ACTA MÉDICA PORTUGUESA

ACTA MED PORT.
ISSN:0870-399X
e-ISSN:1646-0758

5 | 21

Número 5
Série II
Lisboa

Volume 34
Maio 2021
Publicação Mensal

ACTA MÉDICA PORTUGUESA

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Propriedade, Edição, Administração e Sede da Redação: Ordem dos Médicos (NIPC 500 984 492)
Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com
ISSN:0870-399X | e-ISSN: 1646-0758
Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros

AMP34(5) - Maio de 2021

Conselho Científico

Obesidade e COVID-19: Presente e Futuro

Obesity and COVID-19: Present and Future

Maria João GREGÓRIO✉[1,2], Alejandro SANTOS[2], Pedro GRAÇA[1,2]
Acta Med Port 2021 May;34(5):329-331 ▪ https://doi.org/10.20344/amp.15921

Palavras-chave: COVID-19; Obesidade
Keywords: COVID-19; Obesity

Com a chegada da COVID-19 à Europa e depois aos Estados Unidos, começou a avolumar-se a evidência que apontava a obesidade como uma das principais comorbilidades associadas a doença grave por COVID-19.

Um dos primeiros trabalhos sobre esta relação, que analisou as características e os *outcomes* clínicos de 383 doentes com COVID-19, na China, sugeria que os indivíduos com obesidade, em particular os do sexo masculino, tinham maior risco de desenvolver pneumonia grave.[1] Estes primeiros indícios viriam a confirmar-se e atualmente a evidência sobre esta relação já é muito consistente. Uma revisão sistemática com meta-análise, que analisou um total de 75 estudos e 399 461 participantes de 10 países, mostrou que a obesidade aumenta o risco de resultado COVID-19 positivo em mais de 46%, de hospitalização em 113%, de internamento em serviços de Medicina Intensiva em 74% e de mortalidade por COVID-19 em 48%.[2]

A COVID-19 foi declarada pela Organização Mundial da Saúde como pandemia há menos de um ano, contudo, a 6 de fevereiro de 2021 já é possível encontrar 1185 registos na PubMed quando pesquisam os termos 'obesity' e 'COVID-19'. O âmbito destes trabalhos é diverso, abrangendo, por exemplo, artigos que analisam a associação entre a obesidade e diferentes *outcomes* associados à COVID-19, e artigos que exploraram os possíveis mecanismos plausíveis para esta associação. Atualmente, a questão central reside na possibilidade da associação entre a obesidade e a COVID-19 ser de maior gravidade nos grupos mais jovens da população. Um estudo publicado recentemente na *Circulation* parece confirmar estas suspeitas, na medida em que mostra pela primeira vez que os efeitos adversos da obesidade em diferentes *outcomes* associados à COVID-19 são mais expressivos nos doentes com idade inferior a 50 anos, em comparação com os doentes com mais idade.[3] Assim, no que diz respeito ao risco de COVID-19 grave, levanta-se a hipótese de que a 'idade metabólica' possa ser um fator tão importante quanto a idade cronológica.

Noutra revisão sistemática com meta-análise, que analisou um total 28 estudos e 6720 indivíduos, 41% destes apresentavam diversas comorbilidades. Este estudo mostrou que a probabilidade de ter um quadro grave de COVID-19 era muito superior nos doentes com história de doença cerebrovascular, cardiovascular, doença pulmonar crónica, cancro, diabetes e hipertensão.[4] Tendo em conta a elevada prevalência destas patologias em Portugal e a sua associação com a obesidade, identificam-se aqui motivos para preocupação.

Estes dados são particularmente relevantes se considerarmos que o perfil de doentes hospitalizados em Portugal, em enfermaria mas também em serviços de Medicina Intensiva, tem vindo a alterar-se ao longo das diferentes vagas da pandemia. O início da pandemia ficou marcado com um perfil de doentes mais velhos, mas progressivamente foi aumentando a proporção de doentes mais jovens a necessitar de hospitalização no decurso da infeção por SARS-CoV-2.

Estes resultados não são assim tão surpreendentes se se tiver em consideração a evidência gerada durante as pandemias anteriores, desde a pandemia da 'gripe espanhola' de 1918 aos surtos de 'gripe asiática' de 1957 e 1960, à 'gripe de Hong-Kong' de 1968 e até à pandemia de 2009 causada pelo vírus *Influenza* H1N1. A evidência gerada por estas pandemias já indiciava a relação entre a obesidade e as doenças infeciosas.[5] Talvez a diferença relativamente ao momento atual reflita apenas a dimensão do problema da obesidade. Entre 1975 e os dias de hoje, a prevalência da obesidade na população, em geral, triplicou.[6]

Em Portugal, estudos já publicados analisaram as características e *outcomes* clínicos dos doentes com COVID-19 na população portuguesa sem incluírem a obesidade, pelo que ainda não é conhecido o seu impacto no número de hospitalizações, quer em enfermaria, quer em Cuidados Intensivos. A ausência da obesidade neste estudo foi recentemente destacada por Barbosa *et al*.[7] De facto, a obesidade é ainda, por vezes, clinicamente negligenciada enquanto comorbilidade com efeito no prognóstico de algumas situações de doença.

