais importante de morte do que o tipo de hospitalização.

Conclusão: Não foram observadas diferenças significativas nos resultados entre a hospitalização convencional e a domiciliária. A hospitalização domiciliária pode ser considerada um aspeto valioso dos cuidados centrados no doente e na família. No entanto, é de salientar que os doentes com doenças infecciosas tiveram estadias hospitalares mais longas.

Palavras-chave: Cuidados Centrados no Doente; Hospitalização; Segurança do Doente; Serviços Hospitalares de Assistência Domiciliar

INTRODUCTION

Home-based hospitalization (HBH) constitutes a model of care that provides person-centered active treatment in the homes of persons who require acute care.[1] It is a popular response to the increasing demand for acute hospital beds.[2,3] Caplan *et al* conducted a meta-analysis which included 61 randomized controlled trials of HBH models,

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indicating significant reductions in mortality and readmission rates, better patient and caregiver satisfaction, and decreased costs.[4] The central goals of such schemes are cutting costs by avoiding hospital admission and reducing hospital length of stay (LOS).[3]

Delivering acute HBH has been shown to be a safe, effective, and cost-effective alternative to conventional hospitalization (CH).[5,6] Home-based hospitalization can be crucial in decentralizing care, accelerating rapid ramp-ups in bed capacities, and controlling nosocomial infections.[7] The COVID-19 pandemic brought new necessities and motivation to the HBH research field.[3] It highlighted that this model could be viable in caring for inpatients with and without COVID-19 in one of the world's regions with the highest burden, i.e., New York City.[8] Moreover, with the growing aging population worldwide, more extended living can lead to increased demand for care.[9,10] Growing public health care expenditure raises concerns about its long-term sustainability. The European Union's (EU) public health expenditure was 6.6% of the gross domestic product (GDP) in 2019. The projections show that expenditure may only grow to 7.7% of GDP in 2070 due to demographic aging. Therefore, alternatives are needed.[11]

The impact and efficiency of HBH have been widely researched in previous studies for distinct conditions: cancer,[2] chronic obstructive pulmonary disease,[12-17] COVID-19,[3,8] stroke,[18,19] neuromuscular diseases,[20] heart failure,[17,21-25] diabetes,[26] among others.[7,27,28] The impact and efficiency of HBH were also analyzed in different groups (e.g., geriatric,[5,28-30], adult[17] and pediatric[31] populations) and various countries (e.g., Italy,[25] Spain,[21,32] Sweden,[23] Singapore,[33] United Kingdom,[30,34] the United States[3,6,17]), with a focus on specific clinical issues (e.g., ulcer area,[26] changes in forced expiratory volume in one second[13]) and diverse outcomes (e.g., mortality,[4,24,35] LOS[5,7,30]), as well as costs.[4,17,29,34]

Although HBH has been associated with saving costs and improved health outcomes, this model does not seem to represent the change in care burden.[4] A recent meta-analysis suggests that patients with chronic conditions who presented to the emergency department and were treated with HBH interventions had a reduced risk of hospital readmission and long-term care admission compared to those who received CH.[27] Conversely, findings from the meta-analysis revealed that HBH increased the time to readmission, reduced index costs, and improved health-related quality of life among patients requiring hospital-level care for heart failure. However, larger randomized control trials were needed to confirm the effect of HBH on readmissions, mortality, and long-term costs.[24]

Recently, Leong *et al* investigated the safety and effectiveness of HBH according to program type (early supported discharge *versus* admission avoidance) using secondary studies. The early supported discharge reviews generally revealed comparable readmissions to inpatient care, shorter hospital LOS, and unclear cost findings. In contrast, admission avoidance reviews reflected a trend towards lower mortality, costs, and comparable or lower readmissions. In summary, HBH commonly results in similar or enhanced clinical outcomes for proper patients compared with inpatient treatment. It demonstrates greater attention in healthcare systems confronting capacity constraints and rising costs. Finally, when comparing the program type, the prioritization of admission avoidance models over early supported discharge was suggested due to potential advantages in costs and clinical outcomes.[7]

Despite the increasing attention given to early discharge HBH services as a cost-effective alternative to inpatient care, it remains to be seen whether patients receiving personalized care at home have better or comparable health outcomes to those receiving inpatient care.[36] Recent systematic reviews provide evidence of economic benefits, such as reduced LOS or improved health outcomes for patients receiving HBH services.[35] However, patients who receive care at home may experience greater satisfaction with their personalized care because they are often in a more comfortable and relaxed environment.[37] Home-based care enables patients to receive care in a familiar setting, with individualized attention from caregivers who can better understand their unique needs and preferences. As a result, this may lead to increased patient satisfaction and improved quality of care. Therefore, it is evident that personalized healthcare in home-based hospitalization requires further research and evaluation to understand its potential benefits and limitations fully.

Future research should clarify the clinical outcomes of HBH programs given the current low-quality evidence and address evidence gaps on clinical outcomes and adverse events under HBH care[7] in Portugal. The aim of this observational study was to contribute to the limited evidence of HBH services in Portugal by comparing their impact with CH using samples of adult patients. We hypothesized that HBH does not represent a method with clinical inferiority compared to CH regarding clinical outcomes (namely, dependence, ulcers, and falls). The primary aim of this study was to explore the impact and effectiveness of HBH, compared with CH, in the Portuguese adult population for three specific outcomes (dependence, ulcers, and falls). The secondary aim was to compare the LOS and mortality between patients admitted to HBH and CH.

METHODS

Design and database

An observational retrospective study was conducted among patients receiving HBH and CH care from 2020 to

2022. We analyzed data from patients admitted to CUF Hospitals, which originates from the facilities of Tejo, Cascais, Sintra, and Descobertas and the Unidade de Hospitalização Domiciliária CUF Lisboa.

Procedures for data use and storage were in compliance with the General Data Protection Regulation rules and conducted under the Declaration of Helsinki. Data was fully anonymized before being accessed. The study was approved by the Hospital CUF Tejo Ethics Committee (No. 2023310).

The inclusion criteria were: (a) hemodynamically stable medical condition, (b) family member or accompanying person at home, (c) residence during hospitalization in the catchment area of a CUF hospital unit, and (d) patient and caregiver expressed the desire to be accompanied at home. The exclusion criteria were: (a) acute psychiatric condition and suicidal ideation, (b) intravenous drug users, (c) indigent and homeless, and (d) children.

The patients in the study were categorized into four groups: oncological, cardiovascular, infectious, or other diseases. The patients were classified based on their main diagnosis, which was determined using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Patients with a primary diagnosis of infection (such as urinary tract infection) were placed in the infectious diseases group, while patients with a primary diagnosis of circulatory system condition (such as heart failure) were placed in the cardiovascular diseases group. Patients with an active cancer diagnosis (such as uncontrolled cancer pain) were placed in the oncological group, while all other patients were grouped under 'other diseases'.

Patient outcome measures

The primary outcomes were the risk of developing ulcer pressure, level of (in)dependence, and fall risk. These clinical outcome measures were collected during the admission (baseline) and discharge and reported by the clinical team. The secondary outcomes were LOS and mortality.

Data collection

The following instruments were used for data collection:

All-patient refined diagnosis-related groups' severity of illness and risk of mortality

It provides a more accurate predictor of resource use by assigning a severity of illness subclass and risk of mortality subclass to each episode in addition to the Diagnosis-Related Groups. It is important to note that the severity of illness and mortality are Diagnosis-Related Groups-specific and depend on other underlying characteristics of patients (comorbidities). All-Patient Refined Diagnosis-Related Groups' are divided into four Severity of Illness and Risk of Mortality subclasses, ranging from 1 to 4 (1 = 'minor' to 4 = 'extreme'). Risk of Mortality and Severity of Illness are calculated separately based on secondary diagnoses and their interaction with age, primary diagnosis, and procedures. According to the extent of physiological decomposition or loss of organ system function, the severity of illness determines the overall patient condition. At the same time, the risk of mortality estimates the likelihood of in-hospital mortality.[38]

Braden scale

The risk of developing ulcer pressure was evaluated by the Braden scale, a standardized, evidence-based assessment tool commonly used in health care to assess and document a patient's risk of developing pressure injuries. The Braden scale seems to offer the best balance between sensitivity and specificity and the best risk estimate.[39] The Braden scale comprises six subscales. Each subscale assesses the following dimensions: sensory perception, skin humidity, mobility, nutrition, and friction/shear forces. Each subscale has an attributed value and varies between one and four: the lower the value, the more prone to developing ulcer pressure. The Portuguese guidelines support the implementation of regular pressure ulcer risk assessments by applying the Braden scale. It also recommends the patients' categorization into two levels of risk (low and high), defined by a cut-off point of 16. Hence, patients with an evaluation of the Braden scale score lower or equal to 16 have an increased risk of developing pressure ulcers, and patients with a score higher than 16 have a lower risk of developing pressure ulcers.[40,41]

Barthel index

The Barthel index is a tool that can measure a subject's level of (in)dependence to perform ten basic life activities. It includes eating, chair transfer to bed, bathing, gait, and stair climbing.[42] The scoring varies between 0 and 100 (with intervals of five points), where the lowest score corresponds to the highest level of dependence on all activities of daily living and vice-versa. Previous research reports the validity of the Portuguese version as high internal consistency, supported by the α Cronbach = 0.96.[43,44]

Morse fall scale

The likelihood of falling (or falls risk) was analyzed by the Morse fall scale, which consists of six items reflecting risk factors: previous history of falls; the existence of a secondary diagnosis; walking support; intravenous therapy; posture during walking and transference and mental status. The total score of the scale ranges between 0 and 125, and the individuals are classified according to the risk presented as no risk (0 - 24), low risk (25 - 50), and high risk (≥ 51).[45] In 2011, the European Portuguese version of the Morse scale was developed, which revealed that reliability was tested through the degree of agreement of the scores provided by nurses. It demonstrated a high agreement between the

evaluators using the scale.[46]

Data analysis

We present descriptive statistics for HBH and CH (frequency and percentages for categorical and continuous medians and interquartile ranges, as appropriate). Based on the sample size, Shapiro-Wilk was used to verify the normality of the continuous variables. Mann-Whitney U and analysis of covariance (ANCOVA) tests were used to calculate the average differences and the chi-square test for categorical variables. When a significant effect was found, the Tukey-Kramer test detected significant mean differences ($p < 0.05$). During the period of hospitalization between the initial assessment and the time of discharge, various clinical outcomes were evaluated using standardized measures, including the Barthel index, Braden scale, and Morse scale.

By comparing the scores at the time of discharge to those at the time of admission, we could determine the magnitude of improvement or decline in the patient's condition. In the Braden and Barthel scales, a positive difference between scores indicated an improvement in clinical outcomes, while in the Morse scale, a positive difference indicated a decline. Therefore, we calculated the interquartile range (IQR) to determine the extent of improvement or decline and classified the outcomes as worse, equal, or better. Appropriate statistical tests were employed for categorical variables to analyze the data. We conducted an ANCOVA to test the interaction of LOS with the type of hospitalization, primary diagnosis, mortality index, and severity index, with age adjustment. Through logistic regression, secondary exploratory analyses examined the association between the primary outcome measures and the selected predictive variables (including the patient's age, type of hospitalization, severity index, mortality index, and primary diagnosis). We hypothesized that most of these variables could influence patients' mortality in both programs. Analyses were performed using Python (Jupyter notebook), and *p*-values under 0.05 were considered significant.

RESULTS

Demographics

Four hundred and one patients were included from HBH (n = 209) and CH (n = 192). There was no statistically significant difference between the type of hospitalization groups regarding gender, and there was a statistically significant difference in age (Table 1). Regarding the primary diagnosis, the infectious diseases were more prevalent than the other diagnoses in the sample (HBH 74.6% *vs* CH 39.1%; $p < 0.001$) (Table 1). Oncological and cardiovascular were the second and third most reported conditions in the HBH group (12.4% and 7.7%, respectively). In the HC group, cardiovascular, and oncological were the second and third most

Table 1 – Baseline patient characteristics and outcomes, n (%)

Outcome measure	Home-based n = 209	Conventional n = 192	*p*-value
Age (years), median (IQR)	84 (16)	77 (20)	**< 0.001**
Sex (female), n (%)	98 (46.9)	92 (47.9)	0.916
Group primary diagnosis, n (%)			
Cardiovascular	16 (7.7)	44 (22.9)	**< 0.001**
Oncological	26 (12.4)	42 (21.9)	
Infectious	156 (74.6)	75 (39.1)	
Other	11 (5.3)	31 (16.1)	
LOS (days), median (IQR)	9 (7)	7 (10)	**0.002**
Mortality, n (%)	60 (28.7)	23 (12.0)	**< 0.001**
Severity index			
1	37 (17.7)	34 (17.7)	0.918
2	90 (43.1)	88 (45.8)	
3	73 (34.9)	61 (31.8)	
4	9 (4.3)	9 (4.7)	
Mortality index			
1	53 (25.4)	58 (30.2)	0.671
2	87 (41.6)	73 (38.0)	
3	60 (28.7)	55 (28.6)	
4	9 (4.3)	6 (3.1)	

LOS: length of stay; IQR: interquartile range

reported conditions (22.9% and 21.9%, respectively). In terms of mortality, the HBH group had a higher prevalence (p = 0.001) and LOS (p = 0.002) than CH for participants who died during the program. Concerning the Severity and Mortality indexes, there was no difference between the programs (p > 0.05) (Table 1).

Clinical outcomes

Table 2 documents comparative analyses of clinical outcomes regarding distribution, using chi-squared tests. The Braden scale showed significant differences in distribution between groups for both baseline and discharge (p < 0.05) regarding the risk of developing ulcers. The Barthel index at baseline was also significantly different (p < 0.007), measuring the level of independence. Furthermore, the Morse scale differed significantly in distribution between groups at baseline and discharge (p < 0.05) in terms of risk of falls. Table 3 presents a comparison of patient clinical outcomes during different types of hospitalizations, using U Mann-Whitney and chi-squared tests. The table provides insights into the scores, differences between the scores at the time of discharge and admission, and the attributed categories. This analysis aimed to determine if there were any differences in outcomes between baseline and discharge, categorized as worse, equal, or better (as described in the 'Data analysis' section). The results showed that there were no statistically significant differences in the clinical outcomes variation (Barthel index, Braden scale, and Morse scale) between admission and discharge for CH and HBH (p > 0.005), as illustrated in Table 3. These findings suggest no significant variation in patient outcomes between the two types of hospitalizations.

Length of stay

We performed an ANCOVA to test the relationship between the type of hospitalization, age, severity index, mortality index, and primary disease in terms of LOS (Table 4). Significant differences regarding the primary diagnosis

Table 2 – Comparison of patient clinical outcomes in terms of distribution, n (%)

Clinical outcome measures	Home-based	Conventional	*p*-value
Braden at baseline, n (%)			
Low risk	38 (48.1)	78 (67.2)	**0.012**
High risk	41 (51.9)	34 (32.8)	
Braden at discharge, n (%)			
Low risk	90 (49.7)	130 (72.2)	**< 0.001**
High risk	91 (50.3)	50 (27.8)	
Barthel at baseline, n (%)			
Independent	19 (18.8)	14 (23.7)	
Slight dependency	18 (17.8)	24 (40.7)	
Moderate dependency	12 (11.9)	5 (8.5)	**0.007**
Severe dependency	16 (15.9)	7 (11.9)	
Total dependency	36 (35.6)	9 (15.3)	
Barthel at discharge, n (%)			
Independent	20 (26.7)	16 (33.3)	
Slight dependency	18 (24.0)	17 (35.4)	
Moderate dependency	10 (13.3)	3 (6.3)	0.308
Severe dependency	10 (13.3)	6 (12.5)	
Total dependency	17 (22.7)	6 (12.5)	
Morse at baseline, n (%)			
Low risk	13 (15.7)	34 (28.1)	
Slight risk	38 (45.8)	58 (48.0)	**0.032**
High risk	32 (15.7)	29 (24.0)	
Morse at discharge, n (%)			
Low risk	37 (23.4)	48 (36.9)	
Slight risk	72 (45.6)	61 (46.9)	**0.004**
High	49 (31.0)	21 (16.1)	

LOS: length of stay

Table 3 – Comparison of patient clinical outcomes in terms of patient evolution

Clinical outcomes	Barthel		Braden		Morse	
Type of program	HBH	CH	HBH	CH	HBH	CH
N patients	52	41	72	110	70	81
Median entry	55	70	16.5	19	50	35
Median discharge	55	75	16	19	42.5	35
Differences score median	0.0	0.0	0.0	0.0	12.5	0.0
Differences score IQR	[-6.25 – 5.0]	[-5.0 – 0.0]	[-2.0 – 1.0]	[-1.0 – 1.75]	[-20.0 – 10.0]	[-20.0 – 0.0]
Differences score *p*-value	0.694		0.513		0.515	
Clinical outcomes (%)						
Worse	21.2	14.6	8.3	10.9	30	27.2
Equal	65.4	65.9	81.9	79.1	55.7	58
Better	13.5	19.5	9.7	10.0	14.3	14.8
***p*-value**	0.590		0.843		0.928	

HBH: Home-base hospitalization; CH: Conventional hospitalization

($p < 0.001$) and the severity index ($p < 0.001$) were found, including the interaction effect between them, which was also significant ($p < 0.001$). Patients with infectious diseases demonstrated the highest LOS compared to the other groups. In the specific analysis by groups, it was observed that the LOS was significantly longer for patients with infectious diseases [cardio-infectious ($p < 0.05$), oncological-infectious ($p < 0.001$), and other-infectious ($p < 0.05$)].

In terms of severity, we found significant differences between levels 1 and 3 ($p < 0.05$), levels 1 and 4 ($p < 0.05$), and levels 2 and 3 ($p < 0.05$). The post hoc analysis revealed that the LOS was lower in level 1 than in 3 ($p < 0.05$) and 4 ($p < 0.05$), and it was lower in level 2 than in 3 ($p < 0.05$). The LOS was significantly higher in the infectious diseases group (cardiovascular $p < 0.05$, oncological $p < 0.001$, other diagnoses $p < 0.005$). On the other hand, the type of hospitalization and mortality index did not influence the LOS ($p < 0.082$). Therefore, not surprisingly, the interaction between the type of hospitalization jointly with primary diagnosis was not statistically significant ($p > 0.05$). Finally, age did not demonstrate an influence on LOS ($p > 0.05$) (Table 4).

Mortality

An exploratory analysis was conducted using logistic regression to determine which factors might influence death – coded 0 as the reference = did not die during the program and 1 = dead during the stay (Table 5). In summary, the model indicated that the type of hospitalization (HBH) and mortality index (at levels 3 and 5) were significant predictors of death ($p < 0.001$), as well as with increasing age ($p < 0.05$). Moreover, none of the other independent variables demonstrated an influence regarding mortality ($p > 0.05$).

DISCUSSION

The present study investigated patients from two different hospitalization programs (HBH and CH) and evaluated the population in terms of clinical outcomes. To our knowledge, this is the first Portuguese study, including the patient's primary diagnosis as infectious, cardiovascular, oncological, or 'other' diseases in the aforementioned field. In summary, the Morse score was not equally distributed between the groups. Falls were also the second most common adverse event during hospitalization, which can cause critical complications, such as fractures (skull,

Table 4 – Analysis of covariance

Length of stay	Sum SQ	F	*p*-value	Omega SQ
Intercept	37.860	61.120	**< 0.001**	0.101
Type of hospitalization	1.884	3.041	0.082	0.003
Severity index	7.854	4.226	**0.006**	0.016
Primary diagnosis	31.962	17.199	**< 0.001**	0.082
Mortality index	3.267	1.758	0.155	0.004
Type of hospitalization: Primary diagnosis	2.192	1.180	0.317	0.001
Severity index: Primary diagnosis	47.373	8.497	**< 0.001**	0.114
Age	0.009	0.015	0.902	-0.002

Dependent variable (length of stay)

Table 5 – Logistic regression model determining the association between mortality (dependent variable) and selected domains

Inputs	Coeff	Odds ratio	*p*-value	Lower CI	Higher CI
Age	0.030	1.031	**0.026**	1.004	1.058
Type hospitalization					
CH	1.000	1.000	1.000	1.000	1.000
HBH	1.276	3.582	**0.001**	1.893	6.775
Severity index					
1	1.000	1.000	1.000	1.000	1.000
2	0.411	1.508	0.471	0.494	4.602
3	-0.058	0.944	0.927	0.272	3.272
4	-1.669	0.188	0.139	0.021	1.715
Mortality index					
1	1.000	1.000	1.000	1.000	1.000
2	0.948	2.581	0.084	0.881	7.557
3	2.394	10.958	**0.001**	3.318	36.187
4	4.339	76.629	**0.001**	9.607	611.252
Primary diagnosis					
Cardiovascular	1.000	1.000	1.000	1.000	1.000
Infectious	-0.282	0.754	0.518	0.321	1.773
Oncological	0.893	2.443	0.071	0.926	6.445
Other	-0.392	0.676	0.572	0.174	2.629

hips, shoulders, and ribs), while other symptoms, like depression and loss of self-confidence, increase the LOS and medical costs.[47]

Our main results suggested there were no differences in terms of Braden and Barthel's scales regarding the type of hospitalization and between admission and discharge. Regarding the clinical outcomes, namely, the risk of developing ulcers, previous research compared the home care service *versus* hospital-based care in patients with diabetic foot ulcers, concluding that rate of ulcer size reduction in CH was significant ($p < 0.003$) compared with HBH. The study of Sardo *et al* included 8147 Portuguese hospitalized adults, the participants with significantly lower Braden scale scores were older, hospitalized in medical units, admitted for emergency services, with longer hospital stays, and/or had vascular, traumatic injuries, respiratory, infection or cardiac diseases.[41] Like our results,[22] changes in Barthel scores, i.e., levels of (in)dependence over the follow-up period, were negligible. However, it suggested that HBH allows a critical decline in costs during the index episode compared with hospital care whilst preserving equivalent outcomes concerning cardiovascular mortality and morbidity and quality of life at one-year follow-up in patients with cardiovascular disease.[22]

As the primary diagnosis, patients with infectious diseases had a higher LOS compared to patients with other conditions. When comparing the type of program, there was no relationship between LOS. Moreover, the mortality index did not seem to influence the LOS even when associated with the primary diagnosis, which could help explain the variance. Our study suggested that the mortality risk index is a more important predictor of death than the type of hospitalization. While we found that HBH was associated with a higher risk of death compared to CH, it is essential to note that the mortality index may serve as a more robust indicator of future mortality. Despite similar severity indexes and mortality risks, there was a clear predominance of infectious diseases in the HBH group, which may have contributed to the higher mortality. The mortality rate among patients in the HBH group was 3.582, which is higher than that of the CH group. Our results regarding mortality are consistent with those of previous studies[12,13,22,25] but differ from others.[30] For instance, Tibaldi *et al* found no significant difference in mortality between patients receiving care at the geriatric home hospitalization service and those in the general medical ward. However, only geriatric home hospitalization service patients experienced improvements in depression, nutritional status, and quality-of-life scores.[25]

A study conducted by Tierney *et al* used a one-year retrospective design to examine the admission and post-discharge clinical outcomes of patients in a Northern Ireland care of the elderly ward (n = 191) and a consultant-led acute care at home service (n = 314). The study found that HBH was a viable alternative to hospitals for older patients

and could prevent functional decline and the need for domiciliary care or nursing home placement.[30] Albeit, in terms of end-of-life, a Cochrane review reported that HBH end-of-life care increased the likelihood of dying at home compared with conventional care.[36] Although our study did not examine readmissions, previous research has suggested that recurrent readmissions may be linked to a higher mortality rate in certain patient populations.[48] Therefore, future studies should continue to explore the role of various factors, including mortality level and readmission rates, in predicting patient outcomes and mortality.

In the present study, since limited information was available, its findings should be interpreted cautiously due to limited information and the absence of risk adjustment for variables identified as significant in the comparison between groups. This may restrict the generalizability of results to different populations. Risk adjustment was not performed due to limited data availability, which could increase the risk of overfitting. Future research should include risk adjustment to enhance the precision and robustness of findings. Further studies are needed to identify medical conditions suited for home treatment. Patients' multimodal information, such as (e)Health literacy, must be assessed to judge whether a treatment-compliant behavior can be expected. It is also important to highlight that there is a lack of information on the quality of the patient's home. Future studies should consider the quality of the home environment and assess it appropriately. Implementing standard operating procedures would help to standardize patient inspection and ensure patient safety. Patient safety is crucial in healthcare settings, where research is required to carefully select which patients should be treated at home.

Patient selection for HBH should consider the clinical parameters and social and cognitive aspects of each patient, resulting in a more patient-centered approach, therefore, increasing patient safety and satisfaction.[9] The study involved a restricted population and a small sample of patients with some specific primary diagnosis. Additionally, the study was conducted within a private setting at CUF Hospitals, which may limit generalizability. Patients with infectious diseases, especially the elderly, represent a heavy burden for hospitals and, therefore, indirectly to society. Although the present study was not designed to evaluate and compare the economic effects of these approaches, i.e., HBH or CH, previous research suggests that HBH may be cost-effective and have a place in reducing the pressure on hospital beds. Therefore, one limitation of the current study is that it did not evaluate the costs and satisfaction levels of the users involved. However, it has been reported that patients and their families usually express high levels of satisfaction with HBH services.[5,7,9,12,14,17,20,24,35] Future studies should focus on costs and satisfaction with HBH programs in the Portuguese population.

CONCLUSION

The patients analyzed in this study have a high degree of complexity, and the inferiority in outcomes in HBH compared to CH was not found. Interestingly, our results show that the hospitalization type was not associated with the Barthel, Braden, and Morse scores and LOS. However, we found that patients with infectious diseases had longer LOS, even after adjusting for age. The study did not find statistically differences between CH and HBH for the assessed outcomes. In addition, no statistically significant differences were found in the LOS between CH and HBH.

The present study has important implications for healthcare providers and stakeholders. It highlights that more attention needs to be given to HBH, particularly in healthcare systems that face capacity constraints and rising costs. Home-based hospitalization is a service that may be considered part of an integrated response in the inpatient journey, not just for complex patients but as a practice to provide a more humanized healthcare service according to the preferences of patients and their families.

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AUTHOR CONTRIBUTIONS

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

CR, MS: Study design, data collection and critical review of the manuscript.

RG: Study design and data collection.

FGF, EO: Data analysis and writing of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Psychiatric Comorbidities in Neurologic Hospitalizations in Portugal: A Nationwide Retrospective Observational Study

Comorbilidades Psiquiátricas em Doentes Internados por Doenças Neurológicas em Portugal: Estudo Observacional Retrospectivo Nacional

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ABSTRACT

Introduction: Psychiatric comorbidities have a significant impact on patients' quality of life and often go undetected in neurologic practice. The aim of this study was to describe and characterize psychiatric comorbidities among patients hospitalized due to a neurologic disorder in mainland Portugal.

Methods: A retrospective observational study was performed by analyzing hospitalization with a primary diagnosis of neurologic disorder defined as categories 76, 77, 79 - 85, 95, 109 of the Clinical Classification Software for International Classification of Diseases, Ninth Revision, Clinical Modification, occurring between 2008 and 2015 in adult patients (≥ 18 years of age). Psychiatric comorbidities were determined as the presence of a secondary diagnosis belonging to the Clinical Classification Software categories 650 to 670.

Results: A total of 294 806 hospitalization episodes with a primary diagnosis of a neurologic disorder were recorded in adult patients between 2008 - 2015 in Portuguese public hospitals. Approximately 26.9% (n = 79 442) of the episodes had a recorded psychiatric comorbidity (22.1%; 32.2%, female *versus* male hospitalizations). Patients with registered psychiatric comorbidities were younger (66.2 ± 16.2 *vs* 68.6 ± 17.2 with no psychiatric comorbidities, $p < 0.001$), presented lower all-cause in-hospital mortality rates, and significantly longer mean hospital stays. '*Delirium*, dementia, amnestic and other cognitive disorders' were recorded in 7.4% (n = 21 965) of the hospitalizations, followed by alcohol-related disorders in 6.5% (n = 19 302) and mood disorders in 6.1% (n = 18 079). Epilepsy/seizures were the neurologic disorders with the highest proportion of recorded psychiatric comorbidities (39.9%).

Conclusion: Psychiatric comorbidities were recorded in more than a quarter of the hospitalizations with a primary diagnosis of a Neurologic disorder. Psychiatric comorbidities varied among neurological disorders and were associated with different demographic and clinical features.

Keywords: Comorbidity; Hospitalization; Mental Disorders; Nervous System Diseases

RESUMO

Introdução: As comorbilidades psiquiátricas têm um impacto significativo na qualidade de vida dos doentes e passa frequentemente despercebida na prática neurológica. O objetivo deste estudo foi descrever e caraterizar as comorbilidades psiquiátricas em doentes hospitalizados por doença neurológica em Portugal.

Métodos: Foi efetuado um estudo observacional retrospetivo, analisando hospitalizações com diagnóstico primário de doença neurológica definida através das categorias 76, 77, 79 - 85, 95, 109 do *Clinical Classification Software* para *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* ocorridas entre 2008 e 2015 em doentes adultos (≥ 18 anos). As comorbilidades psiquiátricas foram determinadas pela presença de um diagnóstico secundário pertencente às categorias 650 a 670 do *Clinical Classification Software*.

Resultados: Um total de 294 806 internamentos com diagnóstico primário de doença neurológica foram registados em doentes adultos entre 2008 e 2015 nos hospitais públicos portugueses. Aproximadamente 26,9% (n = 79 442) dos episódios tinham uma comorbilidade psiquiátrica registada (22,1%; 32,2%, sexo feminino *versus* masculino). Doentes com comorbidade psiquiátrica registada eram mais jovens (66,2 ± 16,2 *vs* 68,6 ± 17,2 sem comorbilidade psiquiátrica, $p < 0,001$), apresentavam menor taxa de mortalidade hospitalar e tempo de internamento significativamente mais longo. 'Delírio, demência e outros transtornos cognitivos' foram registados em 7,4% (n = 21 965) das hospitalizações, seguidos por perturbações relacionadas com o uso do álcool em 6,5% (n = 19 302) e perturbações de humor em 6,1% (n = 18 079). Epilepsia/convulsões foram os distúrbios neurológicos com proporção de comorbilidade psiquiátrica registada (39,9%).

Conclusão: As comorbilidades psiquiátricas foram registadas em mais de um quarto das hospitalizações com diagnóstico primário de uma doença neurológica. As comorbilidades psiquiátricas variam entre as doenças neurológicas e estão associadas a diferentes características demográficas e clínicas.

Palavras-chave: Comorbilidade; Doenças do Sistema Nervoso; Hospitalização; Perturbações Mentais

INTRODUCTION

Neurological disorders account for nearly 12% of the total number of deaths worldwide and are the leading cause of overall disease burden, represented by the number of years of healthy life lost due to disability.[1] Psychiatric comorbidities, such as major depression, neurocognitive disorder, anxiety, substance use, and schizophrenia-spectrum disorders, are frequent among general medical inpatients, with prevalence rates ranging from 12% to 53%.[1-9]

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Psychiatric illness is common among patients with neurological conditions and is often unrecognized.[1,2,9,10] Up to 50% of patients with neurological disorders develop depression.[1,9-12] Anxiety and adjustment disorders have been commonly described in patients with a diagnosis of migraine.[1,12] Functional neurological symptoms are common; it was reported that 14% of consecutive neurological admissions had no 'organic' basis for their symptoms, while 24% had symptoms not fully explained by the underlying condition.[1,9] Moreover, drugs used in the treatment of neurological diseases may induce psychiatric manifestations.[1,9,13] Nevertheless, in the available studies, the additional referral of neurologic patients to psychiatric services was low, which may contribute to the under-diagnosis and under-treatment of psychiatric comorbidities and consequently worse quality of life, functionality, lower adherence to treatment, higher risk of suicide, and a significant socioeconomic burden.[1,2,9,13,14]

The comorbidities of outpatients and inpatients differ significantly. To date, few studies have reported hospitalizations due to neurological causes and none has been carried out in Portugal.[1,2,15-17]

There is evidence suggesting that the request for a psychiatric consultation in neurological settings is associated with a more accurate diagnosis, better treatment and prognosis, and shorter length of stay,[1,18,19] especially when the consultation occurs earlier in the hospitalization course.[1,18] Thus, the aim of this study was to determine the prevalence of psychiatric diagnoses in patients admitted with a primary diagnosis of a neurologic disorder in Portuguese public hospitals. Secondly, we intended to analyze and describe clinical, sociodemographic, and administrative differences in all hospitalizations with a primary diagnosis of a neurologic disorder with and without psychiatric comorbidities.

METHODS

Study design

A retrospective observational study was conducted following the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) reporting guidelines by analyzing all hospitalization episodes occurring in mainland Portuguese public hospitals between 2008 and 2015. The unit of analysis was the hospitalization episode.

Setting

The database used in this study was provided by the Central Administration of the Health System of the Portuguese Ministry of Health (ACSS) and gathers administrative and clinical data from all hospitalization episodes occurring in all public mainland hospitals of Portugal. In Portugal, most hospitalizations occur in the public sector [approximately 70% according to the National Statistics Institute (INE) (2017)[1,20]].

Participants

All hospitalization episodes with a primary diagnosis of a neurologic disorder, here defined as categories 76, 77, 79 - 85, 95, 109 of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (AHRQ HCUP) Clinical Classification Software (CCS), occurring between 2008 and 2015 in adult patients (≥ 18 years of age) were selected. These groups gather International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes in the following larger groups: acute cerebrovascular disease; meningitis (except that caused by tuberculosis or sexually transmitted disease); encephalitis (except that caused by tuberculosis or sexually transmitted disease); Parkinson's disease (PD); multiple sclerosis; other hereditary and degenerative nervous system conditions; paralysis; epilepsy; headache, including migraine; coma, stupor, and brain damage; other nervous system disorders. We excluded CCS 78: other CNS infection and poliomyelitis. The single-level International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of each group are extensively defined in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20969/15414).

Psychiatric comorbidity was determined as the presence of a secondary diagnosis belonging to CCS categories 650 to 670: adjustment disorders; anxiety disorders; attention-deficit, conduct, and disruptive behavior disorders; delirium, dementia, and amnestic and other cognitive disorders; developmental disorders; disorders usually diagnosed in infancy, childhood, or adolescence; impulse control disorders, NEC; mood disorders; personality disorders; schizophrenia and other psychotic disorders; alcohol-related disorders; substance-related disorders; suicide and intentional self-inflicted injury; screening and history of mental health and substance abuse codes; miscellaneous mental health disorders. The single level ICD-9-CM diagnosis of each group is extensively defined in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20969/15414). Moreover, in each hospitalization episode there may be more than one psychiatric comorbidity code assigned.

Variables

Sociodemographic, clinical, and administrative variables were analyzed from each hospitalization episode. Birth date, sex (male/female), residence address, primary and secondary diagnoses defined by the ICD-9-CM, admission date, discharge date, length of stay (LoS, in days), in-hospital mortality (yes/no), and hospital charges (in euros, €) were extracted from each hospitalization selected. Charlson Comorbidity Index (CCI), specifically the version proposed by Quan *et al* was used to assess patients'

comorbidities, health status, and prognosis.[1,21] Type of admission, coded as a categorical variable into planned/urgent, was also extracted from the database. Clinical Classification Software diagnostic categories were used to group single-level diagnoses of ICD-9-CM.

Data source

The database used was provided by ACSS and gathers administrative, sociodemographic, and clinical features of hospitalization episodes occurring in Portuguese public hospitals. In Portugal, each hospitalization episode is reviewed by a medical doctor with training in diagnostic coding.

Bias

To avoid possible information bias, the authors opted to select the time interval of 2008 – 2015, considering that 2015 was the last year with the diagnosis being coded with the ICD-9-CM in Portuguese public hospitals. The most recent years available (2016 and almost all 2017) in the dataset were transition years to the ICD-10-CM/Procedure Coding System (PCS).

Statistical methods

Statistical analyses were performed using SPSS IBM v26® software. Characteristics of hospitalization episodes were assessed using descriptive statistics: categorical variables were characterized through absolute (n =) and relative frequencies (%) and continuous variables were summarized as mean and standard deviation (mean ± SD) when normal distributions were verified or median and interquartile range (IQR, Q1 – Q3) in skewed distributions. Results were presented for the total sample, for the presence of any comorbid psychiatric diagnosis, and by specific psychiatric diagnostic categories. Independent Sample *t*-tests were used for normally distributed continuous variables. The Mann Whitney-U test was used for non-normally distributed continuous variables, and the chi-square (χ^2) test was used for categorical variables. All analyses were two-tailed. We considered a *p*-value less than 0.05 statistically significant.

Data access and cleaning methods

Access to the database was given upon formal request from the Faculty of Medicine of the University of Porto (FMUP) to ACSS. Patient identification details were anonymized and not provided to the authors. Data cleaning methods were applied as selection criteria, only patients aged 18 or older and with registered LoS > 24 hours were considered.

Data linkage

No data linkage was performed in this study.

RESULTS

From 2008 to 2015, there were 294 806 hospitalization episodes with a primary diagnosis of a neurologic disorder in adult patients in Portuguese public hospitals. Of these, 26.9% (n = 79 442) had a registered psychiatric comorbidity. A significant and constant increase in the register of psychiatric comorbidity was seen between 2008 and 2015 (19.2% to 35.1%; β = 815.429; R = 0.982; R2 = 0.963; $p < 0.001$).

Sociodemographic characteristics and main hospitalization outcomes

Among neurological related hospitalizations with a registered psychiatric comorbidity, 42.6% (n = 33 832) of

Table 1 – Sociodemographic and clinical features of Neurologic related hospitalizations with/with no Psychiatric comorbidity

	With psychiatric comorbidity	With no psychiatric comorbidity	*p*-value
n (%)	79 442 (26.9)	215364 (73.1)	NA
Sex			
Female (n =; $\%_{within\ sex}$)	33 832; 22.1	119 193; 77.9	< 0.001[a]
Male (n =; $\%_{within\ sex}$)	45 610; 32.2	96 171; 67.8	
Age (mean; SD)	66.19; 16.189	68.57; 17.156	< 0.001[b]
In-hospital mortality (n =;%)	6383; 8.0	25 219; 11.7	< 0.001[a]
LoS (median days; IQR)	8.0; 4.0 - 14.0	7.0; 3.0 - 13.0	< 0.001[c]
Charlson Comorbidity Index (n =; %)			
0	8238; 10.4	25 745; 12.0	< 0.001[a]
1	7508; 9.5	17 105; 7.9	
≥ 2	63 696; 80.2	172 514; 80.1	

NA: not applicable; SD: standard deviation; LoS: length of stay; IQR: inter-quartile range.
a: Chi-square test;
b: Independent Sample T-test;
c: Mann–Whitney U test.

patients were female compared to 55.3% (n = 119 193) in the non-psychiatric comorbidity group ($p < 0.001$). Patients with a registered psychiatric comorbidity were significantly younger (66.2 ± 16.2 *vs* 68.6 ± 17.2 with no psychiatric comorbidity, $p < 0.001$), presented a lower all-cause in-hospital mortality rate (8.0%, n = 6383 *vs* 11.7%, n = 25 219, $p < 0.001$), and significantly longer mean hospital stays (8.0 days, IQR = 4.0 – 14.0, *vs* 7.0 days, IQR = 3.0 – 13.0, $p < 0.001$).

Approximately 80% of all hospitalizations with psychiatric comorbidity had a CCI ≥ 2, a similar value to the one found in the non-psychiatric comorbidity group (Table 1).

Psychiatric comorbidities in patients hospitalized for neurological disease

The diagnoses of psychiatric comorbidities that were identified most frequently by clinicians were *delirium*, dementia, amnestic and other cognitive disorders in 7.4% (n = 21 965), followed by alcohol-related disorders in 6.5% (n = 19 302) and mood disorders in 6.1% (n = 18 079). Anxiety disorders were found in 1.3% (n = 3846) of cases. In 8.5% of patients (n = 25 127), there was a history of mental health and substance abuse.