Apesar disso, os relatos dos clínicos dos hospitais

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Recebido: 09 de fevereiro de 2021 - **Aceite:** 10 de fevereiro de 2021 - ***First published*:** 20 de abril de 2021 - ***Online issue published*:** 03 de maio de 2021

portugueses na linha da frente apontam para uma elevada prevalência de doentes hospitalizados com obesidade, e em particular para aqueles que se encontram em serviços de Medicina Intensiva. De igual modo, as orientações para a abordagem ao doente com suspeita/confirmação de COVID-19, bem como o estabelecimento de prioridades para a vacinação, têm acompanhado a evidência científica internacional sobre a identificação da obesidade como um fator de risco para COVID-19 grave. Estes dados levaram a que em Portugal a obesidade tenha sido associada à evolução para COVID-19 grave na Norma 004/2020 – 'COVID-19: Abordagem do Doente com Suspeita ou Confirmação de COVID-19',[8] bem como na segunda fase do plano português de vacinação para a COVID-19, onde está incluído o grupo das pessoas com obesidade. Os ensaios das vacinas para a COVID-19 da Pfizer-BioNTech e da Moderna, apesar de limitados por um poder inadequado para comparar subgrupos e por uma incompleta estratificação de grupos de alto risco, parecem apresentar eficácia semelhante em indivíduos com e sem obesidade. Este dado é relevante, pois temia-se menor eficácia da vacinação nos doentes obesos face à resposta observada a outras vacinas.[9]

No contexto nacional, não só a obesidade é considerada nos documentos técnico-normativos que orientam a resposta concreta à COVID-19, mas também as políticas públicas de saúde em curso, como é o caso do Programa Nacional para a Promoção da Alimentação Saudável da Direção-Geral da Saúde, se organizaram no sentido de definir estratégias de ação para o contexto atual. *The national food and strategy for the Portuguese COVID-19 response*, publicada recentemente no European Journal of Clinical Nutrition, apresenta um modelo de intervenção a três níveis, no qual se destaca a importância da otimização do estado nutricional e do bom controlo metabólico de alguns grupos de risco para a COVID-19, nomeadamente nos indivíduos com pré-obesidade ou obesidade, propondo abordagens de intervenção concretas para o efeito.[10] Destas destaca-se o modelo de aconselhamento breve para a alimentação saudável.

Em Portugal, a pré-obesidade e a obesidade afetam mais de 6,1 milhões de portugueses adultos, doença que tende a ser mais frequente nos grupos da população mais vulnerável (os mais pobres e com menos escolaridade). A obesidade e outras doenças crónicas, como a diabetes, hipertensão e doenças cardiovasculares são patologias onde o descontrolo metabólico se pode agravar em resultado da redução do acesso a cuidados de saúde e da crise económica e social que se vive atualmente. Esta situação, e em particular o crescimento das desigualdades em saúde nesta área, reforça a necessidade de se continuar a priorizar a implementação de políticas públicas intersectoriais para a prevenção e para o combate à obesidade.

São muitos os desafios sem precedentes na promoção da alimentação saudável durante a pandemia COVID e no pós-COVID. A par das fragilidades que já se identificaram no estado de saúde de muitos portugueses com obesidade e outras doenças crónicas associadas a hábitos alimentares inadequados, perspetivam-se outros desafios que podem condicionar a implementação das necessárias medidas para a modificação dos ambientes obesogénicos. Tanto a fragilidade da nossa economia (que abrange a proteção dos operadores económicos do setor alimentar), como a multiplicação dos discursos contra a implementação de medidas sanitárias mais restritivas, serão certamente ameaças à intervenção pública no combate à obesidade. Por último, valerá a pena destacar que o desafio de mudar estilos de vida (alimentação e atividade física) será ainda maior neste atual contexto de ansiedade, incerteza e exposição contínua a restrições severas, fruto das medidas que procuram controlar a propagação da COVID-19.

Alguns destes desafios, que se colocam atualmente às políticas de prevenção e controlo da obesidade na era COVID e pós-COVID, já começam a ser refletidos a nível internacional. Destaca-se o artigo '*Obesity and COVID-19: Blame isn´t a strategy*', a propósito da nova estratégia inglesa para a obesidade. Uma estratégia ambiciosa no que toca à tentativa de uma maior regulação do mercado dos alimentos poucos saudáveis, mas que acaba por ficar marcada pelas críticas à excessiva culpabilização e responsabilização individual que ficou patente no título do comunicado de imprensa da sua divulgação – '*Lose weight to beat COVID-19 and protect the NHS*' - uma abordagem que os autores consideram ser típica da era COVID.[11]

Este será, pois, um período que exigirá um forte investimento na melhoria de prestação de cuidados nutricionais à população, facilitando o acesso a cuidados de saúde especializados e criando condições e modelos de prestação de cuidados que permitam otimizar a intervenção alimentar e nutricional.

CONFLITOS DE INTERESSE

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

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Inherited Retinal Degenerations in Portugal: Addressing the Unmet Needs

Distrofias Hereditárias da Retina em Portugal: Ao Encontro das Necessidades Não Satisfeitas

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Acta Med Port 2021 May;34(5):332-334 ▪ https://doi.org/10.20344/amp.15802

Keywords: Genetic Therapy; Genetic Testing; Portugal; Retinal Degeneration/genetics
Palavras-chave: Degeneração Retiniana/genética; Portugal; Terapia Genética; Testes Genéticos