Less frequently identified diagnoses were developmental disorders with 0.9% (n = 2678), schizophrenia and other psychotic disorders with 0.7% (n = 2030), substance-related disorders with 0.5% (n = 1446), and attention-deficit, conduct, and disruptive behavior disorders (n = 304), personality disorders (n = 287) and adjustment disorders (n = 228), both categories with 0.1%. Rarer diagnoses consisted of suicide and intentional self-inflicted injury (n = 79), disorders that are usually diagnosed in infancy, childhood, or adolescence (n = 48), and impulse control disorders (n = 8). In 0.3% (n = 994), patients were identified as having 'miscellaneous mental health disorders' (Table 2).

Table 2 specifies psychiatric comorbidities by subtype of neurological condition. Epilepsy/seizures were the neurologic disorder with the highest prevalence of psychiatric comorbidities, with 39.9% of hospitalizations associated with a psychiatric comorbidity, followed by Parkinson's disease in 37.6%, and coma, stupor, and brain damage in 36.6%. Below we specify the psychiatric comorbidities coded, in descending order, by neurological condition.

Epilepsy/seizures

Epilepsy/seizures were the neurological conditions associated with the highest prevalence of psychiatric comorbidities (39.9%), and the second with the highest absolute frequency (n = 9456), after acute cerebrovascular disease (n = 55 868). It was also the most frequently associated with alcohol-related disorders (15.8%, n = 3735) – the main psychiatric comorbidity in this group. The second most

Table 2 – Psychiatric comorbidities (defined by the Clinical Classification Software) in hospitalizations with a primary diagnosis of a neurologic disorder in Portuguese public hospitals between 2008 - 2015 (part 1)

Psychiatric comorbidity \ Neurologic disorder	Acute cerebrovascular disease		Meningitis		Encephalitis		Parkinson's disease		Multiple sclerosis		Other hereditary and degenerative nervous system conditions	
	n	%	n	%	n	%	n	%	n	%	n	%
Adjustment disorders	123	0.1	4	0.1	4	0.2	6	0.2	11	0.2	18	0.2
Anxiety disorders	1847	0.9	51	1.4	35	1.4	92	3.2	102	2.1	152	2.0
Attention-deficit, conduct, and disruptive behavior disorders	159	0.1	4	0.1	16	0.7	10	0.3	1	0.0	20	0.3
Delirium, dementia, and amnestic and other cognitive disorders	17 380	8.5	152	4.2	147	6.0	374	13.0	29	0.6	542	7.1
Developmental disorders	1242	0.6	36	1.0	34	1.4	44	1.5	13	0.3	120	1.6
Disorders usually diagnosed in infancy, childhood, or adolescence	11	0.0	1	0.0	0	0.0	2	0.1	0	0.0	4	0.1
Impulse control disorders, NEC	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0
Mood disorders	11 280	5.5	220	6.1	228	9.3	457	15.9	478	9.8	737	9.6
Personality disorders	132	0.1	3	0.1	5	0.2	10	0.3	2	0.0	14	0.2
Schizophrenia and other psychotic disorders	1129	0.5	22	0.6	34	1.4	59	2.1	22	0.4	96	1.3
Alcohol-related disorders	13 534	6.6	236	6.5	150	6.1	52	1.8	32	0.7	266	3.5
Substance-related disorders	554	0.3	70	1.9	58	2.4	19	0.7	23	0.5	47	0.6
Suicide and intentional self-inflicted injury	26	0.0	1	0.0	1	0.0	14	0.5	3	0.1	4	0.1
Screening and history of mental health and substance abuse codes	19 219	9.4	339	9.3	264	10.8	121	4.2	324	6.6	506	6.6
Miscellaneous mental health disorders	472	0.2	14	0.4	6	0.2	63	2.2	24	0.5	47	0.6
Any psychiatric comorbidity	55 868	**27.2**	929	**25.6**	785	**32.2**	1077	**37.6**	913	**18.6**	2124	**27.7**

Table 2 – Psychiatric comorbidities (defined by the Clinical Classification Software) in hospitalizations with a primary diagnosis of a neurologic disorder in Portuguese public hospitals between 2008 - 2015 (part 2)

Psychiatric comorbidity \ Neurologic Disorder	Paralysis		Epilepsy; convulsions		Headache; including migraine		Coma; stupor; and brain damage		Other nervous system disorders		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Adjustment disorders	2	0.1	34	0.1	1	0.0	3	0.2	20	0.1	228	0.1
Anxiety disorders	54	2.9	326	1.4	174	5.6	20	1.1	977	2.6	3846	1.3
Attention-deficit, conduct, and disruptive behavior disorders	3	0.2	62	0.3	3	0.1	2	0.1	19	0.1	304	0.1
Delirium, dementia, and amnestic and other cognitive disorders	42	2.2	2496	10.5	13	0.4	216	11.5	449	1.2	21965	7.4
Developmental disorders	23	1.2	952	4.0	7	0.2	42	2.2	146	0.4	2678	0.9
Disorders usually diagnosed in infancy, childhood, or adolescence	0	0.0	23	0.1	2	0.1	0	0.0	4	0.0	48	0.0
Impulse control disorders. NEC	0	0.0	5	0.0	1	0.0	0	0.0	0	0.0	8	0.0
Mood disorders	162	8.6	1491	6.3	355	11.4	155	8.2	2436	6.5	18079	6.1
Personality disorders	5	0.3	88	0.4	5	0.2	5	0.3	16	0.0	287	0.1
Schizophrenia and other psychotic disorders	12	0.6	390	1.6	4	0.1	38	2.0	210	0.6	2030	0.7
Alcohol-related disorders	67	3.6	3735	15.8	53	1.7	177	9.4	852	2.3	19302	6.5
Substance-related disorders	18	1.0	364	1.5	31	1.0	45	2.4	151	0.4	1446	0.5
Suicide and intentional self-inflicted injury	5	0.3	12	0.1	2	0.1	3	0.2	8	0.0	79	0.0
Screening and history of mental health and substance abuse codes	155	8.2	1523	6.4	342	11.0	156	8.3	2034	5.4	25127	8.5
Miscellaneous mental health disorders	16	0.9	173	0.7	44	1.4	7	0.4	117	0.3	994	0.3
Any Psychiatric comorbidity	455	**24.2**	9456	**39.9**	867	**28.0**	688	**36.6**	6280	**16.8**	79913	**27.0**

frequently identified comorbidity was delirium, dementia, amnestic, and other cognitive disorders, with 10.5% (n = 2496), followed by mood disorders with 6.3% (n = 1491), and developmental disorders in 4.0%. In 6.4%, there was a positive screening and history of mental health and substance abuse (Table 2).

Parkinson's disease

Parkinson's disease was the second neurological condition that was more frequently associated with a psychiatric comorbidity (37.6%), mainly due to mood disorders (15.9%, n = 457), followed by delirium, dementia, amnestic, and other cognitive disorders in 13.0% (n = 374) and anxiety disorders in 3.2% (n = 92). In 4.2% (n = 121), there was a positive screening and a history of mental health and substance abuse. Parkinson's disease contributed the most to the number of intentional suicide and self-inflicted injuries (0.5%, n = 14).

Coma, stupor, and brain damage

Coma, stupor, and brain damage category was the third type most frequently accompanied by psychiatric disease (36.6%), especially by delirium, dementia, amnestic and other cognitive disorders (11.5%, n = 216), alcohol-related disorders (9.4%, n = 177), and mood disorders (8.3%, n = 156). This group comprises the second category that was most frequently associated with alcohol-related disorders, after epilepsy.

Headache, including migraine

Twenty-eight percent of these patients had psychiatric comorbidities, often in the form of mood (11.4%, n = 355) and anxiety (5.6%, n = 174) disorders. It was the group most frequently associated with anxiety disorders (almost twice the other groups), as well as the one with the highest percentage of history of mental health and substance abuse (11.0%, n = 342).

Meningitis and encephalitis

In this group, psychiatric comorbidity was reported in 25.6% and 32.2%, respectively. In both, the most frequently coded psychiatric comorbidities were mood disorders (6.1% and 9.3%, respectively), alcohol-related disorders (6.5% and 6.1%), and delirium, dementia, amnestic, and other cognitive disorders (4.2% and 6.0%).

Acute cerebrovascular disease

It was the neurological condition with the highest absolute number of psychiatric comorbidities (n = 55 868), representing 27.2% of psychiatric comorbidities in these patients. The most frequently described were delirium, dementia, amnestic, and other cognitive disorders in 8.5%

(n = 17 380), followed by alcohol-related disorders in 6.6% (n = 13 534), and mood disorders in 5.5% (n = 11 280).

Multiple sclerosis

Psychiatric conditions were coded in 18.6% of these cases, with the most frequent diagnoses being mood in 9.8% (n = 478) and anxiety disorders in 2.1% (n = 102).

Subgroup analysis by psychiatric comorbidities and relationship with neurological disease (listed in descending order of psychiatric comorbidity)

Delirium, dementia, amnestic, and other cognitive disorders were reported in 7.4% of patients hospitalized for neurological reasons, mainly in Parkinson's disease (13.0%), followed by coma, stupor, and brain damage (11.5%), epilepsy/seizures (10.5%), and acute cerebrovascular disease (8.5%). Headache (0.4%) and multiple sclerosis (0.6%) were the categories least frequently associated with this inpatient diagnosis.

Alcohol-related disorders were coded in 6.5% of all neurologic related hospitalizations, particularly in epilepsy/seizures group (15.8%), coma, stupor, and brain damage (9.4%), and acute cerebrovascular disease (6.6%). This group of disorders was less often described in multiple sclerosis (0.7%) and headache (1.7%) in a neurology ward.

Mood disorders (total of 6.1%) were coded mainly in Parkinson's disease (15.9%), followed by headache (11.4%) and multiple sclerosis (9.8%). In all subtypes, however, these comorbidities were frequent, being coded in more than 5.5% of the cases. Specifically, concerning anxiety disorder (total of 1.3%), this was more often reported in the headache group (5.6%), Parkinson's disease (3.2%), and multiple sclerosis (2.1%). In a severe form, suicide and intentional self-inflicted injury was described in a total of 79 patients, the majority being from the acute cerebrovascular disease group (n = 26, 0.0%), Parkinson's disease (n = 14, 0.5%), epilepsy/seizures (n = 12, 0.1%), multiple sclerosis (n = 3, 0.1%), coma, stupor, and brain damage (n = 3, 0.2%) and headache (n = 2, 0.1%).

Developmental disorders (0.9%) were most frequently reported when associated with epilepsy/seizures (4.0%).

Schizophrenia and other psychotic disorders (0.7%) were coded at lower frequencies, and most frequently in Parkinson's disease (2.1%), coma, stupor, and brain damage (2.0%), and epilepsy/seizures (1.6%).

Substance-related disorders (0.5%) were coded more frequently in coma, stupor, and brain damage (2.4%), encephalitis (2.4%), meningitis (1.9%) and epilepsy/seizures (1.5%) related hospitalizations.

Regarding the impulse control disorders, in the eight coded cases, five were from epilepsy/seizures group, one from headache, one from acute cerebrovascular disease, and one from other hereditary and degenerative nervous system conditions.

DISCUSSION

To our knowledge, this was the first study to assess all neurological-related hospitalizations and their psychiatric comorbidities in Portuguese hospitalized patients.

In our study, 26.9% of all neurologic disorder hospitalizations presented psychiatric comorbidity; it was particularly common in patients with epilepsy/seizures. The three most frequently identified psychiatric comorbidities were delirium, dementia, amnestic, and other cognitive disorders (7.4%), alcohol-related (6.5%), and mood disorders (6.1%). Patients with psychiatric comorbidities were significantly younger, had lower in-hospital mortality, but had more comorbidities, and longer hospital stays.

The frequency of psychiatric comorbidities in hospitalized patients in our study was similar to that reported by Earls *et al* (23.7% in a total of 312 patients)[1,2] and close to that of Bridges and Goldberg's study[1,16] (39% in a total of 100 patients). On the other hand, Jeffries *et al*[1,15] reported a higher percentage (51.3%) of psychiatric comorbidities in neurological patients using a battery of screening questionnaires followed by a psychiatric interview. These authors concluded that these screening questionnaires presented high sensitivity and specificity, representing a cost-effective and acceptable method for improving the identification of psychiatric morbidity and comorbidity, a method not used in the current study.[1,15]

Rates of psychiatric comorbidities in our sample were also close to those reported for Earls *et al*,[1,2] in which mood-related disorders and delirium, dementia, and cognitive disorders were the most commonly registered psychiatric comorbidities in neurologic related hospitalizations. However, in the Jeffries *et al*[1,15] study, these frequencies were higher: 24.8% for mood disorders, 17.7% for cognitive problems, and 12.7% for anxiety. These authors also found that 4.5% of the patients had a somatoform disorder. On the other hand, Dawood *et al*,[1,9] including 129 referrals of inpatients on the wards of a regional neuroscience center in London found that depression (50%), functional neurological symptoms (27%), anxiety (22%), cognitive decline/confusion (17%), agitation/aggression (13%), suicidal ideation/behavior (12%), and psychotic symptoms (12%) were the most frequently cited reasons for referral to psychiatry. In this study, the final diagnoses documented by a psychiatrist were mood disorders in 3% of cases, followed by somatoform disorders in 2.5%, and delirium, dementia, and cognitive disorders in 0.88%.

Regarding the sociodemographic characteristics in our study, patients with psychiatric comorbidities were more often male (female:male ratio of 1:1.35; 42.6% of women)

than the ones without these comorbidities (female:male ratio of 1.24:1; 55.3% of women). This disagrees with what was found in the study of Dawood *et al*,[1,9] which reported a female:male ratio for referral patients to a psychiatric observation of 1.35:1. One of the possible explanations may be the fact that we did not include in our study the functional neurological disorders, which are more frequently described in women. As previously described, psychiatric comorbidities were associated with longer mean hospital stays, reinforcing the impact they have in neurologic inpatient treatment. This increase might occur due to the comorbid effect of psychiatric disorders, increasing the complexity of treatment and worsening the hospitalization outcomes of those patients.

Neurological patients with psychiatry comorbidities presented longer median hospital stays. Multiple reasons may contribute to this: less autonomy to self-care, poor compliance with medication, additional diagnoses that delay discharge from the hospital (psychotic symptoms, for instance).

Psychiatric comorbidities were identified in 39.9% epilepsy/seizures related hospitalizations, mainly due to alcohol-related (15.8%), cognitive (10.5%), and/or mood disorders (6.3%). In agreement, a recent systematic review found that the prevalence of any psychiatric disorder in patients with epilepsy was up to 43.3%, particularly up to 51% in idiopathic generalized epilepsy, and 43.1% in temporal lobe epilepsy.[1,22] These authors showed that the most frequent psychiatric comorbidities in these patients were mood/affective disorders (23% for current occurrence), anxiety (15.6% for current occurrence), personality (11% in juvenile myoclonic epilepsy), and psychotic disorders (4% of patients, associated with longer duration of epilepsy).[1,22] In this review, current and lifetime mood disorders appeared to be less frequently encountered in idiopathic generalized epilepsy, and more prevalent in focal drug-resistant epilepsy (mainly in temporal lobe epilepsy).[1,22] In focal epilepsies, cognitive depression was found to be associated with a left-lateralized seizure focus, and with cognitive impairment (semantic and autobiographic memory, delayed auditory-verbal and visual recall).[1,22] In idiopathic generalized epilepsy, depression was associated with hypoechogenic brainstem raphe.[1,22]

Regarding the suicidal risk and suicidal attempts, our study showed that 12 hospitalization episodes (0.1%) were coded with suicide and intentional self-inflicted injury, while Baldin *et al*,[1,23] using the Diagnostic Interview Survey for Children (DISC-IV), found a prevalence of 16 and 5.1%, respectively, in adults with childhood-onset epilepsy.[1,23] The suicidal risk seems to be reported only for adults with childhood-onset epilepsy and in this population, it had no significant relation with epilepsy.[1,22] On the other hand, in our inpatients, anxiety disorders were present in only 1.4%; other studies reported anxiety disorders in 5.6% of adults with childhood-onset epilepsy and 30.8% in a sample from a general population of epilepsy outpatients from a tertiary referral center.[1,22,24]

Concerning the prevalence of psychotic disorders in epilepsy inpatients, we found a percentage of 1.6%. Only four studies reported it[1,22]; when DSM criteria were used, 3.3% of the epilepsy patients from a tertiary epilepsy center were diagnosed with a current psychotic episode.[1,24]

Furthermore, in our study, epilepsy was the most frequent condition associated with concurrent alcohol-related disorders.[1,25] A study conducted by Hamerle *et al*,[1,26] including 310 patients with epilepsy followed at the Epilepsy Outpatient Clinic in Berlin, Germany (a Western country with high alcohol consumption), showed that two-thirds of interviewed subjects (n = 204) had consumed alcohol within the last 12 months, with seizures worsening related to it in 37 of 204 patients (18.1%). These authors found that the amount of alcohol intake before alcohol-related seizures was at least seven standard drinks (equivalent to 1.4 L of beer or 0.7 L of wine), and in 95% of cases, the alcohol-related seizures occurred within 12 hours after cessation of alcohol intake.[1,26] In this study, being on antiepileptic monotherapy was an independent risk factor for alcohol consumption in the multivariable analysis. Moreover, independent predictors for alcohol-related seizures were generalized genetic epilepsy (six times more likely) and chronic heavy alcohol use (nine times more likely).[1,26] In another study in China (n = 425), 24.2% of patients with epilepsy had used alcohol during the same period, and 52.4% of them complained of worsening seizure control.[1,27] These authors suggested that heavy alcohol use and frequent alcohol use were independently associated with worsening seizure control. In addition, male patients with a history of alcohol use were more likely to use it after a diagnosis of epilepsy.[1,27]

The second major inpatient neurological condition with psychiatric comorbidities was Parkinson's disease, present in more than one third of these patients, mainly mood (15.9%), cognitive (13.0%), and anxiety disorders (3.2%).

Psychiatric illness is a major comorbidity among PD patients, leading to similar level of disability as motor symptoms.[1,28,29] Mood and anxiety disorders are the most common neuropsychiatric syndromes associated with this disease reported in multiple studies.[1,28,29] One study, including 110 inpatients hospitalized with PD (n = 71) or atypical parkinsonian syndromes (APS) (n = 39), found that the prevalence of psychiatric comorbidity was 77.0% in PD and 71.8% in APS patients: much higher percentages than the ones reported in our study. However, these authors used the Mini International Neuropsychiatric Interview.[1,28] In agreement with this study, mood disorders were the most

frequent psychiatric comorbidity in PD patients in our study. Indeed, in the study mentioned above, half of the patients in the two neurological disorders had multiple psychiatric comorbidities; these patients had higher odds of being female, higher Unified Parkinson's Disease Rating Scale (UPDRS) part-1 scores, rapid eye movement (REM) sleep behavior disorder, poor sleep quality, and caregiver stress.[1,28] On the other hand, in PD outpatients, depressive and anxiety disorders were also frequent psychiatric diagnoses, reported in 20% - 50% and about 40% of patients, respectively, both from the premotor to the late stage of PD disease.[1,29-31] In PD, symptoms such as irritability and dysphoria were more frequent than in major depression not related to PD, while guilt, self-blame, and suicide attempts were less frequent.[1,31] The prevalence of suicidal ideation in these patients was reported to be between 17% and 30%, two times higher than the general population.[1,31] In our study, PD contributed the most to the number of intentional suicide and self-inflicted injuries, but only in 14 patients (0.5% of the PD patients). Anxiety appears to be underrecognized in PD patients due to diagnostic imprecision, symptom overlaps with motor and cognitive features, healthcare access and resources, as well as under-reporting of symptoms by patients and caregivers.[1,31]

Parkinson's disease dementia is reported in more than 80% of PD outpatients, mainly in later forms of the disease.[1,31] Subcortical features include bradyphrenia, impaired working memory, executive dysfunction, and visuospatial constructional deficits; cortical features are comprised of memory impairment and language dysfunction.[1,31] This type of dementia is generally associated with many comorbid behavioral symptoms, including depression (58%), anxiety (49%), hallucination (44%), apathy (54%), disinhibition, and irritability.[1,31]

As expected, in our study, an altered state of consciousness – namely coma, stupor, and brain damage – was frequently associated with psychiatric comorbidities, especially with cognitive symptoms, alcohol-related disorders, and mood disorders, as it occurred in meningitis and encephalitis.

Psychiatric comorbidities in patients with a headache diagnosis are common, and their association is complex since they can have uni- or bi-directional mechanisms or share genetic and environmental risk factors.[1,32,33] According to a recent large genome-wide association study, when compared to other neurological disorders, migraine showed a higher genetic correlation with psychiatric disorders suggesting common genetic bases or pathways.[1,34] The coexistence of headache and mental disease appears to worsen the clinical situation and increase the risk of chronicity, pain intensity, and the rate of treatment failure.[1,32] In our study, 28% of patients with a primary diagnosis of headache had at least one psychiatric comorbidity, often in the form of mood and anxiety disorders, in agreement with other studies.[1,32,33,35,36] Some authors suggested that these two psychiatric disorders are approximately two to 10 times more prevalent in patients with migraine than compared to general population.[1,33,35,36] In migraine patients, the prevalence of depressive disorders was variable according to studies and methodology, varying between 6.1% to 73.7%,[1,33] and twice as frequent in patients with chronic *versus* episodic migraine.[1,32] This prevalence was similar in cluster and tension-type headache.[1,32]

Regarding the involved mechanisms, twin studies suggest that about 20% of the variability in both migraine and depression can be attributed to shared genes with a bidirectional pattern.[1,37,38] The serotonin (5-HT) system seems to play an important role in the association of these two conditions: a chronic interictal 5-HT availability reduction could predispose to cortical spreading depression and increased sensitivity of trigeminovascular pathways[1,39]; on the other hand, a polymorphism in the 5-HT transporter gene has been linked to migraine and depression.[1,40]. Other mediators associated with these conditions include dopamine and gamma-aminobutyric acid (GABA).[1,33] A third proposed mechanism is hypothalamic-pituitary-adrenal axis dysregulation in the form of an imbalance between pro-inflammatory and anti-inflammatory cytokines, resulting in abnormal increased pro-inflammatory cytokines.[1,33]

The risk of suicide attempts was increased in patients with headache and depressive/anxiety disorders, more often in chronic cluster headache (22% of the patients), and less in migraine patients (4%).[1,41] In our study, two hospitalizations (0.1%) were associated with suicide and intentional self-inflicted injury.

Moreover, comorbidity of headache disorders and bipolar affective disorder is expected, estimated at 8.6% in chronic migraine, 4.5% in chronic tension-type headache, and 6.6% in chronic cluster headache; both conditions have a periodicity generated in the hypothalamus, relate to the sleep pattern, share neuroendocrine changes, and have an adequate response to specific therapies such as lithium.[1,32,42] Headache has also been associated with personality disorders, post-traumatic stress disorder, and with substance overuse.[1,32,33]

Given the frequency of this co-condition, optimizing the pharmacological and non-pharmacological treatment of either headache and/or its psychiatric comorbidities might help clinicians to attenuate the burden of both these conditions, either by preventing harmful adverse effects or by allowing the choice of drugs adapted to both conditions.[1,33]

In our study, acute cerebrovascular disease was the largest contributor to neurologically related hospitalizations. In this group, psychiatric comorbidities were reported in

27.2% of the cases, mostly in form of cognitive (including delirium and dementia), alcohol-related, and mood disorders. In a similar study, Pedroso *et al*[1,43] found a higher percentage of psychiatric disorders (55%) in 60 patients with acute stroke during the first week of hospitalization in Brazil. These authors applied the Mini International Neuropsychiatric Interview-Plus. The most frequently identified psychiatric comorbidities were mood and anxiety disorders.[1,43] Specifically, they identified major depression (26.7%), alcohol abuse/dependence (11.7%), specific phobia (8.3%), generalized anxiety disorder (6.7%), psychosis (5.0%), social phobia (3.3%), adjustment disorder (3.3%) and panic disorder (1.7%).

Multiple authors reported an important frequency of depression, anxiety, psychosis, or dementia at any stage after a stroke.[1,44] The association between neurological disease and psychiatric comorbidity appears to be complex with underlying bidirectional influences.[1,44] Chemerinski and Robinson have shown that the frequency of depression among inpatients during the acute phase of a stroke is approximately 22% for major depression and 17% for other forms of depression.[1,45] In outpatient samples, depression affected nearly a third of all stroke survivors within five years,[1,46] and its severity seemed to predict the extent of impairment in activities of daily living after the stroke.[1,47] Anxiety disorders were also common after strokes.[1,45] Between 25% and 50% of patients developed a generalized anxiety disorder during the first months after a stroke, with a small reduction in incidence within the following three years.[1,48] Poststroke delirium was described in 13% to 48% of the cases, leading to prolongation of hospital stay, poorer functional outcome, and increased risk of developing dementia.[1,44] Dementia was identified in about 10% of cases after the first stroke and 30% after the recurrent one.[1,49] That is, psychiatric conditions can arise before or after the stroke. A large body of data supports the notion of mental illness as a potentially modifiable stroke risk factor.[1,44] Hoyer *et al*[1,44] showed more severe strokes and a higher prevalence of poor outcome in patients with a documented psychiatric diagnosis at the time of the stroke, as well as a higher rate of psychiatric complications during the initial treatment phase (46.7 in patients with a pre-documented psychiatric diagnosis *versus* 28.9% with no comorbidities; $p < 0.0001$). Some authors hypothesized that having a psychiatric disorder could be associated with an unhealthier lifestyle, with a potential higher prevalence of other risk factors for strokes (such as smoking, sedentary lifestyle, among others), and an increased risk of therapeutic noncompliance.[1,44] Other mechanisms could include increased inflammation, overactivity of the hypothalamus-pituitary-adrenal axis, and endothelial dysfunction, which may mediate the link to vascular disease and stroke.[1,44] On the other hand, having a stroke also predisposes the patient to a psychiatric condition, since a multiplicity of behavioral and affective changes can be associated with vascular lesions of the central nervous system, with the possibility of acute damage to circuits associated with the processing of emotions and cognition.[1,43]

Finally, inpatient multiple sclerosis hospitalizations were also associated with an important frequency of psychiatric comorbidities (18.6%), the most frequent diagnoses being mood (9.8%) and anxiety disorders (2.1%). In an outpatient sample, McKay *et al*,[1,50] including 2312 incident cases of adult-onset multiple sclerosis followed for a mean of 10.5 years, found that 35.8% of them met the criteria for a mood or anxiety disorder. The presence of a mood or anxiety disorder was associated with a higher Expanded Disability Status Scale (EDSS) score. These authors concluded that the optimization of the management of these comorbidities should be explored as a means of potentially mitigating disability progression in multiple sclerosis.[1,50] Once again, a bidirectional relationship remains possible. For some individuals, a psychiatric condition may either develop or be more readily diagnosed in response to worsening disability in multiple sclerosis.[1,50] Indeed, the high prevalence of psychiatric disorders in multiple sclerosis and their association with a disability may reflect both biological and psychosocial factors.

Strengths and limitations

To the best of our knowledge, this was the first national study analyzing hospitalizations with a primary diagnosis of a neurological disorder and psychiatric comorbidities. The database used in this study gathers hospitalization episodes from all mainland Portuguese public hospitals which increases the external validity of the aforementioned results.

The use of secondary data in health research is limited to the intrinsic quality of the data; therefore, one of the possible limitations of the study is linked to the reliability of the clinical diagnosis, record, and coding in the database. In Portugal, only medical doctors with specialized training in medical coding are responsible for this procedure, which increases the quality of diagnostic coding. Interobserver differences may arise since coding doctors vary between institution. The diagnoses of mental disorders in the database were not specifically identified by psychiatrists or might not have been the result of specific diagnostic interviews. Furthermore, these conditions may have manifested concomitantly or prior to the hospitalization episode and do not represent their lifetime prevalence. Psychiatric comorbidities were defined accordingly to the ICD-9-CM classification and grouped using the CCS categories, described in detail in the methods section. Mental disorders and neurologic disorders may overlap or present in the same clinical

condition (e.g., dementia with behavioral disturbances), leading to an artificial separation of both clinical entities. As such, the interpretation of mental and neurologic disorders as a group when analyzing data related to neuropsychiatric disorders should be cautious.

CONCLUSION

Psychiatric disorders are common in patients hospitalized with a neurological disorder, as more than one in each four neurological hospitalizations were associated with a psychiatric comorbidity in Portugal. Among psychiatric comorbidities, depression and alcohol-related disorders are some of the most prevalent conditions reported in all groups of neurological disorders.

The treatment of neurologic conditions should be tailored to consider the presence of psychiatric comorbidities, considering the potential beneficial or synergistic effects, as well as treatment complications. Secondary data represents an important tool to assess clinical and sociodemographic trends in neurological disorder hospitalizations, namely allowing to better depict the important link between psychiatric and neurological disorders.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

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

EA is the president of the Association for Neurovascular Diseases Research, the vice-president of the Portuguese Neurosonology Society, the co-chair of the Council of Nations and member of the executive committee of the European Society of Neurosonology and Cerebral Hemodynamics, the co-chair of the scientific panel of Neurosonology of European Academy of Neurology, a member of the steering committee for certification of the European Reference Neurosonology Centers, and the adjunct-director of the National Priority Program for the Cerebro and Cardiovascular Diseases.

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ACTA MÉDICA PORTUGUESA
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Spinal Cord Stimulation in Refractory Postherpetic Neuralgia in Portugal: A Case Report

Neuroestimulador Medular no Tratamento da Nevralgia Pós-Herpética Refratária em Portugal: Um Caso Clínico

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ABSTRACT

Postherpetic neuralgia is one of the most severe complications after herpes zoster infection. Patients who experience persistent pain despite conservative treatment may benefit from interventional therapies, such as spinal cord stimulation. We present the case of a patient with severe refractory postherpetic neuralgia in the right T8 to L1 distribution who responded effectively to spinal cord stimulation. After its implantation, the patient had improvements in pain intensity, pain-related interference, quality of life, and satisfaction, with a simultaneous reduction of previous medications. This case report highlights the role of spinal cord stimulation in refractory neuropathic pain secondary to herpes zoster.
Keywords: Neuralgia, Postherpetic/therapy; Pulsed Radiofrequency Treatment; Spinal Cord Stimulation

RESUMO

A nevralgia pós-herpética é uma das complicações mais graves após infeção por herpes zoster. Os doentes que mantêm dor persistente, apesar do tratamento conservador, podem beneficiar de intervenções terapêuticas, como a neuroestimulação medular. Apresentamos um caso de nevralgia pós-herpética severa e refratária, localizada nos dermátomos direitos de T8-L1, que respondeu eficazmente à neuroestimulação medular. Após a sua colocação, houve uma melhoria na intensidade da dor, interferência relacionada com a dor, qualidade de vida e satisfação, com simultânea redução da medicação prévia. Este caso enaltece a relevância da neuroestimulação medular em situações refratárias de dor neuropática secundária a infeção por herpes zoster.
Palavras-chave: Neuroestimulação Medular; Nevralgia Pós-Herpética/tratamento; Tratamento por Radiofrequência Pulsada

INTRODUCTION

Postherpetic neuralgia (PHN) is one of the most severe complications after herpes zoster infection.[1] The typical presentation of PHN is neuropathic pain distributed over the dermatomal innervation of the affected nerve for more than three months.[2] Patients who experience persistent pain despite conservative treatment may benefit from interventional therapies. Spinal cord stimulation (SCS) is most often used to treat persistent spinal pain or complex regional pain syndromes, and can reduce chronic opioid use.[3] Additionally, it may be used to treat other chronic pain syndromes arising from the peripheral nervous system.[4,5] We present the case of a patient with severe refractory PHN in the right T8 to L1 distribution, who responded effectively to SCS.

CASE REPORT

A 48-year-old woman had a four-year history of PHN in the right T8 to L1 dermatomes. Her previous pharmacological regimen included many different gabapentinoids, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and opioid medicines without sustained improvement in symptoms. Capsaicin patch, quadratus lumborum block and lidocaine infusion were applied without adequate pain relief. Despite several therapeutic strategies, she remained with severe pain and was referred to our Chronic Pain Unit (CPU).

At first evaluation in the CPU, she reported a constant, sharp, deep, and burning pain on the right thoracic wall. The physical examination revealed allodynia and hyperalgesia in the right T8 to L1 dermatomes. On Brief Pain Inventory (BPI),[6] 'the average pain intensity' score was 9/10, the 'pain-related interference with general activity' score was 10/10 and the 'pain-related interference with sleep' score was 8/10. Oral morphine (40 – 50 mg/daily), pregabalin (450 mg/daily), paracetamol (3 g/daily), and duloxetine (60 mg/daily) were prescribed.

In the following evaluation, the patient denied improvement in pain severity pain and mentioned daytime drowsiness and constipation. The Brief Pain Inventory was obtained with the same previous scores.

Given her refractory pain, the decision was made to offer a trial of SCS. To ensure the patient was met eligibility criteria for SCS, a multidisciplinary evaluation was obtained. Psychiatric illness and other medical conditions were ruled out, namely coagulopathies or active infections.

After meeting the eligibility criteria, a unilateral octopolar electrode was placed on the epidural space,

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percutaneously under fluoroscopic guidance, at the T2-T4 level. The patient was awake during the procedure to guide the electrode placement and device programming. At the end of the procedure, the patient reported a substantial improvement in pain severity. On the next day, she was discharged from hospital.

One week later, the patient was reexamined in our CPU and reported an 'average pain intensity' score of 2/10, representing a 78% reduction compared to her initial assessment. Additionally, her 'pain-related interference with general activity' score was 3/10 and her 'pain-related interference with sleep' score was 0/10. According to this scenario, she was a candidate for permanent SCS, which she accepted. The procedure was uneventful, and she was discharged home on postoperative day one.

Two months after the procedure, she was very satisfied with the procedure and referred a substantial improvement in her quality of life. The Brief Pain Inventory was applied, and she reported an 'average pain intensity' score of 0/10, 'pain related interference with general activity' score of 0/10 and 'pain related interference with sleep' score remained 0/10. The physical examination revealed that allodynia was abolished and the presence of mild hyperalgesia in the right T9 to T12 dermatomes. Gradually, we attempted to deprescribe most of her medication. Presently (one year after SCS implant), her current medication is pregabalin 150 mg/daily and duloxetine 30 mg/daily.

DISCUSSION

According to the latest version of the International Classification of Diseases (ICD-11) and the International Association for the Study of Pain (IASP), PHN is defined as pain persisting for more than three months after the onset or healing of HZ. The innervation territory of the first (ophthalmic) branch of the trigeminal nerve and thoracic dermatomes are the most frequently locations affected in PHN.[7] Currently, the Neuropathic Pain Special Interest Group (NeuPSIG) of IASP presents Level A evidence for both first- and second-line treatments, which includes tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, pregabalin, gabapentin, tramadol, capsaicin (8%) patches, and lidocaine patches.[8] The number needed to treat these treatments ranges from 11 to 25.[8] A recent systematic review regarding interventional treatments for PHN concluded that botulinum toxin A or triamcinolone, transcutaneous electrical nerve stimulation, peripheral nerve stimulation, and stellate ganglion block are recommended, followed by paravertebral block and pulsed radiofrequency.[9] If severe pain persists, SCS could be considered, especially in patients with comorbidities.[10] In our case, some interventional therapies were previously used without success. Due to the patient's severe allodynia in the affected area, cutaneous approaches were not considered. According to our clinical assessment, patient preferences, and the CPU's experience, SCS was proposed. Afterwards, a SCS trial was successful and a permanent implant maintained its efficacy in pain severity reduction, namely pain intensity and pain related interference.

Previous studies have used SCS to treat intractable HZ-related pain in subacute and chronic stages of PHN.[9] SCS mechanisms of action are complex and remain not fully understood.[11] Gate control theory mechanisms are implicated, namely, neural signal transmission regulation by the dorsal horn of the spinal cord, where A-beta fibers inhibit the transmission of pain signals carried by C-fibers. This explains why electrical SCS could reasonably modulate pain.[12] It has been suggested that patients suffering from pain and allodynia, caused by central sensitization, and those with preserved neuronal and dorsal column function would respond well to SCS,[10] like in the case of our patient. By contrast, patients with marked sensory loss and those experiencing constant pain without allodynia would not benefit from SCS, as deafferentation and degeneration of the dorsal column might be the dominant mechanism.[10]

A recent review of the literature about neuromodulation in PHN found 16 reports with permanent SCS. Long-term pain relief from a permanent SCS was achieved in 47.1% of the reported PHN patients, with an average pain reduction of 79.0%, and an average long-term pain relief of 50.84 months.[13]

Even though spinal cord stimulation is mainly used for persistent spinal pain or complex regional pain syndromes, its use in other chronic pain syndromes is evolving. Nevertheless, it is rarely offered to patients with PHN. To the best of our knowledge, this was the first PHN patient treated with SCS in Portugal. The implantation of SCS for PHN treatment may offer a worthwhile option for pharmacological non-responders with anatomically intact neural pathways. Although more studies are required to determine if SCS provides better and more sustainable analgesia than other interventional procedures, it could be considered in more resistant cases. As for the prevalence and impact of PHN, this case report is expected to highlight the possibility to consider SCS as a 'rescue therapy' in patients with severe or refractory PHN, particularly when there is presence of allodynia.

AUTHOR CONTRIBUTIONS

AS: Study design and writing of the manuscript.

MB: Critical review of the manuscript.

PB, AG: Study design, writing and critical review of the manuscript.

LG: Literature search and critical review of the manuscript.

All authors approved the final version to be published.

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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ACTA MÉDICA PORTUGUESA
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Acute Iron Poisoning: A Case of Fulminant Hepatic Failure

Intoxicação Aguda por Ferro: Um Caso de Falência Hepática Fulminante

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ABSTRACT

Acute iron poisoning is an exceedingly rare occurrence, mainly when resulting from intentional ingestion in adults. It can lead to multi-organ toxicity and, in severe cases, may evolve into acute liver failure and cardiovascular collapse, which are the main causes of death. The clinical outcome is largely dependent on the amount of elemental iron ingested and the readiness of treatment, which includes support, early intestinal decontamination and deferoxamine. Despite timely intervention, acute liver failure can be life-threatening, with liver transplantation being the only potentially life-saving measure. In this case report, we describe a case of severe acute iron poisoning due to intentional ingestion that led to fulminant liver failure, which was successfully managed with liver transplantation.
Keywords: Drug Overdose/complications; Ferrous Compounds/poisoning; Liver Failure, Acute/chemically induced

RESUMO

A intoxicação aguda por ferro é uma condição extremamente rara, especialmente em contexto de ingestão intencional no adulto. Pode causar disfunção multiorgânica, podendo, em casos severos, evoluir para falência hepática aguda e colapso cardiovascular, que são as principais causas de mortalidade associadas a esta condição. O *outcome* clínico depende especialmente da quantidade de ferro elementar consumido e da rapidez de tratamento, que inclui suporte, descontaminação intestinal precoce e deferoxamina. Perante o prognóstico reservado associado à falência hepática aguda, a transplantação hepática surge como potencial medida *life-saving*. Neste relato de caso clínico descreve-se um caso de intoxicação aguda grave por ferro, secundária a ingestão intencional, que resultou em falência hepática fulminante, tratada com sucesso com transplante hepático.
Palavras-chave: Compostos Ferrosos/intoxicação; Falência Hepática Aguda/induzida quimicamente; Overdose de Medicamentos

INTRODUCTION

The epidemiology of acute iron poisoning (AIP) varies greatly depending on the type of ingestion, although the literature on this entity is still scarce. This condition is rare in adults and in this population it is typically associated with intentional ingestion, often as a result of suicide attempts. In one of the first institutional reviews of patients with this condition, 80% of intentional ingestions occurred in female patients and mortality was higher in this type of ingestion when compared to unintentional AIP.[1] Iron poisoning can cause gastrointestinal, cardiovascular, metabolic, hepatic, and central nervous system toxicity.[1-3] The severity of symptoms and the toxic dose are not well established and are determined by the iron formulation and the dose ingested: intakes ≥ 60 mg/kg of elemental iron are commonly linked to severe toxicity and death.[2-4] Severe AIP can lead to acute liver failure (ALF) and cardiovascular collapse, the main causes of death in AIP.[1-4] The clinical outcome depends mainly on the amount of elemental iron ingested, other drugs ingested and the timing of initiation of treatment and support.