INTRODUCTION

Inherited retinal dystrophies/degenerations (IRDs) are a clinically and genetically heterogenous group of rare eye diseases. Despite their low prevalence (~1:3000 individuals),[1] IRDs are an important cause of severe visual impairment and blindness in children and young adults. Over the past three decades, major advances in molecular biology and human genetics have contributed to uncover the molecular basis of these disorders. Most excitingly, treatment of a particular form of congenital retinal degeneration is now possible. In December 2017, the Food and Drug Administration (FDA) approved voretigene neparvovec (Luxturna, Spark Therapeutics Inc.) to treat *RPE65* mutation-associated retinal degeneration, which inevitably progresses to complete blindness by the third/fourth decade of life. Gene augmentation therapy delivers a normal copy of the native human RPE65 cDNA to the diseased retinal pigment epithelium (RPE) cells after subretinal injection of a recombinant adeno-associated virus. The transduced RPE cells then produce the RPE65 protein and the biochemical pathway leading to production of 11-cis retinal is restored, thus improving photoreceptor function.[2] Results from a phase III trial demonstrated improved light sensitivity, visual fields, and navigational ability under dim lighting conditions in patients with *RPE65* mutation-associated retinal degeneration.[3] The clinically meaningful effect, which is nearly maximal by 30 days after the administration, is maintained at least for four years, with observations ongoing.[4] In November 2018, the European Medicines Agency (EMA) granted Novartis AG marketing authorization for the use of Luxturna in Europe and several European countries have already started treatment. Not only has this newly approved therapy changed the lives of people previously destined to live a life of blindness, but it has fueled interest in developing additional gene therapy reagents targeting numerous other genetic forms of inherited retinal disease.[2] The lack of a consistent *RPE65* mutation–to–phenotype correlation underscores the need for widespread genetic screening in order to identify IRD patients who might benefit from this or other potential future gene therapies.

Despite some common ground, IRD genetic profiles have been shown to vary considerably among regions and ethnic groups,[1,5] thus highlighting the importance of obtaining reference population-based data. A recent survey from the European Vision Institute for Clinical Research Network (EVICR.net)[6] underlined the significant heterogeneity between centers and across countries regarding the current management of IRD patients in Europe. This applies not only to genetic testing and genetic counselling, but also to referral pathways, access to expert centers, ancillary diagnostic tests, among others. To improve the care of IRD patients in Portugal, we need to urgently address four pivotal unmet needs: 1) improve disease awareness and education; 2) provide equitable access to genetic testing and genetic counselling; 3) establish referral pathways; and 4) develop a national IRD registry.

Disease awareness and education

One of the most important issues is the dis- and/or misinformation that exists towards IRDs. It is crucial to raise awareness and educate decision/policy-makers, the general public, clinicians, and other healthcare workers about these visually incapacitating diseases. Only with this background work can patients be granted full clinical, familial, social, and economic support. Strategies to improve disease awareness include position papers written by experts in the field, targeted conferences/lectures/courses/preceptorships for healthcare professionals, media coverage and even social media actions. Ophthalmologists, pediatricians, and general practitioners (GPs) / family physicians are usually the first clinicians to encounter an IRD patient, thus

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Recebido: 26 de janeiro de 2021 - **Aceite:** 01 de fevereiro de 2021 - ***First published*:** 08 de abril de 2021 - ***Online issue published*:** 03 de maio de 2021

making up the group where targeted educational actions are most needed. Recognizing clinical clues/red flags like nystagmus, low vision, constricted visual field, night blindness (nyctalopia) and photophobia is crucial for a timely referral to an IRD expert center. In preverbal children, abnormal visual behavior and nystagmus observed and reported by the parents should prompt an appropriate ophthalmological workup for IRD.[7]

Genetic testing and genetic counselling

Remarkable progress in understanding the genetics of IRDs resulted in the identification of roughly 300 disease-causing genes (https://sph.uth.edu/retnet/). Several studies have confirmed that next-generation sequencing (NGS) panel-based genetic testing can be highly accurate, sensitive and reproducible in the molecular diagnosis of IRDs.[8] However, this wealth of information is only slowly being translated into genetic diagnoses for individual patients, as significant barriers to testing still exist. In Portugal, the overall prevalence and genetic architecture of IRDs is largely unknown since access to genetic testing is not equitable. A critical goal for moving the field forward is to obtain a genetic diagnosis for every IRD patient, the importance of which cannot be overemphasized. In fact, having a genetic diagnosis is likely to be the single most important factor for gaining access to an approved treatment or clinical trial based on gene therapy.[9] Furthermore, it allows accurate genetic counselling for the patient and other family members, along with prenatal testing. Additionally, it is a singularly important strategy for advancing the classification of mutations and corresponding phenotypes, and for evaluating the prognosis of specific disease-causing genes. In order to provide all IRD patients with the opportunity to undergo genetic testing, patient referral pathways must be in place so that patients may access expert centres easily. Portugal must draw up clinical recommendations or guidelines for genetic testing in IRDs, aiming to grant an equitable access to genetic testing and genetic counselling.

Referral pathways

Timely referral of patients with presumed IRDs to an ophthalmologist is critical. This applies especially to children since visual rehabilitation during the appropriate stages of visual development may prevent amblyopia. If the initial suspicion of IRD is confirmed by the ophthalmologist, the patient should be referred for genotyping. Now that treatment of *RPE65* mutation-associated retinal degeneration is possible, establishing a genetic diagnosis is even more important. Given the degenerative nature of IRDs, a window of opportunity for gene therapy exists and gene therapy candidates must be identified as soon as possible. A list of national IRD experts and IRD expert centers should be created and made available to ensure a smooth referral process. The European Reference Network for Rare Eye Diseases (ERN-EYE) is a unique and innovative cross-border cooperation platform between specialists for the diagnosis and treatment of rare or low prevalence complex eye diseases, where IRDs are included. The only Portuguese healthcare provider that integrates the ERN-EYE is Centro Hospitalar e Universitário de Coimbra (CHUC). However, appropriate dissemination of this information is warranted, especially to those that deal with IRD patients – ophthalmologists, pediatricians and GPs.

National IRD registry

A national, web-based registry for IRDs is able to empower patients and community organizations, while supporting formal partnerships with investigators and stakeholders in the global aim to develop high-value, high-utility research.[10] In 2020, the IRD-PT registry (www.retina.com.pt) was launched with the mission to generate important knowledge and collect high-quality longitudinal data on the epidemiology, genomic landscape, genotype–phenotype correlations and natural history of IRDs in Portugal.[10] Hopefully, this invaluable resource will both boost and excel clinical research in the field of IRDs in our country, while facilitating patient access to clinical trials or new therapies.

CONCLUSION

Although rare in the general population, IRDs occupy a key position in current efforts to develop innovative therapies for blinding diseases. Despite remarkable advances witnessed in the field, complex challenges subsist. This position paper from the Ophthalmic Genetics Group of the Portuguese Society of Ophthalmology identifies four pivotal unmet needs along with reasonable solutions to address them, aiming to improve management of IRDs and preparing the upcoming approval of voretigene neparvovec in Portugal.

COMPETING INTERESTS

The authors declare they have no conflicts of interest.

FUNDING SOURCES

No funding was available for the elaboration of this manuscript.

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Correlation of Estimated Creatinine Clearance and Glomerular Filtration Rate in Very Elderly Patients and Antibiotic Prescribing Errors: A Cohort Study

Correlação entre a Clearance da Creatinina Estimada e a Taxa de Filtração Glomerular Estimada nos Doentes Muito Idosos e Erros de Prescrição dos Antibióticos: Um Estudo de Coorte

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Acta Med Port 2021 May;34(5):335-341 ▪ https://doi.org/10.20344/amp.12408

ABSTRACT

Introduction: Determination of renal function is particularly important when prescribing antibiotics to elderly patients. This study aims to determine the correlation between estimated creatinine clearance and the estimated glomerular filtration rate, for a hospitalized population of very elderly patients, and to audit antibiotic prescribing errors.

Material and Methods: Retrospective cohort study of all patients ≥ 80 years hospitalized with antibiotic. Creatinine clearance was calculated using Cockcroft-Gault equation and estimated glomerular filtration rate by Modification of Diet in Renal Disease Study and Chronic Kidney Disease Epidemiology Collaboration equations. Dosing errors were determined through adjustment of daily define dose to renal function.

Results: The study included 589 patients. The correlation of Cockcroft-Gault with Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration was *r* = 0.98 and 0.96 for the minimum serum creatinine, and 0.97 and 0.93 for the maximum serum creatinine. Based on Cockcroft-Gault, there were errors in the daily defined dose in 45% in the minimum serum creatinine, and 52% in the maximum serum creatinine day. There was a discrepancy in the recording of errors of 14% to 16% when Cockcroft-Gault was compared with Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration.

Discussion: There was a good correlation of Cockcroft-Gault with the estimated glomerular filtration rate by Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration. Regardless of the equation used to estimate renal function there was a high rate of antibiotic dosing errors documented in this population.

Conclusion: This study supports the maintenance of the Cockcroft-Gault equation for drug dosing in the very elderly population. Further studies are needed to investigate underlying causes of prescribing errors.

Keywords: Aged, 80 and over; Aging; Anti-Bacterial Agents; Creatinine; Glomerular Filtration Rate; Medication Errors

RESUMO

Introdução: A determinação da função renal é particularmente importante na prescrição de antibióticos em doentes idosos. O objetivo deste estudo é correlacionar a *clearance* de creatinina com a taxa de filtração glomerular estimada, numa população hospitalizada de doentes muito idosos, e auditar os erros de prescrição antibiótica.

Material e Métodos: Coorte retrospetivo de todos os doentes ≥ 80 anos hospitalizados com antibioterapia prescrita. A *clearance* de creatinina foi calculada através da equação Cockcroft-Gault, e a filtração glomerular estimada através das equações *Modification of Diet in Renal Disease* e *Chronic Kidney Disease Epidemiology Collaboration*. Os erros de prescrição foram determinados pelo ajuste da dose diária definida à função renal.

Resultados: Foram incluídos 589 doentes. A correlação da Cockcroft-Gault com *Modification of Diet in Renal Disease* e *Chronic Kidney Disease Epidemiology Collaboration* foi *r* = 0,98 e 0,96 para a creatinina sérica mínima, e 0,97 e 0,93 para a creatinina sérica máxima. Com base na Cockcroft-Gault, a taxa de erro na dose diária definida foi 45% no dia da creatinina sérica mínima e 52% no dia da creatinina sérica máxima. Quando a Cockcroft-Gault foi comparada com a *Modification of Diet in Renal Disease* e a *Chronic Kidney Disease Epidemiology Collaboration* houve uma discrepância no registo de erros de 14% a 16%, respetivamente.

Discussão: Verificou-se uma boa correlação entre a Cockcroft-Gault e as equações que calculam a filtração glomerular: *Modification of Diet in Renal Disease* ou *Chronic Kidney Disease Epidemiology Collaboration*. Independentemente da equação utilizada para estimar a função renal, foi documentada uma taxa elevada de erros na dose de antibióticos prescrita nesta população.

Conclusão: Este estudo reforça a manutenção do uso da equação de Cockcroft-Gault para calcular a dose adequada de antibióticos na população muito idosa. Mais estudos são necessários para investigar as causas subjacentes aos erros de prescrição.