Most of the current literature on AIP with ALF reports cases with multiple drug overdose, usually with other hepatotoxic drugs. In this case report, we present the case of a female patient with an isolated AIP due to intentional ingestion, who progressed to fulminant liver failure, requiring liver transplantation.

CASE DESCRIPTION

A 38-year-old woman intentionally ingested 90 tablets of ferrous sulphate (329.7 mg) in a suicide attempt. The total dose of ferrous sulfate was 29.7 g which corresponds to 9.5 g of elemental iron (130 mg/kg). Her past medical history included depression and iron deficiency anemia. The patient presented at the emergency department four hours after ingestion, reporting gastrointestinal symptoms and exhibiting drowsiness while remaining hemodynamically stable. Gastric lavage was performed and activated charcoal was administered. Chelation iron therapy with deferoxamine was started, as an intravenous infusion, at a rate of 15 mg/kg/h, according to guidance from the national poison control center. An infusion of N-acetylcysteine, flumazenil 0.5 mg and fluid therapy were also administered.

The arterial blood gas test presented metabolic acidosis and hyperlactatemia. The complete blood count showed hypochromic microcytic anemia and leukocytosis. Iron testing suggested iron overload as represented in Table 1. Liver parameters were normal at presentation.

The patient was admitted to the Intermediate Care Unit for surveillance. As the clinical condition deteriorated the patient developed acute liver failure with progressive

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Table 1 – Analytic values

Parameter	Value	Reference value
Hemoglobin	8.3 g/dL	12 – 16 g/dL
Leucocytes	20 200 /uL	4800 – 10 800 /uL
Serum iron level	1045 mcg/dL	50 – 170 mcg/dL
Transferrin saturation	210%	20% – 50%
Transferrin	354 mg/dL	250 – 380 mg/dL
Ferritin	4.2 ng/mL	10 – 291 ng/mL

increase in liver enzymes, worsening of coagulopathy, grade 1 - 2 encephalopathy and hypoglycemia.

Following contact with the liver transplant team, the patient was transferred to our hospital 48 hours after ingestion and was admitted to the Intensive Care Unit. On admission, she was drowsy but easily arousable and cooperating. Flapping and focal neurological deficits were absent. Vasopressor therapy with norepinephrine was started, while maintaining adequate urine output. The medical team decided to maintain deferoxamine infusion and continuous venovenous hemodiafiltration was started, without anticoagulation or ultrafiltration.

Despite these measures, clinical status deteriorated with rapidly progressive liver failure and worsening neurological dysfunction which included flapping, increasing drowsiness and impaired verbal response. Additionally, nonoliguric kidney injury was also present. Deferoxamine was interrupted after 48 hours of infusion due to the lack of clinical improvement.

A multidisciplinary assessment, including psychiatric evaluation, deemed the patient eligible for transplant surgery. However, she was considered to be at risk for impulsive behavior, and additional psychiatric and psychological support was considered necessary.

The patient underwent urgent liver transplantation five days after ingestion. The procedure was complicated by intraoperative hemorrhage. Nevertheless, the patient achieved clinical improvement, with hemodynamic stability and extubation was possible two days after the procedure. She developed partial graft dysfunction that improved during hospitalization and was transferred to the transplantation ward four days after surgery. At the six month follow up, there was no evidence of further complications.

DISCUSSION

Mechanisms of iron toxicity are not completely understood. Due to the iron's direct effect on the gastrointestinal mucosa, ingestion of 10 - 20 mg/kg of iron may cause gastrointestinal symptoms. Systemic symptoms of intoxication usually occur with doses of 40 mg/kg and those who ingest 60 mg/kg or more usually develop serious toxicity, which can be fatal.[3] This patient ingested 130 mg/kg of iron which led to gastroenteritis and development of severe systemic intoxication symptoms, including fulminant hepatic failure and acute renal failure. There are few cases described in the literature of adults with fulminant liver failure due to iron intoxication solely[4] and an even smaller number of survivors.[5]

The clinical manifestations of acute iron poisoning are typically divided into five stages that often overlap. The gastrointestinal phase (stage I) occurs 30 minutes to 6 hours after ingestion and is characterized by major gastrointestinal manifestations. After 6 to 24 hours of ingestion (stage II – latent phase) there is apparent stabilization with resolution of gastrointestinal symptoms, despite the severity of the intoxication. Stage III is associated with mitochondrial dysfunction and usually begins about 6 to 72 hours after iron intake. At this stage, coagulopathy, acute tubular necrosis, metabolic acidosis, and shock may appear. Hepatotoxicity (stage IV) due to iron toxicity develops within 12 to 96 hours after ingestion and appears to be a dose-related phenomenon.[4] In addition to liver damage, excessive free radical production can also cause acute lung and kidney injury. After two to eight weeks (stage V), late complications may arise due to gastrointestinal scarring that can cause obstruction.[1-4]

Treatment of iron toxicity includes intensive supportive therapy, early intestinal decontamination, deferoxamine, and, as a last resource, liver transplantation. Deferoxamine is the antidote of choice for severe acute iron poisoning, as it is a specific iron chelating agent. However, in the literature there is evidence of significant pulmonary toxicity after intravenous infusions of deferoxamine for more than 24 hours.[6]

The rescue treatment for acute liver failure is liver transplantation, but the outcomes are unpredictable in patients with iron overdose.[7] However, liver transplantation should be immediately considered in these cases.[4]

Despite the high severity of the case, this patient's evolution was positive, with complete resolution after liver transplantation.

CONCLUSION

Iron overdose, primarily resulting from voluntary intoxication in adults, is an exceedingly rare occurrence. Severe cases pose a significant risk of complications, multiple organ failure and even death, underscoring the critical importance of prompt recognition and treatment. Despite the available interventions, acute liver failure remains a harsh reality, making liver transplantation a last-resort lifesaving measure. The positive outcome observed in this patient, with complete resolution post-liver transplantation, highlights the potential for successful management even in severe cases.

AUTHOR CONTRIBUTIONS

MBR, IP, RP: Literature review, drafting of the manuscript.

JRM, AM: Critical review of the manuscript.

All authors approved the final version to be published.

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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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Giant Proliferating Trichilemmal Tumor of the Scalp

Tumor Triquilémico Proliferativo Gigante do Couro Cabeludo

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Keywords: Scalp/pathology; Skin Neoplasms
Palavras-chave: Couro Cabeludo; Neoplasias da Pele

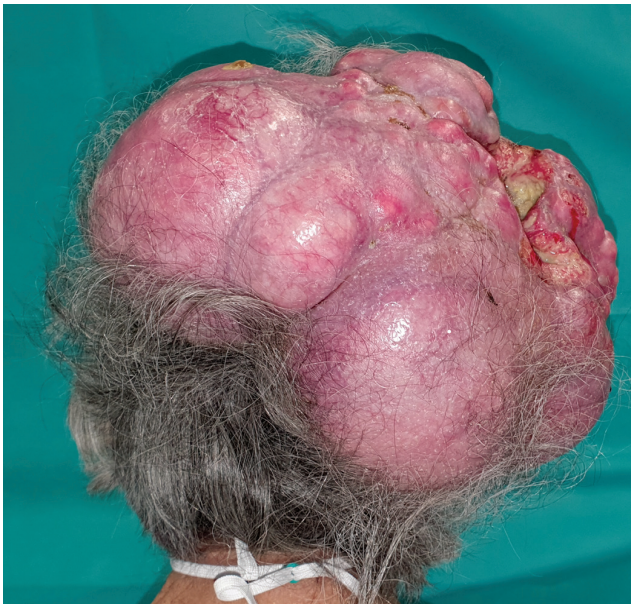

Figure 1 – Posterior view of proliferative trichilemmal tumor of the scalp

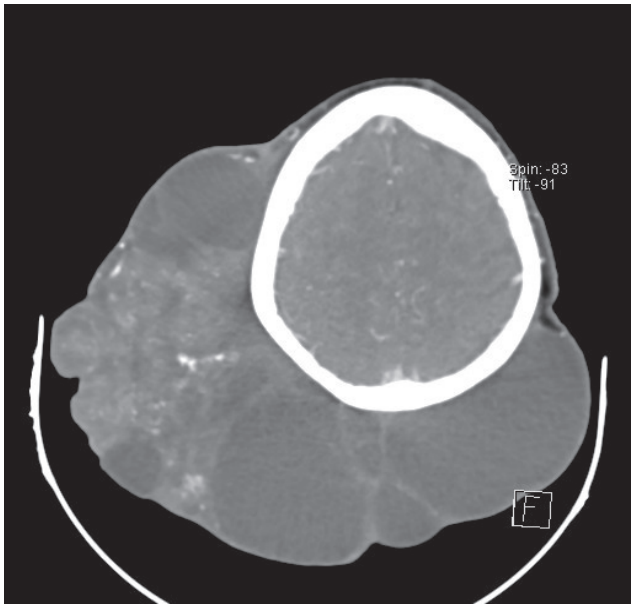

Figure 2 – CT scan without bone invasion of the cranial vault

A 76-year-old female presented with a massive, exophytic, multinodular and well-circumscribed lesion of the scalp, with two years of evolution, measuring 28.3 x 25.4 x 22.9 cm.

The lesion was partially necrotic with both solid and cystic areas (Fig. 1). A computed tomography scan did not reveal distant dissemination, nor bone invasion of the cranial vault (Fig. 2). She underwent extended excision of the lesion with preservation of the periosteum and reconstruction of the defect with a partial-thickness skin graft. The histological examination revealed a benign proliferative trichilemmal tumor (PTT) without atypia. To the best of our knowledge this is one of the largest PTT ever reported. It is a benign and rare adnexal neoplasm of follicular lineage with probable origin in a trichilemmal cyst, more frequent in elderly females and the most common location is the scalp. This neoplasm has a high rate of recurrence and may rarely become malignant.[1-4]

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Recomendações para o Diagnóstico e Tratamento da Infeção Não Complicada por *Chlamydia trachomatis* (Não- Linfogranuloma Venéreo) em Portugal

Guidelines for the Diagnosis and Treatment of Uncomplicated (Non-Lymphogranuloma Venereum) *Chlamydia trachomatis* Infection in Portugal

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RESUMO

A infeção por *Chlamydia trachomatis* é a infeção bacteriana sexualmente transmissível mais frequente a nível global. A sua abordagem diagnóstica é desafiante pela existência de um grande número de portadores assintomáticos, e requer uma disponibilização apropriada de testes laboratoriais à população em risco. Em Portugal, a incidência da infeção tem crescido de forma consistente nos últimos anos, pelo que se impõe a necessidade de cuidados redobrados na identificação de casos, rastreio de contactos sexuais e aplicação de medidas terapêuticas eficazes. As presentes recomendações resultam da adaptação à realidade portuguesa dos consensos internacionais em termos de diagnóstico e terapêutica da infeção por *Chlamydia trachomatis*, e foram formuladas com o objetivo de uniformizar a gestão clínica e laboratorial dos casos sintomáticos e portadores não sintomáticos da infeção em Portugal à luz dos conhecimentos atuais.

Palavras-chave: Chlamydia trachomatis; Infecções por Chlamydia/diagnóstico; Infecções por Chlamydia/tratamento

ABSTRACT

Chlamydia trachomatis infection is the most prevalent sexually transmitted bacterial infection in the world. Being associated with a large number of asymptomatic carriers, the diagnosis is frequently challenging and requires appropriate laboratory testing. In Portugal, the incidence of the disease has been consistently increasing in recent years, meaning that special awareness is required for case identification, contact tracing and application of appropriate treatments. These recommendations result from the adaptation of the international consensuses on the diagnosis and treatment of *Chlamydia trachomatis* infection to the Portuguese healthcare setting, with the aim of standardizing the clinical and laboratory approach to symptomatic and non-symptomatic carriers of the disease.

Keywords: Chlamydia Infections/diagnosis; Chlamydia Infections/therapy; Chlamydia trachomatis

INTRODUÇÃO

A infeção da mucosa urogenital por *Chlamydia trachomatis* (CT) é considerada a infeção sexualmente transmissível (IST) de causa bacteriana mais comum na generalidade dos países europeus, Austrália e Estados Unidos da América,[1-7] sendo causada pelas estirpes D-K deste microrganismo intracelular obrigatório.[1-4,6,8] Tem sido evidenciada uma incidência crescente desta infeção a nível global desde a década de 1990.[2] Na União Europeia, esta tendência persiste nos relatórios epidemiológicos mais recentes, sendo favorecida pela maior frequência de práticas sexuais de risco acrescido para a transmissão de IST, em particular a redução progressiva do uso de métodos de proteção de barreira e o aumento do número médio de parceiros sexuais, que surgem a par da evolução farmacológica do tratamento da infeção pelo vírus da imunodeficiência humana (VIH) e da generalização do acesso a profilaxia pré-exposição (PrEP)[9,10]; a pandemia da infeção por SARS-CoV-2 também terá contribuído significativamente para o aumento da incidência a partir do ano 2020.[11] Em Portugal, a infeção por CT é definida como doença de declaração obrigatória

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desde 2014[12]; os dados disponíveis desde então mostram uma incidência crescente da doença, tendo sido diagnosticados em 2021 um total de 874 casos.[9,10] A interpretação dos dados epidemiológicos nacionais é limitada pela conhecida subnotificação da infeção que é justificada, entre outros motivos, pela limitação ou dificuldade de acesso aos meios técnicos necessários para o diagnóstico na generalidade das unidades de saúde.[13]

A infeção transmite-se por contacto muco-mucoso geralmente em contexto sexual,[2] tendo um período de incubação curto (uma a quatro semanas)[4] e uma prevalência similar em homens e mulheres.[2] São considerados fatores de risco (Tabela 1): idade inferior a 25 anos; contacto sexual com novo parceiro; mais do que um parceiro sexual; uso inconsistente de métodos de proteção de barreira; parceiro sexual com múltiplos parceiros; parceiro sexual com diagnóstico de IST; antecedentes ou diagnóstico recente de IST; contexto de trabalho sexual; institucionalização em unidade prisional ou de reclusão.[2-6,8]

O risco de transmissão é elevado mesmo nos casos de contacto sexual único, justificando as elevadas taxas de concordância de resultados positivos entre parceiros e de infeção concomitante das mucosas urogenital e extragenital[2,3]; o envolvimento das mucosas anorretal e orofaríngea é igualmente frequente em homens que têm sexo com homens (HSH) e em mulheres heterossexuais.[2,3,6,14]

A transmissão da doença pode também ocorrer em contexto peri-parto (com risco de 50% - 75%),[2] nomeadamente com atingimento da conjuntiva e vias respiratórias do recém-nascido.[2,3,6]

Quando não tratada, a infeção resolve espontaneamente num grande número de casos: até 50% em um ano,[2,3] 82% em dois anos[2] e 95% em três anos.[2] No entanto, o risco de sequelas graves em infeções de curso arrastado é significativo, mesmo quando assintomáticas,[2,3] pelo que a instituição de métodos de rastreio e diagnóstico/tratamento precoces é fundamental.[2] A ocorrência de infeção por CT não confere imunidade contra uma reinfeção pelo mesmo agente.[1]

Tabela 1 – Fatores de risco para infeção por *Chlamydia trachomatis*

Idade inferior a 25 anos
Contacto sexual com novo parceiro
Contacto com mais de um parceiro sexual
Uso inconsistente de métodos de proteção de barreira
Parceiro sexual com múltiplos parceiros
Parceiro sexual com diagnóstico de IST
Antecedentes pessoais ou diagnóstico recente de IST
Trabalho sexual
Institucionalização em unidade prisional ou de reclusão

Clínica

A infeção urogenital é assintomática em mais de 70% dos casos no sexo feminino e em mais de 50% no sexo masculino.[2,4,8] Quando sintomática, pode originar corrimento vaginal/uretral, disúria, prurido ou edema uretral, hemorragia pós-coital ou intermenstrual, dor hipogástrica ou dispareunia[1-3]; à colposcopia pode evidenciar-se edema, friabilidade, hipersensibilidade e/ou ulceração cervicais.[1-4]

As infeções anorretal e orofaríngea são por norma assintomáticas,[2,3] embora possam cursar respetivamente com clínica de proctite com corrimento e dor anorretal e odinofagia com eritema e exsudato faríngeos.[1-3]

A infeção conjuntival em adultos é tipicamente unilateral, e geralmente pouco ou moderadamente sintomática.[2-3]

Em recém-nascidos infetados pode desenvolver-se conjuntivite (nos 30 dias após nascimento) e broncopneumonia (nos primeiros três meses de vida).[2,3,6]

Complicações

No sexo masculino as complicações associadas à infeção urogenital por CT são incomuns, e incluem epididimite e orquite[2-4]; não existem evidências inequívocas de compromisso da fertilidade embora alguns estudos sugiram a possibilidade de perturbação da espermogénese.[2,3,8]

No sexo feminino as complicações são frequentes e potencialmente graves: a doença inflamatória pélvica (DIP) pode ocorrer em até 30% dos casos não tratados, aumentando o risco de gravidez ectópica, infertilidade (por dano tubar) e dor pélvica crónica.[2,3,8]

A artrite reativa sexualmente adquirida, anteriormente designada síndrome de Reiter, é rara (0,03% - 0,04%) e tem maior expressão em homens HLA-B27 positivos[2]; sendo tipicamente seronegativa, surge geralmente em contexto de uretrite e conjuntivite e por vezes com manifestações cutâneas características (queratodermia blenorrágica e balanite circinada).[1-3,7,15]

As complicações descritas, nomeadamente as do foro ginecológico, têm vindo a ser reportadas com frequência decrescente, provavelmente pela maior acessibilidade e fiabilidade dos exames diagnósticos que permitem tratar precocemente um maior número de casos.[2,3,6]

Diagnóstico

O uso de testes de amplificação de ácidos nucleicos (TAAN) é recomendado para diagnóstico de infeções urogenitais e extragenitais por CT,[1,2,5,6] apesar de nem todos os testes comercialmente disponíveis terem aprovação formal para uso em amostras extragenitais (sendo possível nestes casos um diferencial de sensibilidade e especificidade).[2,6]

Quando indisponível, poderá recorrer-se a outras técnicas diagnósticas (isolamento em cultura celular, ensaios imunoenzimáticos ou imunofluorescência direta), apesar

de não serem recomendadas pela menor sensibilidade.[2,16] A serologia não tem valor diagnóstico na infeção urogenital não complicada devido ao longo período de latência até seroconversão, frequentemente com títulos de anticorpos baixos e de difícil interpretação, podendo no entanto ser útil nas formas crónicas ou complicadas de doença (por exemplo DIP ou artrite reativa), na infeção por estirpes LGV ou em recém-nascidos.[2,6,13,16,17]

Os testes rápidos baseiam-se, na sua generalidade, na deteção do antigénio lipopolissacarídeo da CT por imunocromatografia e, apesar de invocarem uma relação custo-efetividade não negligenciável, não devem ser usados em alternativa aos TAAN por apresentarem especificidade muito reduzida e sensibilidade inferior à da cultura.[2,6,13,16,18] Na atualidade, apesar de não recomendados, os testes rápidos poderão ser considerados em situações pontuais de indivíduos sintomáticos com risco elevado de não comparência a uma segunda consulta e, portanto, de desenvolvimento de complicações por ausência de tratamento. Nos últimos anos têm vindo a ser desenvolvidos e disponibilizados testes rápidos baseados em TAAN (por PCR, LAMP ou RPA), com sensibilidade sobreponível aos TAAN clássicos, que oferecem resultados em cerca de 90 minutos, mas que exigem equipamento especial e domínio da aplicação informática de leitura de resultados, acarretando custos globais superiores aos métodos laboratoriais convencionais[2,13,16,18]; no futuro, estes novos testes poderão vir a permitir a abordagem imediata dos indivíduos com resultado positivo e respetivos parceiros, evitando tratamentos empíricos desnecessários e a necessidade de uma segunda visita para comunicação de resultados obtidos pelos TAAN convencionais, embora não tenham ainda aplicabilidade prática real.