Palavras-chave: Antibacterianos; Creatinina; Envelhecimento; Erros de Medicação; Idoso de 80 Anos ou mais; Taxa de Filtração Glomerular

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Recebido: 06 de junho de 2019 - **Aceite:** 30 de dezembro de 2019 - ***First published*:** 29 de julho de 2020 - ***Online issue published*:** 01 de março de 2021

INTRODUCTION

Most drugs and their metabolites are excreted by the kidney through glomerular filtration. The overall size, mass and effective area of filtration decrease with increasing age.[1,2]

Therefore, there is an increased risk of drug and active metabolite accumulation in older patients, which accounts for the greater incidence of adverse drug reactions in this age group.[1]

Adverse drug events are between the fourth and sixth leading cause of death in the United States[3] and are responsible for one in six hospital admissions of older adults.[4]

Antibiotics are the second most common cause of adverse drug events in the ambulatory setting among seniors.[5]

Most guidelines recommend drug dosing adjustments in older adults with or without renal disease. The focus should be placed on reaching the optimal balance between improved outcomes while minimizing potential for drug toxicity. Therefore, the evaluation of renal function is of the essence. In order to determine renal function, several equations have been studied and validated using serum creatinine level as a marker for renal clearance. The Cockcroft-Gault (CG) equation, despite inaccurate in the elderly, remains the most widely used equation for determining the creatinine clearance. For more accurate assessment of estimated glomerular filtration rate (GFR), two other equations have been developed using larger populations: the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[1,6]

In comparisons between the CG, MDRD and CKD-EPI in the elderly, MDRD and CKD-EPI have been shown to more accurately assess estimated GFR than CG[6]; however, the MDRD Study equation has not been validated in elderly persons (> 70 years of age).[7]

The aim of this study is to determine the correlation between estimated creatinine clearance by CG equation with estimated GFR by MDRD and CKD-EPI equations, for a hospitalized population of very elderly patients (aged 80 years and older), and to audit antibiotic prescription, namely adjustment to renal function.

MATERIAL AND METHODS

Retrospective cohort study of all patients aged 80 years and older, admitted to Hospital de Santo António, Centro Hospitalar Universitário do Porto (HSA-CHUP), to whom antibiotic therapy was prescribed with intention to treat (antibiotic prophylaxis was not included). It was conducted over a three- month period, between 1st January 2017 and 31th March 2017. Ethical approval was obtained from the Ethical Committee for Health of HSA-CHUP, on March 2019 – N/REF.ª 2018.224(194-DEFI/193-CES).

Clinical characterization and approach

In the study period, prescribed antibiotic regimens, the loading doses, the daily defined doses (DDD) – in the day of maximum and minimum serum creatinine – and the total period of antibiotic therapy were obtained from the clinical records. In every patient, only the first cycle of antibiotic treatment in each hospitalization was considered. If modifications were made to the prescribed antibiotics, the reasons stated in the clinical records were also obtained. Patients with end-stage renal disease undergoing hemodialysis, peritoneal dialysis, or kidney transplantation, those prescribed with topical antibiotics or antibiotics with a prophylactic intent or those in whom the treatment lasted less than 48 hours were excluded.

Patients' age, gender, race, body weight and height were obtained from the clinical records. Patients' comorbidities were determined and used to obtain the Charlson Comorbidity Index (CCI) score.[8] The degree of functional impairment was determined according to the Karnofsky Performance Status Scale (KPS), using the information provided by clinical records.[9] This variable was then categorized in two groups: a group of patients with preserved autonomy in activities of daily living (score ≥ 70%) and a group of patients with some degree of dependence (score < 70%). The prescribing software used for inpatients was also used to assess if the patients' weight and creatinine were registered for automatic calculation of creatinine clearance.

Renal function calculation equations

For each patient, renal function was estimated using three creatinine-based equations: the CG equation,[10] which was further adjusted based on body weight and body mass index (BMI), since this equation appears to become less accurate in weight extremes (underweight and particularly overweight and obesity)[11]; the 4-variable MDRD Study equation[12]; and the CKD-EPI equation.[13] The MDRD Study and CKD-EPI equations calculate the estimated GFR normalized to a standard body surface area (BSA) of 1.73 m^2 and generally are reported in mL/min/1.73 m^2. These BSA-adjusted values were converted through the Dubois formula,[14] so that all were expressed in units of mL/min, the units of GFR that are expressed in the majority of drug dosing labels.

Antibiotic prescribing errors

A prescription was classified as a dosing error if it did not follow the recommended guidelines for drug adjustment to the renal function, according to The Sanford Guide to Antimicrobial Therapy,[15] whether it was by exceeding the maximum DDD – excess dosing – or by giving a lower dose than recommended – under dosing. An incorrect loading dose was also classified as a dosing error. In the case that more than one antibiotic was prescribed simultaneously, and only one presented a dosing error, that error prevailed upon the correct dosing; if both presented different types of dosing errors (e.g.: under and excess dosing), under dosing was prioritized. As three different equations for estimating renal function were used, the impact that using different formulas to estimate renal function had on the number of dosing errors was also compared. The association of dosing errors

with patient age, gender, race, comorbidities, functional status, body weight (real, ideal, adjusted), height, BMI, weight and/or creatinine registry in the prescribing software were also examined. All dosing errors were based on the same day creatinine.

Statistical analysis

Categorical variables were described as proportions and compared using chi-square or Fisher's exact test. Continuous variables were described by mean and standard deviation. Comparisons of continuous variables were performed using student *t*-test, after confirming its normal distribution through histogram.

Correlation was studied with Pearson correlation coefficient.

The association between the dependent variable (antibiotic prescribing error) and the other variables was studied through univariate logistic regression. Those with a clear association in the univariate analysis (p-value < 0.1) were selected for the multivariable analysis. The results of the multivariable models are expressed as odds ratio (OR) with 95% confidence interval ($CI_{95\%}$) and p-values. The calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The significance level was defined as $p < 0.05$.

The statistical analysis was performed in IBM SPSS (Statistical Package for the Social Sciences)® 25 (SPSS Inc., Chicago IL).

RESULTS

Clinical characterization and correlation between estimated CG and estimated GFR

During the study period, 929 patients aged 80 years or older undergoing antibiotic therapy were admitted to HSA-CHUP. Of these, a total of 340 patients (36.6%) were excluded from this study (Fig. 1): 12 (1.3%) had end-stage renal disease undergoing hemodialysis, peritoneal dialysis or kidney transplantation; 7 (0.8%) were on topical antibiotics; 89 (9.6%) had antibiotic prophylaxis; 104 (11.2%) had antibiotic therapy for less than 48 hours; 21 (2.3%) did not have serum creatinine values available in the clinical records during the antibiotic therapy period; and 107 (11.5%) did not have weight and/or height data available in the clinical records.

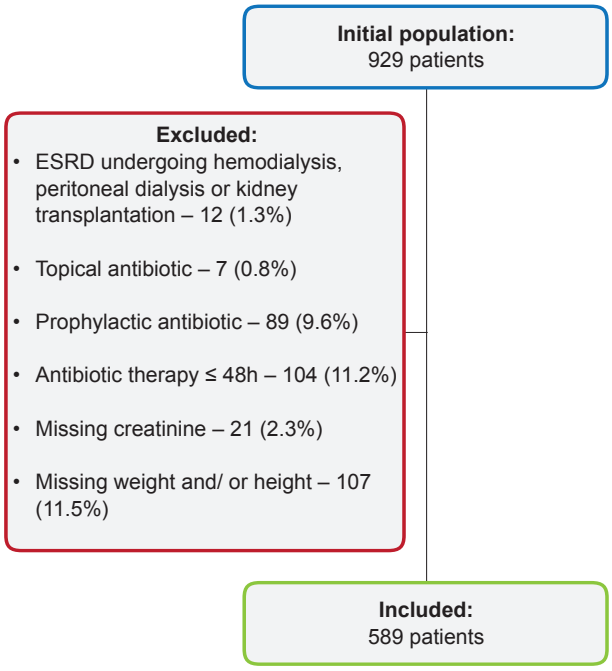

Figure 1 – Flow diagram of included patients
ESRD: end-stage renal disease

The clinical characteristics of the 589 patients included in the study population are listed in Table 1. The mean age of the cohort was 87 ± 4 years. The male gender accounted for 42% of patients. Only one patient of this population was black. Regarding the KPS, 37% of patients were independent in activities of daily living (Karnofsky score above 70%).

Considering the baseline serum creatinine, mean creatinine clearance estimated with CG equation was 42 ± 17 mL/min and mean estimated GFR with MDRD Study and CKD-EPI equations were 63 ± 27 and 57 ± 20 mL/min, respectively ($p < 0.001$). The correlation of CG equation with MRDR ($r = 0.95$, $p < 0.001$) is shown in Fig. 2A and with CKD-EPI ($r = 0.96$, $p < 0.001$) in Fig. 2B.

Considering the minimum serum creatinine, mean creatinine clearance from CG equation was 36 ± 19 mL/min and mean estimated GFR from MDRD Study and CKD-EPI equations were 54 ± 31 and 49 ± 24 mL/min, respectively ($p = 0.002$). The correlation of CG equation with MRDR obtained an $r = 0.98$ ($p < 0.001$) and with CKD-EPI an $r = 0.96$ ($p < 0.001$).

Considering the maximum baseline serum creatinine, mean creatinine clearance from CG equation was 46 ± 22 mL/min and mean estimated GFR from MDRD Study and CKD-EPI equations were 70 ± 38 and 59 ± 24 mL/min, respectively ($p < 0.001$). The correlation of CG equation with MRDR obtained an $r = 0.97$ ($p < 0.001$) and with CKD-EPI an $r = 0.93$ ($p < 0.001$).

Table 1 – Clinical characteristics

Characteristic	
Age (years), mean ± SD	87 ± 4
Male gender, n (%)	246 (42)
KPS scale ≥ 70, n (%)	216 (37)
CCI score, mean ± SD	7 ± 2
Weight (kg), mean ± SD	65 ± 14
Ideal body weight (kg), mean ± SD	56 ± 10
Adjusted body weight (kg), mean ± SD	60 ± 10
Height (cm), mean ± SD	161 ± 9
BMI (kg/m^2), mean ± SD	30 ± 5
CG (mL/min), mean ± SD	42 ± 17
MDRD (mL/min), mean ± SD	63 ± 27
CKD-EPI (mL/min), mean ± SD	57 ± 20
Antibiotic therapy period (days), median (IQR)	8 (6 – 10)

SD: standard deviation; KPS: Karnofsky Performance Status scale; CCI: Charlson Comorbidity index; BMI: body mass index; CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation; IQR: interquartile range