Grupos-alvo para realização de testes diagnósticos

Os testes laboratoriais de diagnóstico deverão ser realizados em todos os indivíduos em contexto de risco para infeção por CT (especificados na Tabela 2), com realce particular para mulheres e HSH sexualmente ativos com idade inferior a 25 anos.

Em contexto de gravidez, é recomendada a realização de testes de diagnóstico na primeira visita médica após confirmação da gestação em:

- todas as mulheres grávidas com idade igual ou inferior a 25 anos[6];
- mulheres grávidas assintomáticas com idade superior a 25 anos com fatores de risco para infeção por CT (Tabela 1).[6]

Caso os critérios de risco para infeção por CT se mantenham no decurso da gravidez, deverão ser realizados novos testes no último trimestre da gestação para prevenção de complicações perinatais na gestante e no recém-nascido.[6]

Amostras biológicas e métodos de colheita

No sexo masculino, a amostra biológica preferencial para diagnóstico de infeção urogenital por CT é a urina (colheita da primeira porção, com volume inferior a 20 mL e pelo menos uma hora após a micção anterior).[2-6] A colheita de exsudato uretral poderá ter uma sensibilidade ligeiramente inferior e condiciona desconforto significativo, pelo que não deverá ser usada como amostra biológica preferencial[3]; quando realizada deverá implicar inserção da zaragatoa 2 a 4 cm a partir do meato uretral, com rotação prévia à remoção.[3] Não está recomendada a realização de colheita de sémen ou de exsudato/raspado da mucosa ou

Tabela 2 – Grupos-alvo para realização de testes de diagnóstico de infeção por *Chlamydia trachomatis*

Indivíduos assintomáticos sexualmente ativos com idade inferior a 25 anos,[1,2] particularmente se do sexo feminino ou HSH[6]
Indivíduos assintomáticos com idade superior a 25 anos e fatores de risco para infeção por CT (Tabela 1) ou sob PREP[1,2,6]
Homens com clínica de uretrite [corrimento uretral mucopurulento ou ardor/prurido uretral com > 5 leucócitos polimorfonucleares (PMN) por campo de grande aumento, ou teste de esterase leucocitária positivo ou > 10 PMN à microscopia de sedimento de urina 1º jato] e mulheres com cervicovaginite de causa não conhecida e com fator de risco para infeção por CT[1,2,4,6]
Homens com epidídimo-orquite e idade inferior a 40 anos ou risco para infeção por CT (Tabela 1)[2]
Mulheres com dor pélvica aguda ou clínica de DIP[1]
Indivíduos com proctocolite e risco para infeção por CT (Tabela 1)[2,6]
Recém-nascidos com conjuntivite purulenta ocorrendo nos primeiros 30 dias após nascimento ou em adultos (nestes últimos particularmente se unilateral)[2,3]
Lactentes com pneumonias atípicas neonatais nos primeiros três meses de vida[2,3]
Indivíduos com diagnóstico de outra IST no último ano[1,2]
Parceiros sexuais de indivíduos com diagnóstico conhecido de IST ou DIP[1,2]
Mulheres sujeitas a procedimentos invasivos uterinos por via vaginal, se risco para infeção por CT (Tabela 1)[1,2]
Progenitoras de recém-nascidos com infeção por CT confirmada[3]
Vítimas de abuso sexual, incluindo crianças[3]
Presidiários ou indivíduos institucionalizados em centros de reabilitação social, com idade inferior a 35 anos[6]

pele penianas.[2]

No sexo feminino a amostra biológica de eleição deverá ser o exsudato vaginal ou endocervical,[2-6] o primeiro geralmente colhido por introdução da zaragatoa cerca de 5 a 8 cm no canal vaginal, com rotação antes da remoção.[3] A colheita de exsudato vaginal por colposcopia não oferece benefício no que diz respeito à sensibilidade do exame.[2,3] A colheita de urina (primeira porção) não está recomendada no sexo feminino por apresentar menor sensibilidade, podendo, no entanto, ser útil quando a colheita de exsudato vaginal ou endocervical não for praticável (por exemplo, em mulheres grávidas ou em situações de desconforto extremo ou recusa).[2,6] Também não é recomendado o recurso ao escovado cervical para citologia (Papanicolau) como amostra para TAAN, dada a sua sensibilidade inferior relativamente à colheita convencional de exsudato cervicovaginal,[2,6] apesar de já existirem testes com aprovação formal para esse fim.[2,6]

A autocolheita de exsudatos uretral, vaginal, anorretal e orofaríngeo não parece implicar menor sensibilidade do exame comparativamente com as colheitas realizadas por profissionais de saúde,[2,3,6] embora nas duas últimas localizações seja difícil garantir a qualidade da amostra.

A colheita de exsudatos anorretal e orofaríngeo deverá ser realizada de forma sistemática em HSH e ponderada em outras populações de acordo com o risco e historial de contacto sexual local,[2,6] tendo em conta que um resultado laboratorial negativo numa amostra genital não exclui a existência de infeção extragenital.[6] A colheita de exsudato anorretal poderá ser realizada de forma dirigida mediante realização de anuscopia ou por simples introdução e rotação da zaragatoa no orifício anal[3]; da mesma forma, o exsudato faríngeo poderá ser colhido por rotação da zaragatoa na parede posterior da orofaringe.

Quando aplicável, a colheita de exsudato conjuntival deverá ser realizada com rotação da zaragatoa na pálpebra evertida, de forma a colher componentes celulares.[3,6]

Em caso de suspeita de pneumonia neonatal por CT a colheita de exsudato deverá ser realizada por zaragatoa na mucosa nasofaríngea[3,6]; quando aplicável, o aspirado traqueal e peças de biópsia pulmonar são igualmente adequados.[6]

Em indivíduos transgénero, as recomendações de testagem e colheita deverão ser adaptadas ao risco e anatomia individuais; em particular, a colheita cervicovaginal não deverá ser ignorada em caso de persistência de vagina/cervix em homens transgénero.[6]

Em contexto de abuso sexual, incluindo crianças, as colheitas deverão ser realizadas em todos os locais onde tenha ocorrido penetração e/ou contacto com fluidos corporais.[3]

Identificação de serotipos responsáveis por linfogranuloma venéreo (LGV)

A identificação de estirpes LGV de CT (L1 - L3) deverá ser considerada em todos os casos de TAAN positivo para CT, sendo particularmente recomendada em caso de:

- infeção anorretal com ou sem clínica de proctocolite, adenopatias unilaterais e/ou história de úlcera genital, particularmente em indivíduos HSH, seropositivos para VIH ou sob PrEP[1,19];
- infeção de outras áreas anatómicas se persistência de sintomas ou TAAN positivo após medidas terapêuticas convencionais.[19]

Nestes contextos pode recorrer-se ao uso de TAAN comercialmente disponíveis específicos para as estirpes LGV e/ou à amplificação, sequenciação e análise bioinformática do gene *ompA*; os primeiros não identificam especificamente as estirpes L1, L2 ou L3, mas distinguem-nas das não-LGV com base na pesquisa no gene *pmpH,* ou de outro gene que lhes seja característico.

Tratamento: considerações gerais

São candidatos a tratamento todos os indivíduos com diagnóstico laboratorial confirmado de infeção por CT ou em situação de infeção provável, conforme discriminado na Tabela 3.

O tratamento deverá ser instituído da forma mais célere possível após realização da colheita dos exsudatos, com vista a prevenir complicações e propagação da infeção.[6] Sempre que possível, as tomas dos esquemas terapêuticos de dose única e a primeira toma dos de dose múltipla deverão ser administradas sob observação do profissional de saúde.[6]

Tabela 3 – Candidatos a tratamento de infeção por *Chlamydia trachomatis*

Indivíduos com teste positivo para CT em amostra biológica[2]
Indivíduos com contacto sexual recente com portador de infeção por CT[2]
Mãe de recém-nascido portador de infeção por CT[2]
Indivíduos sujeitos a abuso sexual recente[2]
Homens com uretrite ou mulheres com cervicite/vaginite mucopurulenta na ausência de testes diagnósticos disponíveis ou previamente à confirmação laboratorial se elevado índice de suspeição de infeção por CT (devendo ser ponderada associação de terapêutica contra *Neisseria gonorrhoeae* consoante recomendações em vigor)[1,2]

Tratamento de adolescentes e adultos (Tabela 4)

Tratamento de primeira linha:

- doxiciclina 100 mg 2x/dia *per os* durante 7 dias.[1,2,5,6]

Tratamento de segunda linha:

- azitromicina 1 g *per os*, toma única[1,6];
- levofloxacina 500 mg 1x/dia *per os* durante 7 dias.[2,6]

Tratamento de terceira linha:

- ofloxacina 200 mg 2x/dia *per os* durante 7 dias[2,5];
- eritromicina 500 mg 2x/dia *per os* durante 7 dias[2,5]; ou
- josamicina 500 mg 3x/dia *per os* durante 7 dias, ou 1000 mg 2x/dia *per os* durante 7 dias (quando disponível).[2]

O uso de azitromicina como tratamento de primeira linha não é atualmente recomendado por apresentar uma taxa de eficácia inferior à doxiciclina, e, portanto, um número superior de falências terapêuticas, particularmente nas infeções anorretal ou orofaríngea[3,5,8]; tem vindo a assumir-se a possibilidade de a dose única de azitromicina ser subterapêutica quando comparada com esquemas posológicos mais prolongados, embora não haja evidências inequívocas que sustentem esta afirmação.[2] A crescente resistência à azitromicina observada em agentes microbianos frequentemente associados à infeção CT, como *Mycoplasma genitalium* e *Neisseria gonorhoeae*, tem motivado alertas relativamente à frequência da sua utilização.[5,6,20] Ainda assim, a azitromicina mantém uma elevada eficácia para tratamento de infeções por CT cervicovaginal ou uretral e poderá ser considerada uma alternativa nessas situações.[2,5,6,8]

A eritromicina parece ser globalmente menos eficaz do que a doxiciclina e azitromicina[2,3,6]; tratamentos mais longos parecem ter uma eficácia superior (> 95% para tratamentos de 10 - 14 dias),[3] mas são frequentemente comprometidos pela frequente ocorrência de intolerância gastrointestinal.[6]

Deverá ser considerado o risco de desenvolvimento de colite por *Clostridium difficile* e de rutura tendinosa aquando do tratamento com quinolonas.[3]

O tratamento com minocicilina (100 mg 2id *per os* durante sete dias) ou claritromicina (200 mg 2id *per os* durante sete dias) aparenta ser também eficaz,[8] embora não figure na generalidade das recomendações internacionais.

Tratamento de indivíduos com infeção VIH (Tabela 4)

O tratamento da infeção por CT em indivíduos seropositivos para VIH deverá ser preconizado de forma semelhante à população geral exceto no caso da infeção anorretal quando a identificação/exclusão de serotipos LGV não for possível – nestes casos deverá ser cumprido tratamento com doxiciclina 100 mg 2x/dia per os durante 21 dias.[2,3,6]

Tabela 4 – Tratamento da infeção não complicada por *Chlamydia trachomatis*

Adolescentes e adultos	
Primeira linha	**Doxiciclina 100 mg 2id 7 dias***
Segunda linha	Azitromicina 1 g toma única
	Levofloxacina 500 mg id 7 dias
Terceira linha	Ofloxacina 200 mg 2id 7 dias
	Eritromicina 500 mg 2id 7 dias
	Josamicina 500 mg 3id 7 dias (ou 1000mg 2id 7 dias)§
Grávidas ou lactantes	
Primeira linha	**Azitromicina 1 g toma única**
Segunda linha	Amoxicilina 500 mg 3id 7 dias
Terceira linha	Eritromicina 500 mg 4id 7 dias (ou 500 mg 2id 14 dias)
	Josamicina 500 mg 3id 7 dias (ou 1000 mg 2id 7 dias)§
Recém-nascidos e crianças com peso inferior a 45 kg	
Primeira linha	**Eritromicina 50 mg/kg/dia em 4 tomas diárias, 14 dias**
Segunda linha	Azitromicina 20 mg/kg/dia id 3 dias
Crianças com peso superior a 45 kg	
Primeira linha	**Azitromicina 1 g toma única**
Segunda linha (se idade superior a 8 anos)	Doxiciclina 100 mg 2id 7 dias

* exceto indivíduos portadores de infeção VIH com infeção anorretal e impossibilidade de exclusão de LGV, em que deve ser cumprido tratamento durante 21 dias.
§ quando disponível

Tratamento de grávidas ou lactantes (Tabela 4)

Tratamento de primeira linha:

- azitromicina 1 g *per os*, toma única.[1,2,5,6]

Tratamento de segunda linha:

- amoxicilina 500 mg 3x/dia *per os* durante 7 dias.[5,6]

Tratamento de terceira linha:

- eritromicina 500 mg 4x/dia *per os* durante 7 dias ou 500 mg 2x/dia *per os* durante 14 dias (em caso de intolerância gastrointestinal)[2,3,5,6];
- josamicina 500 mg 3x/dia *per os* durante 7 dias, ou 1000 mg 2x/dia *per os* durante 7 dias (quando disponível).[2]

A utilização de levofloxacina, ofloxacina e doxiciclina está contraindicada na gravidez.[2,6] O uso de macrólidos, apesar de não formalmente contraindicado, deverá ser realizado com prudência dada a associação recentemente descrita a abortamento e complicações neurológicas do recém-nascido.[6]

Tratamento de recém-nascidos (Tabela 4)

O uso de eritromicina oral é aplicável em todas as formas de infeção (50 mg/kg/dia, repartido em quatro tomas diárias durante 14 dias), com eficácia estimada de 80%.[3,5,6] Quando justificado, poderá ser ponderado tratamento alternativo com azitromicina oral (20 mg/kg/dia) em toma diária durante três dias.[5,6]

Em ambos os casos está descrita uma associação com o desenvolvimento de estenose hipertrófica do piloro, embora seja mais frequente com a eritromicina, pelo que os recém-nascidos tratados deverão ser sujeitos a monitorização.[5,6]

Não está indicada a realização de tratamento tópico (conjuntival) ou sistémico preventivo na ausência de sintomatologia ou confirmação laboratorial de infeção.[3,6]

Tratamento de crianças (Tabela 4)

Em crianças com peso inferior a 45 kg, o tratamento deverá consistir em eritromicina oral (50 mg/kg/dia) dividida em quatro tomas diárias durante 14 dias.[6]

Em crianças com peso igual ou superior a 45 kg está recomendado tratamento com azitromicina 1 g *per os* em toma única.[3] Em crianças de idade superior a oito anos poderá realizar-se em alternativa tratamento com doxiciclina 100 mg 2x/dia *per os* durante sete dias.[3]

Perante a evidência de uma infeção por CT em crianças com idade superior a três meses a possibilidade de abuso sexual deverá ser considerada como muito provável,[6] com a salvaguarda de que pode haver persistência de CT viáveis transmitidas em contexto perinatal nas mucosas orofaríngea, urogenital e anorretal da criança durante dois a três anos.[3] Havendo suspeita de abuso sexual, é mandatório reportar o caso às autoridades competentes e acionar todas as medidas necessárias para garantir a sua abordagem multidisciplinar.[6]

Tratamento pós-exposição (PEP)

O tratamento pós-exposição com doxiciclina oral nas primeiras 24 - 72 horas após o contacto sexual de risco tem sido apresentando como viável na redução do risco de infeção por CT, a par de outras IST bacterianas.[21] O seu uso rotineiro não é recomendado por não estar validado um esquema posológico consensual, e pelos riscos de se sobrepor à necessária testagem e monitorização laboratorial e de potenciar o desenvolvimento de resistências microbianas.[6,21]

Tratamento de infeções complicadas (DIP) ou associadas a LGV

O tratamento de formas complicadas de infeção por CT ou com envolvimento de estirpes LGV deverá obedecer a recomendações específicas que não se enquadram no âmbito desta publicação.

Abordagens complementares

É obrigatória a notificação de todos os casos confirmados e prováveis de infeção por CT na plataforma do Sistema Nacional de Informação de Vigilância Epidemiológica (SINAVE).[22]

Perante um caso confirmado de infeção por CT deverá proceder-se a um adequado esclarecimento do indivíduo para garantia de cumprimento das medidas terapêuticas que, na generalidade dos casos, são eficazes na resolução da infeção e na prevenção de complicações[3,6]; sempre que possível, deverá ser dada informação e aconselhamento sobre medidas de prevenção de IST, de forma verbal e escrita.[3,6,23]

Nos indivíduos com esquemas terapêuticos de tomas múltiplas a atividade sexual poderá ser retomada após a sua conclusão (sete dias) se ausência de sintomas[1-3,6]; em caso de recurso a tratamentos de toma única, deverão ser evitados contactos sexuais nos sete dias seguintes.[1-3,6] Paralelamente, deverá ser desaconselhado o contacto sexual com os parceiros antes que estes realizem os respetivos rastreios e tratamentos, particularmente se houver historial de contacto nos seis meses anteriores ao diagnóstico.[1-3,6]

É sempre recomendada realização de rastreio de outras IST (nomeadamente gonorreia, sífilis, hepatites B e C e infeção por VIH) e repetição dos respetivos testes laboratoriais dependendo do período de janela correspondente, bem como promoção da vacinação contra hepatite B e vírus do papiloma humano, caso aplicáveis e não realizadas.[1-3,6,24] Poderá ser ponderada a referenciação

Tabela 5 – Indicações para realização de teste de cura

Indivíduos com infeção urogenital não complicada sujeitos a tratamentos de terceira linha[2]
Indivíduos com infeção extragenital (particularmente se infeção anorretal sujeita a tratamento com azitromicina)[1,2,6]
Mulheres grávidas, recém-nascidos e crianças sujeitos a tratamento[1-3,6]
Indivíduos com infeções complicadas sujeitas a tratamento[2]
Indivíduos com persistência de sintomas após tratamento[2]

para consulta de PrEP, se cumpridos critérios nacionais definidos pela Norma 001/2024 de 22/03/2024 da Direção Geral de Saúde,[25] particularmente em HSH seronegativos com infeção anorretal por CT.[6]

A confirmação de infeção urogenital não complicada por CT em mulheres portadoras de DIU não é indicação para a sua remoção.[1,3]

Rastreio e tratamento de contactos

Todos os indivíduos com historial de contacto sexual com o caso *index* nos seis meses anteriores à data de diagnóstico ou de desenvolvimento de sintomas deverão ser identificados, notificados e encaminhados para realização de rastreio laboratorial por profissionais de saúde especializados[1-3]; o parceiro mais recente deverá ser sempre rastreado mesmo que o contacto tenha ocorrido há mais de seis meses.[6]

Apesar de não substituir ou excluir a necessidade de testes laboratoriais confirmatórios e/ou redes robustas de notificação, é válida a prescrição de tratamento dirigido aos parceiros por intermédio do caso *índex* sempre que se verifique risco de ausência de comparência para rastreio e tratamento, com vista a limitar a propagação da infeção e reduzir os riscos de reinfeção e complicações.[1,2,6]

Teste de cura

Nas infeções urogenitais não complicadas sujeitas a tratamento de primeira ou segunda linha com resolução de sintomas não está indicada a realização da prova de cura.[1-3,6]

As indicações formais para a sua realização estão especificadas na Tabela 5. Nestes casos, a colheita deverá ser realizada após pelo menos quatro semanas depois da conclusão do tratamento, para evitar a deteção de resíduos de ácidos nucleicos de CT não viáveis (falsos positivos).[1-3,6]

Monitorização

De uma forma geral, deverá ser recomendada a realização de TAAN para rastreio de reinfeção a todos os indivíduos com diagnóstico de infeção por CT nos primeiros seis a 12 meses após tratamento.[1-3,6]

Em indivíduos sexualmente ativos com idade inferior a 25 anos é recomendável a repetição de testes de rastreio com periodicidade anual, atendendo ao maior risco de reinfeção nesse período[1-3,6]; poderá ser ponderada uma periodicidade menor (três a seis meses) em indivíduos HSH, sob PrEP, com infeção VIH ou mantendo prática sexual com múltiplos parceiros.[6]

Não está recomendada repetição rotineira de testes de rastreio em indivíduos com mais de 25 anos a não ser que apresentem contexto de risco.[3]

CONCLUSÃO

O controlo epidemiológico da infeção por CT é cada vez mais desafiante dada a elevada frequência de portadores assintomáticos ou pouco sintomáticos e o grande potencial de transmissibilidade numa sociedade em que as práticas sexuais se tornam gradualmente mais liberais, a par da perda de popularidade das medidas clássicas de proteção individual contra IST. A incidência crescente desta infeção a nível global reflete a insuficiência das medidas preventivas, diagnósticas e terapêuticas instituídas pela generalidade dos sistemas de saúde.