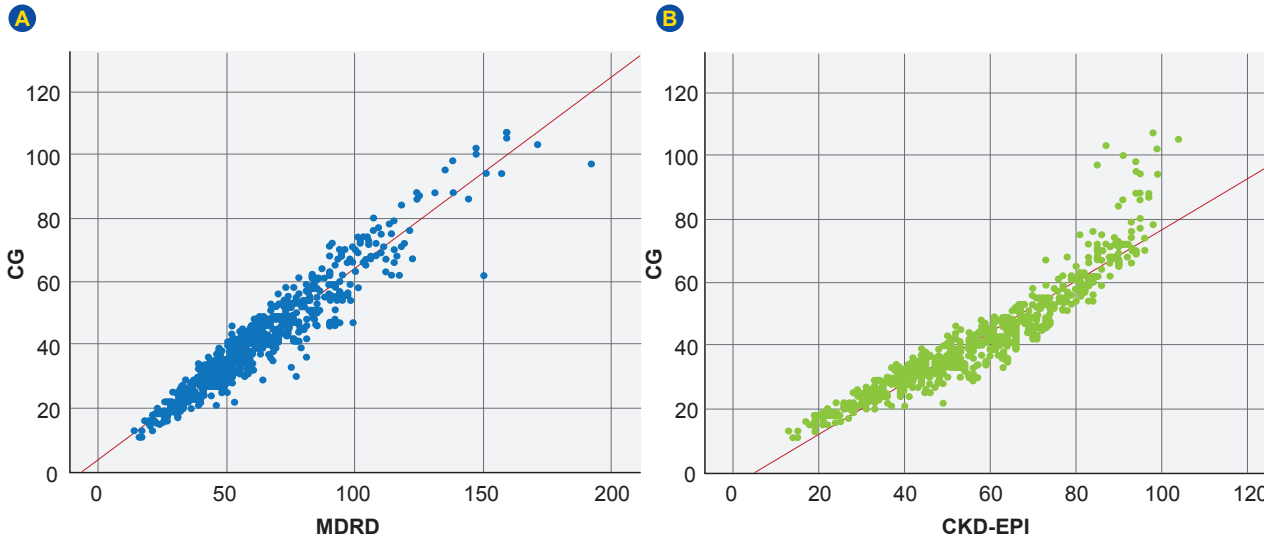

Figure 2 – (A) Correlation between baseline estimated CG and estimated GFR by MDRD equation (mL/min); (B) Correlation between baseline estimated CG and estimated GFR by CKD-EPI equation (mL/min).
CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

Antibiotic prescribing errors

Dosing errors in the loading dose were observed in 264 patients (44.8%): 226 (38.4%) in excess and 38 (6.5%) in under dosing.

Considering the CG equation, there were errors in DDD in 52.0% of the patients in the minimum creatinine day and 47.7% of the patients in the maximum creatinine day. Errors in the DDD according to the different renal function calculation equations are presented in Table 2. Error rates varied from 46.7% to 52.0%, in the day of minimum creatinine, and 40.1% to 53.7%, in the day of maximum creatinine.

Table 3 compares dosing errors obtained according to the MDRD and CKD-EPI equations compared to the CG equation. Using MDRD to calculate GFR, there were 85 patients (14.4%) in whom dosing errors were classified differently from the CG equation for creatinine clearance for minimum creatinine and 98 (16.6%) for maximum creatinine. Using the CKD-EPI equation, there were 83 patients (14.1%) classified differently when compared to the classification based on the CG equation for the minimum serum creatinine and 92 (15.6%) for the maximum serum creatinine.

The study of risk factors associated with error in DDD is presented in Table 4. The final multivariate logistic model retained, with an adjusted OR ($CI_{95\%}$), without available data on weight = 1.571 (1.123 - 2.197), for the minimum creatinine day, and ideal body weight = 0.982 (0.966 - 0.998) per kg for the maximum creatinine day. The Hosmer and Lemeshow test did not show evidence of lack of fit.

Prescribed antibiotics were modified in 154 cases (26.1%) and only in five patients it was due to side effects. Of these five patients, and according to the CG equation, four presented excess dosing either in the minimum creatinine day, maximum creatinine day or in the loading dose, and only one did not present any dosing errors at all.

DISCUSSION

In this population of very old patients there was an excellent correlation of CG with MDRD and CKD-EPI for different levels of renal impairment. Regardless of the equation used to estimate renal function there was a high rate of antibiotic dosing errors documented in this population.

In the elderly, MDRD and CKD-EPI have been shown to more accurately estimate GFR when compared with CG.[6]

Table 2 – Dosing errors in the daily defined dose of antibiotic therapy according to the different renal function calculation equations in the day of minimum and maximum serum creatinine

Errors in daily defined dose, n (%)	CG	MDRD	CKD-EPI
Minimum Cr			
Under	157 (26.7)	186 (31.6)	193 (32.8)
Excess	149 (25.3)	89 (15.1)	90 (15.3)
Total	306 (52.0)	275 (46.7)	283 (48.0)
Maximum Cr			
Under	89 (15.1)	117 (19.9)	192 (32.6)
Excess	192 (32.6)	119 (20.2)	124 (21.1)
Total	281 (47.7)	236 (40.1)	316 (53.7)

Note: 'Under' refers to dosing errors in which lower daily doses than recommended were given; 'excess' refers to dosing errors in which the maximum daily dose was exceeded.
Cr: creatinine; CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation

Table 3 – Comparison of dosing errors using MDRD and CKD-EPI formulas compared with the CG equation