As diferentes recomendações internacionais para a abordagem da infeção por CT têm sofrido alterações múltiplas nos últimos anos e revelam diferenças regionais significativas; a inexistência de normas de consenso formalizadas em Portugal fazem com que a abordagem clínica da doença seja, por esse motivo, pouco uniforme no território nacional. As presentes recomendações têm, assim, como propósito oferecer à comunidade médica portuguesa as informações e ferramentas necessárias para o diagnóstico e tratamento da infeção não complicada por CT.

É fundamental que todas as populações de risco tenham acesso a testes de diagnóstico adequados, e que a todos os casos suspeitos ou confirmados de doença sejam oferecidos os meios terapêuticos e de gestão de contactos de forma atempada e atualizada. A notificação sistemática pelas equipas clínicas e laboratoriais é também crucial para adaptar em tempo útil as medidas de controlo da infeção à evolução epidemiológica da doença.

CONTRIBUTO DOS AUTORES

PA: Redação, revisão crítica e aprovação do manuscrito.

JA, CL, CF, MJB, JBC, JR, FS, AS, JA: Revisão crítica e aprovação do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

CONFLITOS DE INTERESSE

JR recebeu apoio da Medinfar para a participação no Congresso IUSTI 2021.

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

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Submission to Healthcare Ethics Committees in Portugal: Our Experience

Submissão às Comissões de Ética para a Saúde em Portugal: A Nossa Experiência

Keywords: Clinical; Ethics Committees; Portugal; Research
Palavras-chave: Clínica; Comissão de Ética; Investigação; Portugal

Dear Editor,

Ethics Committees in health care are instrumental in upholding ethical standards within the life sciences, ensuring the protection of human dignity and integrity.[1] However, they encounter challenges pertaining to time constraints and limited logistical resources.[2] In Portugal, since 2018, the mandate for an Ethics Committee in human research institutions has introduced a degree of variability in resource allocation and methods of ethical evaluation. This has led to increased complexity in national-level projects, which often require approvals from several local ethics committees. Furthermore, with the implementation of local health units, the number of ethics committees is set to rise from five to potentially 39 across mainland Portugal.

In this letter, we describe the procedures and response times experienced when submitting an identical protocol to the five ethics committees of the regional health administrations in mainland Portugal. The study in question was a European cross-sectional survey, endorsed by the European General Practice Research Network and previously approved by an Ethics Committee at the University of Zagreb. Our goal was to gather a representative sample of Portuguese family physicians, considering recruitment through their institutional email, thus requiring approval from each respective regional ethics committee.

We provide a comparative analysis of the ethics committees' submission processes and response times in Table 1.

Each committee's website provided submission guidelines, but these often lacked clarity, leading to ambiguities. A notable challenge was the diversity in submission rules, protocol structures and required documents across committees. Additionally, many required submissions in Portuguese, complicating matters further for international studies. Predicting response times was often challenging due to the non-publication of meeting dates or the absence of contact emails. Response times varied, frequently exceeding the national 31.3-day average,[3] but the feedback received was detailed and provided valuable insights.

Based on our experience, we recommend researchers conducting nationwide studies in primary health care allocating a minimum of 120 days for the ethics committee approval process. For the committees, we advocate for standardized submission procedures and procedures for mutual recognition of decisions. This streamlining is crucial, given the dual research and clinical duties of most researchers. Furthermore, we suggest institutions enhance their support for ethics committees, ensuring they have adequate secretarial support and allocated time for members. This is particularly relevant at a time when there is a reorganization of the Portuguese National Health Service, which is transitioning from five regional administrations to a multitude of local health units.

AUTHOR CONTRIBUTIONS

DIR, CS: Literature search, writing of the manuscript.
GP: Critical review of the manuscript.
JA: Writing of the manuscript.
BH: Study design, critical review of the manuscript.
All authors approved the final version to be published.

COMPETING INTERESTS

BH was a consultant for the Healthcare Ethics Committee of the Lisbon and Tagus Valley Region.

All other authors have declared that no competing interests exist.

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Table 1 – Comparative analysis of the Ethics Committees' submission processes and response times

Ethics Committee	Northern Region	Center Region	Lisbon and Tagus Valley Region	Alentejo Region	Algarve Region
Submission	Online platform (only accessible through PC/laptop)	E-mail	E-mail	E-mail	E-mail
Does it accept the protocol in English?	No	Yes	Yes, with a mandatory abstract in Portuguese	No	No
Time until approval	79 days (Submission on 05/11/2022, approval on 23/01/2023)	47 days (Submission on 05/11/2022, approval on 22/12/2022)	40 days (Submission on 04/12/2022, approval on 13/01/2023)	419 days (Submission on 23/12/2022, approval on 15/02/2024)	53 days (Submission on 05/11/2022, Ethics Committee approval on 28/12/2022; Executive Board approval on 12/06/2023)

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Spindle Cell Lipoma of the Hallux: A Rare Entity

Lipoma de Células Fusiformes do Hálux: Uma Entidade Rara

Keywords: Hallux; Lipoma
Palavras-chave: Hálux; Lipoma

Spindle cell lipoma (SCL) is an uncommon histological entity of benign lipogenic tumors, characterized by mature adipocytes and small uniform spindle cells.[1-3] This tumor usually manifests in middle-age male patients and the most common sites are the posterior neck, shoulder, and posterior trunk.[1,4,1] Spindle cell lipomas rarely occur in the distal extremities. Clinical studies analyzing a total of 897 lipomas, reported only three lipomas located in the foot (0.33%).[6]

A 77-year-old male was referred to the Plastic Surgery Department of our university hospital for evaluation of a large and longstanding mass of the dorsal aspect of the right hallux. The lesion was noticed 20 years ago, and it has gradually enlarged in size particularly in recent months, causing increased difficulty in wearing footwear. The clinical examination revealed a 50 x 40 mm nodular tumor, firm, not painful on palpation with distended but intact overlying skin. There was no evidence of bone changes or calcifications on dorsoplantar and lateral x-ray views of the foot. The ultrasound revealed a hypoechoic subcutaneous circumscribed oval mass measuring 44 x 35 mm that resembled an epidermoid cyst.

Surgical excision of the lesion was performed under local anesthesia. Intraoperatively, the mass was in the subcutaneous layer of the hallux abutting and distorting the extensor tendon apparatus with close contact with the bone. Macroscopically, the mass was pale yellow, oval shaped, with an elastic consistency and encircled by a fibrous tissue layer, weighed 26 g, measuring 41 x 31 x 23 mm (Fig. 1A). Microscopically, it was an adipocytic tumor composed mainly of mature adipocytes, but also bland spindle cells and ropy collagen (Fig. 1B). CD34 antibody was positively expressed in the spindle cells of this tumor (Fig. 1C). These findings were consistent with the diagnosis of SCL.

Most of these soft tissue tumors found in the foot were reported to be benign (87%).[6] Regarding malignant soft tumors, dorsal synovial sarcoma, and clear cell sarcoma of the foot account for the most common. Although rare, giant cell tumor is the most locally aggressive with a high recurrence rate.[6,7] An accurate diagnosis is essential, because a wide excision can cause serious disabilities. It is a very rare location for this benign tumor and as such the clinical differential diagnosis does not usually encompass it. Although not commonly described in the field of Plastic Surgery, the diagnosis of SCL can be clearly made by pathologists. Knowledge of patient history, physical examination and radiological imaging is important but can be nonspecific. Therefore, it can be difficult to characterize soft tissue tumors in unusual locations. Proper management with surgical excision and histological evaluation is essential for differential diagnosis from other rare malignant neoplasms, since SCL is a benign tumor, and even though it can be locally invasive, it has a good prognosis and can be cured by complete excision.

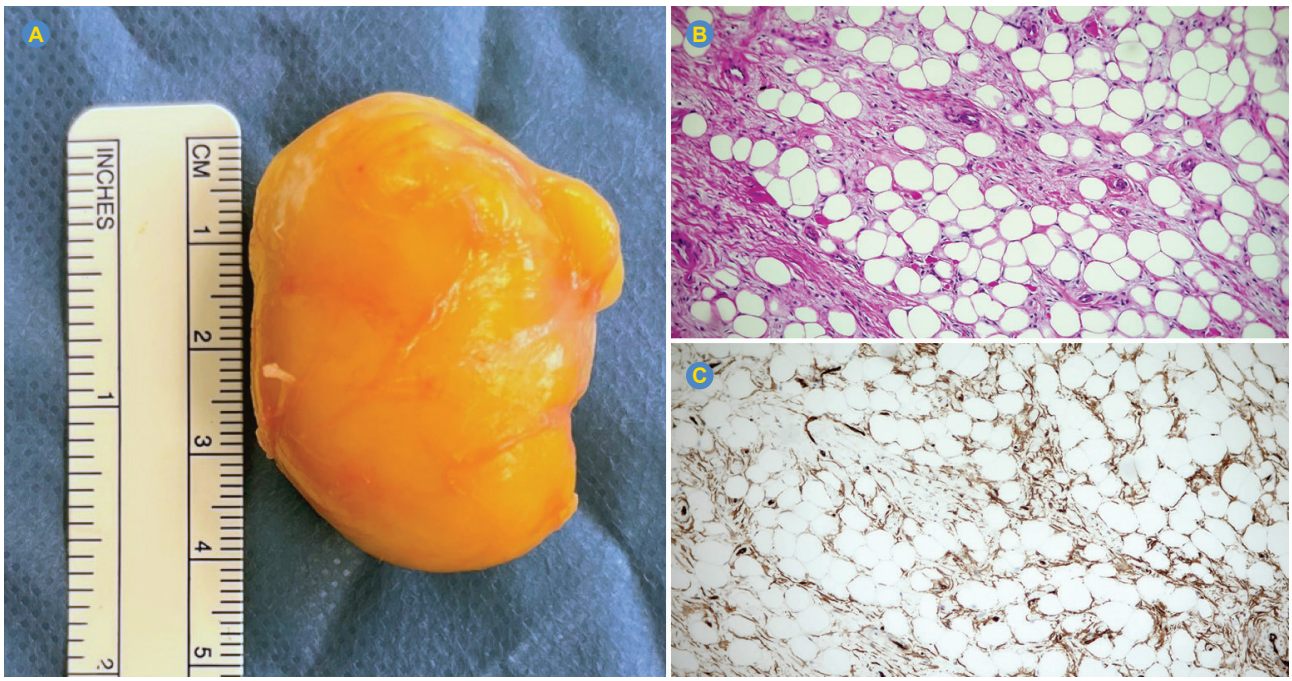

Figure 1 – Spindle cell lipoma of the hallux dorsum with 41 mm width: pale yellow oval shaped mass, with elastic consistency and encircled by a fibrous tissue layer (A). Hematoxylin and eosin staining of the tumor: mature adipocytes mixed with a bland spindle cell proliferation and ropy collagen (amplification x100) (B). Anti-CD34 immunohistochemical staining of the tumor (amplification x100) (C).

AUTHOR CONTRIBUTIONS

SMS: Data collection, writing and critical review of the manuscript.

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All authors approved the final version to be published.

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

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Duas Críticas Éticas ao Editorial Acerca da Nova Lei de Saúde Mental

Two Ethical Criticisms of the New Mental Health Law

Palavras-chave: Portugal; Psiquiatria/ética; Psiquiatria/legislação e jurisprudência; Saúde Mental; Tratamento Psiquiátrico Involuntário
Keywords: Involuntary Treatment, Psychiatric; Mental Health; Portugal; Psychiatry/ethics; Psychiatry/legislation & jurisprudence

Caro Editor,

Lemos, com interesse, o recente editorial acerca da nova Lei de Saúde Mental (nLSM) por Vieira *et al*.[1,2] Nele, os autores justificam a necessidade da nLSM, identificam diferenças relevantes relativamente à lei anterior (aLSM) e antecipam desafios que a nLSM poderá suscitar. Também nós aplaudimos a chegada da nLSM, que consagra uma necessidade de maior exigência nos exercícios deliberativos para a aplicação do tratamento involuntário (TI).

Embora acolhamos o tom geral do editorial, existem nele considerações expostas como evidentes, que arriscam terraplanar, sem benefício aparente, o difícil lugar de debate de onde emerge o TI.

A primeira afirmação discutível centra-se no presumível carácter científico da "imperiosa necessidade" do TI.[2] Ora, se há matéria cientificamente controversa, é precisamente a eficácia, em várias medidas, dos TI — da compulsividade dos tratamentos, entenda-se —, nas suas várias modalidades.[3,4] Isto não é dizer que o TI seja dispensável, é antes afirmar que a discussão sobre a sua necessidade se faz num âmbito supracientífico, no plano da ética e da responsabilidade, como médicos e sociedade, perante o doente singular que observa a sua autonomia cerceada pela doença mental. Se nos guiássemos apenas pela ciência neste capítulo, não haveria TI, pois a evidência será equívoca, no máximo.[4] A questão está em saber para que exigências deliberativas contribui a informação que nos presta a ciência: é este o seu papel aqui. Assim, invocar a autoridade da ciência para estabelecer bases indiscutíveis nesta matéria pode prejudicar tanto a ciência quanto a nossa condição de agentes morais, numa discussão cujos pressupostos são inerentemente problematizáveis e contendíveis.

Uma segunda questão reside numa presumível interpretação limitada da aLSM, aparentemente tornada clara pela nLSM: o envio da avaliação clínico-psiquiátrica (ACP) ao Ministério Público, mesmo em caso de tratamento voluntário ou não tratamento (n.º 2; artigo 31.º).[1] Esta disposição constitui o ponto mais controverso numa lei que procura, valorosamente, potenciar a autonomia dos doentes. Embora a figura da ACP faça parte do procedimento legal, ela não existe no abstrato: é dotada de informação de indivíduos que não são meros objetos procedimentais. O conteúdo da ACP não deixa de ser nem um dado sensível pertencente ao internando, nem fruto da responsabilidade epistémica do médico. Assim, se utilizarmos o enquadramento de ponderação ética médica principialista,[4,5] pretender enviar conteúdo clínico — caso não se conclua pela necessidade de TI em sede de ACP —, a entidades terceiras, constitui um acto desprovido de proporcionalidade ou sequer de adequação, que sacrifica a privacidade e o sigilo sem reciprocidade objectivável, isto é, sem qualquer ganho no sentido do propósito a alcançar. Igualmente, não vislumbra que, nesta fase processual, de acordo com n.º 3 do art.º 135.º de Código de Processo Penal,[6] fosse atendível qualquer princípio da prevalência do interesse preponderante que transformasse, mecanicamente, o médico num funcionário judiciário, derrogado na sua autonomia técnico-científica e deontológica, e o obrigasse a disponibilizar, a mando judicial, sem qualquer consentimento do doente, informação clínica que não fosse apenas aquela que justificasse a necessidade de TI. Havendo de a enviar, os psiquiatras devem — entendemos —, não se concluindo pelo TI, dotar os relatórios de ACP apenas dessa conclusão, e nada mais.

CONTRIBUTO DOS AUTORES

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SPA: Revisão crítica.

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

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Perspetiva de um Grupo de Médicos Internos a Propósito do Artigo "Strategies for the Promotion of Primary Health Care Research in Portugal: A Qualitative Study"

Perspectives of a Group of Residents Regarding the Article "Strategies for the Promotion of Primary Health Care Research in Portugal: A Qualitative Study"

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 da Acta Médica Portuguesa,

Foi com grande interesse que analisámos o artigo "*Strategies for the Promotion of Primary Health Care Research in Portugal: A Qualitative Study*".[1] Trata-se de um tema amplamente discutido entre médicos internos de Medicina Geral e Familiar (MGF), pelo que gostaríamos de partilhar algumas reflexões.

Como referido pelos autores, acreditamos que a promoção da investigação no âmbito dos Cuidados de Saúde Primários (CSP) é determinante para a sua qualidade e o internato médico constitui um momento privilegiado para desenvolver esta competência. Consideramos, no entanto, que a produção científica não deve ser imposta, mas incentivada.

A adequada capacitação dos internos para a produção de ciência de qualidade deveria sobrepor-se à valorização da quantidade, e não o oposto. Este aspeto pode ser observado, por exemplo, nos resultados do estudo de Abreu *et al.*[2] A grelha de avaliação curricular contempla de forma relevante a produção original pelo interno, em múltiplas tipologias; no entanto, o guião de formação não incita a essa capacidade, limitando-se à análise e interpretação crítica da evidência. O programa de internato atual exige a produção sem assegurar a capacitação.

A aquisição destas competências requer a colaboração de mentores experientes, ou estruturas que possam orientar os médicos internos quando confrontados com dificuldades na elaboração dos seus projetos de investigação. Este papel não pode ser incutido exclusivamente ao orientador de formação, sendo uma preocupação comum a inexistência de recursos de referência capazes de orientar o processo de produção científica.

A ausência destas estruturas, aliada à pressão para a produção, levam inevitavelmente ao desenvolvimento de trabalhos com conteúdo científico de relevância questionável ou com metodologias discutíveis, comprometendo a qualidade necessária ao avanço científico desta especialidade.

Consideramos ainda que aumentar a proximidade às comissões de ética facilitaria o processo de elaboração, revisão e implementação dos protocolos de investigação em tempo útil, potenciando a sua concretização ao longo do internato.

Por fim, destacamos a pertinência das sessões de aprendizagem relacional, momentos protegidos de tempo não assistencial. Estas reuniões semanais garantem, entre outras vantagens, um tempo dedicado à análise e produção científica, constituindo-se como um espaço para partilha de questões relevantes e facilitando o desenvolvimento de trabalhos multicêntricos e de maior qualidade.

A MGF é uma especialidade privilegiada para a produção relevante de ciência de qualidade. A sua promoção deve ser objeto de reflexão por parte de todos os futuros e atuais médicos especialistas em MGF.

CONTRIBUTO DOS AUTORES

MB: Conceção e desenho do estudo, pesquisa bibliográfica, revisão crítica.

MM: Desenho do estudo, pesquisa bibliográfica, redação.

MC: Desenho do estudo, redação, revisão crítica.

RV: Redação, revisão crítica.

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Sacral Stress Fracture: A Diagnosis to Remember

Fratura Sacral de Stress: Um Diagnóstico a Considerar

Keywords: Adolescent; Athletic Injuries; Fractures, Stress/diagnosis; Sacrum/injuries
Palavras-chave: Adolescente; Fracturas de Stress/diagnóstico; Lesões Desportivas; Sacro/lesões

Sacral stress fractures (SSF) in adolescence are rare, and their incidence in the pediatric age is unknown. Despite their scarcity, lumbar-sacral lesions are one of the most common causes of sports-related low back pain in the pediatric age.[1] These fractures result from a mechanical overload applied to healthy bone.[2]

This is a challenging diagnosis and requires a high index of suspicion. It usually occurs at an early age resulting from repetitive exercises or recent abnormal escalation in the training schedule.[3] The standard clinical finding of sacral stress fractures' is insidious pain, which can be nonspecific, or localized in the lower back, pelvis, or gluteal region.[1]

We present the case of a fourteen-year-old female who presented to the emergency department with a two-week history of right posterior sacroiliac pain. She used to play basketball regularly but had stopped for two years. A few weeks before the start of the complaints she had returned to practice and trained for two hours, two to three times a week. She had no systemic complaints; denied having a history of eating disorders or menstrual abnormalities – eating disorders, amenorrhea and osteopenia comprise the female athlete's triad.[1]

There was no history of previous acute trauma, infection, pelvic disease, or neurologic dysfunction.

The pain was described as a mechanical low back pain, which radiated to the right lower limb, and worsened with right leg weight-bearing.

On physical examination, sacrum compression triggered diffuse marked tenderness over the right sacroiliac joint. The pain worsened in the right sacroiliac region with lumbar flexion and extension, weight-bearing on right leg and right sided flexion, abduction and external rotation (FABER) sign.

Plain radiography revealed no abnormalities. However, a magnetic resonance imaging (MRI) test (gold-standard) of the sacroiliac joints revealed a vertical fracture line along the anterior cortex of the right wing of the sacrum, with marked bone marrow edema (Fig. 1A). Imaging studies must include cuts of lumbar pedicles and sacral ala, as most SSF injuries occur there.[4]

The patient was treated conservatively with analgesia (non-steroidal anti-inflammatory drugs should be avoided for at least three to four weeks because of its potentially deleterious effect on bone healing, rest and non-weight-bearing physical activities.

She was reassessed after two weeks and was asymptomatic. Computerized tomography (CT) after four weeks revealed right sacral wing sclerosis (Fig. 1B). The patient resumed normal daily-life activities and physical activity four months after the injury.

In conclusion, with the increasing number of children/adolescents engaging in sports, it is essential for physicians to be aware of this condition. It is important to avoid unwarranted, and often invasive, tests, since the clinical presentation of these injuries may mimic malignancies and infections which require an immediate approach,[5] and therefore highlights the importance of a thorough investigation in order to reach a correct diagnosis.

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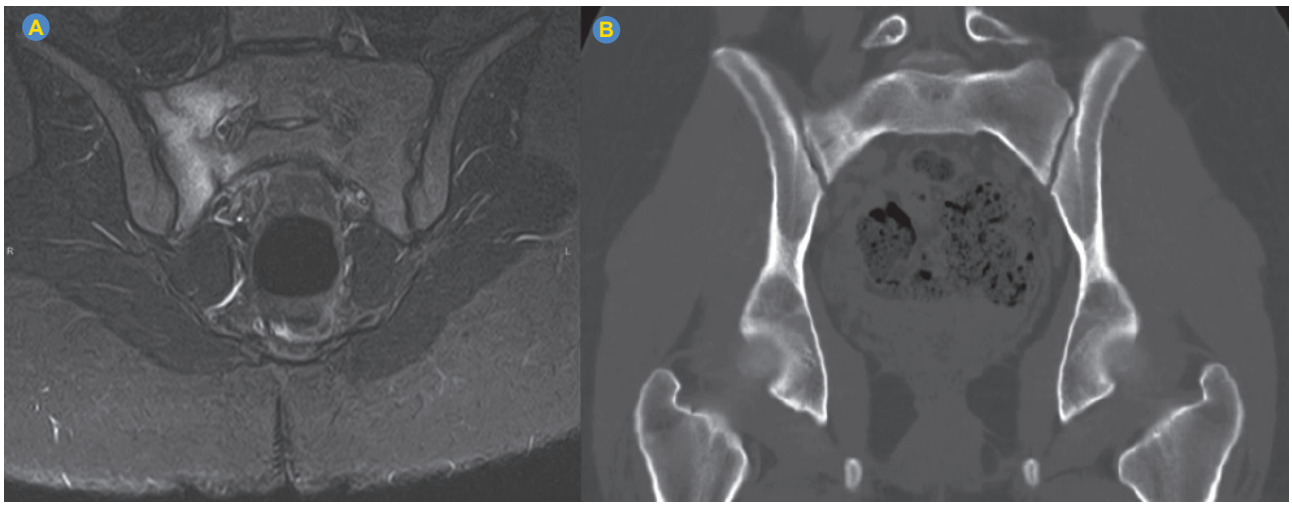

Figure 1 – Coronal section of MRI (at diagnosis) where a trace of vertical fracture (parallel to the sacroiliac joint) is observed along the anterior cortical of the right wing of the sacrum, associated with bone marrow edema, without reaching the posterior surface of the sacrum (A). Coronal section of CT that revealed mild sclerosis of the right wing of the sacrum (exam performed four weeks after symptom onset) (B) .

PREVIOUS AWARDS AND PRESENTATIONS

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

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Comment on "Ophthalmology Census 2021: A Demographic Characterisation of Ophthalmologists in Portugal"

Comentário sobre "Ophthalmology Census 2021: A Demographic Characterisation of Ophthalmologists in Portugal"

Keywords: Ophthalmologists/statistics & numerical data; Ophthalmology; Portugal
Palavras-chave: Oftalmologia; Oftalmologistas/estatísticas e dados numéricos; Portugal

To the Editor,

Regarding the article "Ophthalmology Census 2021: A Demographic Characterization of Ophthalmologists in Portugal" published in your esteemed journal, I would like to address several points raised by this study. The article highlights that while the number of ophthalmologists in Portugal meets international recommendations, there is a shortage in the public sector, with most ophthalmologists practicing in large urban centers.[1]

The uneven distribution of ophthalmologists mirrors the broader pattern of physician distribution across Portugal. There is a concentration of medical professionals in areas such as Porto, Coimbra, and Lisbon, while regions like Alentejo and Algarve suffer from shortages.[2]

The need for ophthalmology care among the elderly is increasing in Portugal, which is is expected to have a population of over 35% elderly by 2050.[2] Additionally, the time allocated to teaching ophthalmology in medical education has decreased in various parts of the world, including in the United States, where it declined from 68% in 2000 to 30% in 2004.[3] Consequently, we may end up with generalist physicians lacking basic knowledge to address common ophthalmology issues, further driving demand for specialist care.[3]

For instance, the direct ophthalmoscopy examination, which should be within the skill set of all generalist physicians, presents challenges. In a study conducted at a Canadian university involving 208 students, 47% felt inadequately confident in performing direct ophthalmoscopy.[4] This contradicts the International Council of Ophthalmology's recommendation that generalist physicians should possess at least a basic level of ophthalmology knowledge, including recognizing the red reflex and examining the optic nerve, identifying conditions that can threaten not only the patient's vision but also the patient's life, such as papillary edema.[4]

Addressing these issues requires establishing better working conditions and remuneration for ophthalmologists in the public healthcare system, where the bulk of patient care is concentrated. Additionally, there's a need to emphasize the training of generalist physicians to handle basic ophthalmology problems. This can be achieved through the development of new teaching methodologies, including low-cost teaching models that enable students to grasp the fundamental principles of direct ophthalmoscopy and enhance their skills, thus increasing their confidence in examinations where diagnostic sensitivity and specificity are directly linked to physician training.[5]

Another consequence of the deficiencies in ophthalmology education and care is the growing development of artificial intelligence algorithms for triaging diseases such as diabetic retinopathy, cataracts, glaucoma, and even prescribing glasses, which also indicates a consequence of technological development in these areas. This can lead to more reliable diagnoses and treatment recommendations, regardless of geographical location or individual clinician expertise.[5]

In this way, the irregular distribution of ophthalmologists hampers access to healthcare for a significant portion of the population reliant solely on the public healthcare system. The solution to this problem lies not only in increasing the number of specialists in the public healthcare system but also in implementing public policies to enhance the value of the medical profession, improve the quality of ophthalmology education in medical schools, and advance new technologies.

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The Dark Side of Beauty: Contact Dermatitis with Post-Inflammatory Hyperpigmentation Following Temporary Henna Tattooing

A Face Negra da Beleza: Dermatite de Contato com Hiperpigmentação Pós-Inflamatória Após Tatuagem Temporária com Henna

Keywords: Dermatitis, Allergic Contact/etiology; Hyperpigmentation/chemically induced; Phenylenediamines/adverse effects; Tattooing/adverse effects
Palavras-chave: Dermatite de Contacto Alérgica/etiologia; Fenilenodiaminas/efeitos adversos; Hiperpigmentação/induzida quimicamente; Tatuagem/efeitos adversos

A healthy 25-year-old female patient received a black henna tattoo on her left hand during a trip to Morrocco. Subsequently, she developed a pruritic vesicular erythema at the tattoo site that progressively worsened with development of hand edema (Fig. 1A). Ten days later, she was treated with systemic corticosteroids, antihistamines, and paracetamol at an emergency department, with slight improvement. Upon discharge, the patient was prescribed daily topical hydrocortisone, antihistamines, and analgesics as needed. Although the symptoms resolved one month later, hyperpigmentation at the tattoo site persisted for 16 months thereafter (Fig. 1B).

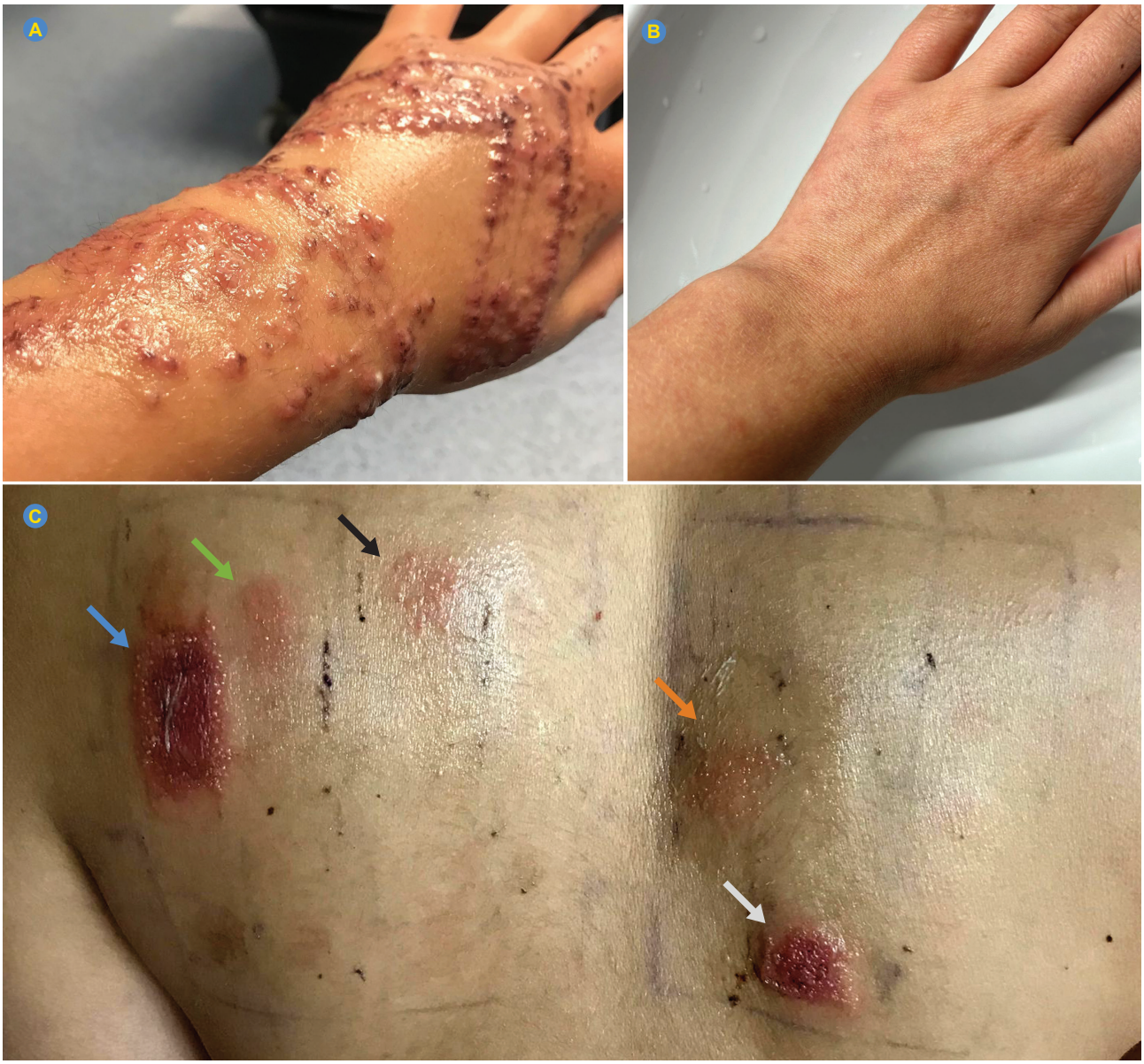

Figure 1 – Acute reaction with vesicular erythema and hand edema at the site of the henna tatto (A). Hyperpigmentation at the tattoo site that persists 16 months after the reaction (B). Patch tests results at 72 hours (C). Patch tests were performed using the Portuguese Contact Dermatitis Research Group Baseline Series, applying IQ ultraTM (Chemotechnique MB Diagnostics AB) applied on the upper back for 48 hours. A positive reaction was observed p-phenylenediamine (PPD) (+++; blue arrow), N-isopropyl-N-phenyl-4-phenylenediamine (IPPD) (++; black arrow), paraben mix (+; green arrow), disperse orange (+; orange arrow) and textile dye mix (+++; grey arrow).

Allergic contact dermatitis (ACD) to para-phenylenediamine (PPD), N-isopropyl-N-phenyl-4-phenylenediamine (IPPD), paraben mix, disperse orange, and textile dye mix was diagnosed after performing a patch test, namely the baseline series from the Portuguese Contact Dermatitis Research Group (Fig. 1C). The patient was advised to avoid these substances. However, despite this advice, she applied a hair dye that she had previously tolerated to the tips of her hair and developed facial edema 12 hours later, without any other symptoms.

Allergic contact dermatitis is an inflammatory skin condition induced by an immune reaction after sensitization to an allergen, diagnosed through patch tests.[1] Henna, derived from the leaves of *Lawsonia inermis*, is commonly used as a dye for coloring hair, nails and creating temporary henna tattoos, which are increasingly popular worldwide.[2] Henna can be combined with PPD to create black henna, which accelerates the dyeing process and enhances pattern definition. It is estimated that approximately 2.5% of black henna tattoos users can become sensitized to PPD, leading to ACD to other PPD-containing products such as hair dyes.[3] Additionally, post-inflammatory hyperpigmentation, a reported side effect, can persist over time, resulting in aesthetic repercussions.[1]

Sensitizations to allergens other than PPD may be due to cross-reactivity, and could occur due to the metabolic conversion of textile dyes in the skin to PPD.[1,4] The subsequent reaction to a hair dye containing PPD highlights the importance of reinforcing avoidance measures.

Although henna is considered to have low allergenicity, the addition of PPD can trigger ACD. Para-phenylenediamine in skin products is strictly prohibited in the European Union.[2] However, in some regions such as the Arab nations, the concentration of PPD in henna tattoos varies widely and may lack regulation. Travelers should be aware that black henna tattoos, despite their temporary nature, pose an increased risk of ACD, due to the incorporation of PPD.[5]

AUTHOR CONTRIBUTIONS

MB: Conceptualization, methodology, investigation, drafting, and critical review of the manuscript.

MJV, APC: Conceptualization, methodology, investigation, and critical review of the manuscript.

All authors approved the final version to be published.

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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Duodenal Duplication Cyst in Adulthood: Case Report and Brief Review of Literature

Quisto de Duplicação Duodenal no Adulto: Caso Clínico e Breve Revisão da Literatura

Keywords: Adult; Cysts; Duodenal Diseases; Duodenum/abnormalities
Palavras-chave: Adulto; Doenças Duodenais; Duodeno/anomalias congénitas; Quistos

Dear Editor,

Duodenal duplication cysts (DDC) account for 2% - 12% of all intestinal duplications. Its incidence is below 1 in 100 000 live births. They are typically cystic, non-communicating, and located at the medial border of the second part of the duodenum.[1]

Diagnosis is usually made in childhood, but up to one-third of cases may be found in the adult population, because the clinical presentation is variable.[2]

Common symptoms include upper abdominal pain, nausea, and vomiting, but the first episode of DDC can be a complication rather than the typical symptoms.[3] Complications such as acute pancreatitis, obstructive jaundice, luminal obstruction, gastrointestinal bleeding and infection have been reported.[1,3] Therefore, due to the heterogeneous clinical presentation, the diagnosis may be challenging, and imaging and endoscopy play crucial roles in identifying DDC.[4]

We report the case of a 45-year-old male patient with recurrent abdominal pain and cholestasis [aspartate transaminase 425 U/L (normal < 35 U/L); alanine transaminase 221 U/L (normal < 45 U/L); total bilirubin 3.2 mg/dL (normal 0.2 – 1.2 mg/dL)]. A duodenal lesion was detected using an abdominal computerized tomography scan. Further investigations including upper gastrointestinal endoscopy, endoscopic ultrasound, and magnetic resonance cholangiopancreatography confirmed a 50 mm oval and subepithelial lesion, with intracystic lithiasis, occupying two thirds of the duodenum lumen and involving the major duodenal papilla (MDP) (Fig. 1A). Following a multidisciplinary group discussion, a suspected diagnosis of Todani's type III choledochal cyst (CC) or DDC was raised, since DDC is lined by duodenal mucosa and is proximal to the MDP and CC is covered by biliary epithelium and is distal to the MDP. The final decision was surgical partial resection and marsupialization, considering the size of lesion and the proximity of biliary ducts (Fig. 1B).

Asymptomatic DDC cases are usually managed conservatively, although some authors advocate for excision. The approach to excision can be either endoscopic or surgical.[4]

The classical treatment for DDC has involved surgical management, encompassing total or partial resection or pancreaticoduodenectomy.[1] However, there has been an increase in the number of patients being treated endoscopically, which signalled a shift in the treatment paradigm.[5] When endoscopy cannot visualize the entire cyst, its relationship to surrounding structures is complex or the risk of malignant transformation is higher, surgery should be performed.[4,5]

The definitive diagnosis was established through histopathologic examination, which confirmed a DDC.

In conclusion, DDC are rare, and their diagnosis and treatment are difficult. It is crucial to be aware of this condition as a potential differential diagnosis for patients with abdominal symptoms.

AUTHOR CONTRIBUTIONS

CL, ON, MR: Study design, writing and critical review of the manuscript.

AP: Critical review of the manuscript.

JGT: Study design and critical review of the manuscript.

All authors approved the final version to be published.

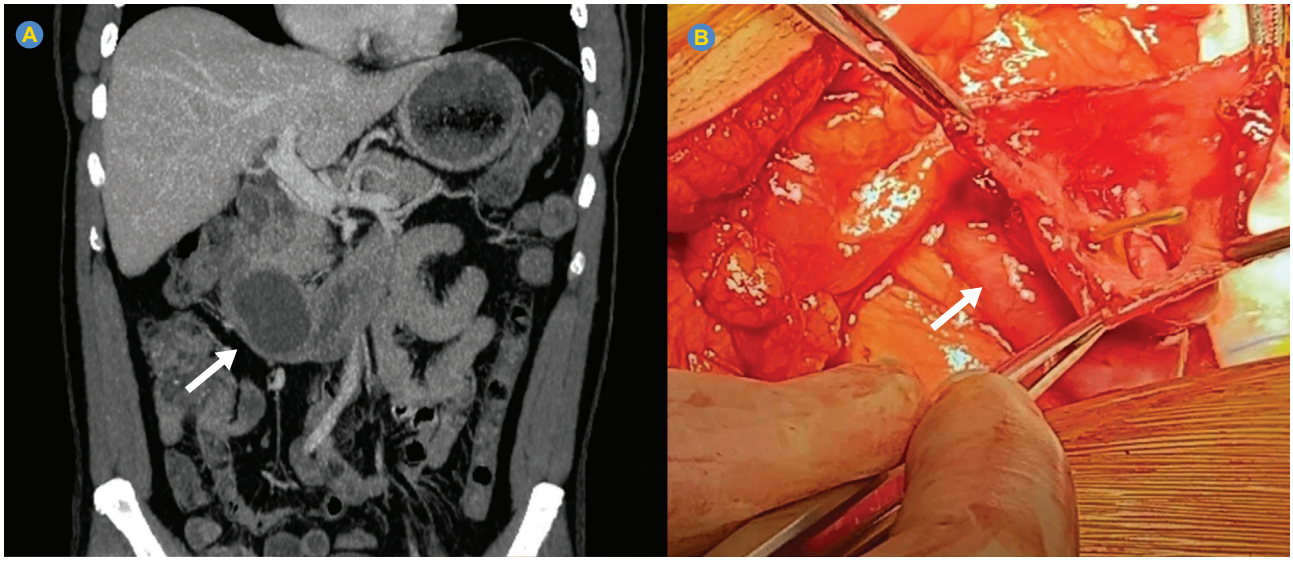

Figure 1 – Cystic lesion in the second portion of the duodenum (white arrow) – abdominal computerized tomography scan (A); intraoperative image of DDC after its incision, removal of biliary stones, identification, and cannulisation of true MDP inside the DDC (B).

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

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COMPETING INTERESTS

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