Equations	Dosing errors		CG					
			Minimum Cr			Maximum Cr		
			Under	Correct	Excess	Under	Correct	Excess
MDRD	**Under**	Count	157	25	4	89	25	3
		% within total	26.7	4.2	0.7	15.1	4.2	0.5
	Correct	Count	0	258	56	0	283	70
		% within total	0	43.8	9.5	0	48.0	11.9
	Excess	Count	0	0	89	0	0	119
		% within total	0	0	15.1	0	0	20.2
CKD-EPI	**Under**	Count	157	24	12	89	22	4
		% within total	26.7	4.1	2.0	15.1	3.7	0.7
	Correct	Count	0	259	47	0	286	66
		% within total	0	44.0	8.0	0	49.1	11.2
	Excess	Count	0	0	90	0	0	122
		% within total	0	0	15.3	0	0	20.7

Note: 'Under' refers to dosing errors in which lower DDD than recommended were given; 'correct' refers to the lack of dosing errors; and 'excess' refers to dosing errors in which the maximum doses were exceeded. The blue-colored cells refer to dosing errors classified in the same way by both equations; and the yellow-colored cells refer to dosing errors classified differently by both equations.
CG: Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease Study equation; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation.

However, pharmacokinetic studies over the last few years have used the CG equation to determine the level of renal function for dosage adjustment in drug labels. As a result, it has become a common practice for drug dosing. Furthermore, most of the published information on dosage adjustments in renal impairment is based on creatinine clearance estimated from the CG equation.

Based on the CG equation, there were errors in DDD in approximately half of the study population; this value is within the range described by Long *et al*, a review that included 4 studies conducted in inpatient settings that describes renal dosing guideline noncompliance rates between 19% and 67%.[16] Although these studies considered drugs other than antibiotics, most of the medications prescribed at unadjusted doses were antibiotics. A recent retrospective observational study performed in two geriatric hospitals found that 20% of inpatients were prescribed a drug with incorrect adjustment for renal function based on the CG equation.[17]

Dosing errors reported in this study were due to both under and excess dosing. In the loading dose, excess dosing was more frequent; in the DDD, under dosing was slightly more frequent in the minimum creatinine day, whereas over-dosing was more frequent in the maximum creatinine day. Any form of dosing error can be harmful. Over-dosing a drug may lead to administration of inappropriately large doses and possible toxicity. Among the five patients in whom the initial antibiotic was changed due to side effects, there was over-dosing of the prescribed antibiotic in four. Conversely, under dosing may result in compromised therapeutic efficacy, resistance development and poor prognosis.

Table 4 – Factors associated with error in daily defined dose

	DDD error in the minimum creatinine day (n = 306)			**DDD error in the maximum creatinine day** (n = 281)		
Risk factor		Crude OR	*p* value		Crude OR	*p* value
Age (years), mean ± SD	87 ± 4	1.020 per year	0.300	87 ± 5	1.017 per year	0.359
Male gender, n (%)	123 (40)	0.874	0.422	107 (38)	0.748	0.083
KPS scale ≥ 70, n (%)	111 (36)	0.965	0.835	93 (33)	0.744	0.086
CCI, mean ± SD	7 ± 2	1.044 per point	0.311	7 ± 2	0.992 per point	0.843
Real body weight (kg), mean ± SD	65 ± 15	1.003 per kg	0.643	65 ± 15	1.001 per kg	0.849
Ideal body weight (kg), mean ± SD	56 ± 10	0.995 per kg	0.546	55 ± 10	0.982 per kg	**0.032**
Adjusted body weight (kg), mean ± SD	60 ± 10	0.999 per kg	0.917	59 ± 10	0.989 per kg	0.217
Height (cm), mean ± SD	161 ± 9	0.995 per cm	0.612	161 ± 9	0.981 per cm	**0.035**
BMI (kg/m^2), mean ± SD	25 ± 6	1.014 per kg/m^2	0.393	25 ± 5	1.021 per kg/m^2	0.193
Baseline serum creatinine (mg/dL), mean ± SD	1.1 ± 0.4	1.401 per mg/dL	0.077	1.1 ± 0.4	1.012 per mg/dL	0.948
Electronic weight registry absent, n (%)	173 (57)	0.637	**0.008**	176 (63)	1.085	0.632

DDD: daily defined dose; OR: odds ratio; SD: standard deviation; KPS: Karnofsky Performance Status; CCI: Charlson Comorbidity Index; BMI: body mass index

When comparing CG with MDRD and CKD-EPI for the calculation of antibiotic dosing, there was a discrepancy in 14% to 16% of patients. In all these patients, if the antibiotic dosing was based on MDRD or CKD-EPI, a higher dose of antibiotic would have been recommended, because the MDRD and CKD-EPI equations overestimate creatinine clearance.[17-22] However, according to the study by Delanaye *et al*, the assertion that CG must be favored because it gives systematically lower results, and thus prevents over-dosing is an oversimplification. The authors found that CKD-EPI did not always overestimate creatinine clearance since this was not true in obese geriatric patients.[23] Also, new creatinine-based GFR estimating equations have been reported. A recent study, in a group of patients 65 years and older, compared four equations – including the CKD-EPI equation – with the reference inulin-measuring method. The authors found that none of the equations had a better diagnostic performance and that each equation had limitations regarding accuracy.[24] Thus, for patients with extreme characteristics, like those with morbid obesity, one may opt for a specific equation for an optimum result, while for common patients, the CG equation is more practical because it is already established in clinical practice with good results and there is no compelling evidence supporting change (either clinical benefits or pharmacokinetic evidence). In light of these findings, the use of the MDRD or CKD-EPI equations interchangeably with the CG equation in drug dosing cannot be advocated.[17-22]

This study also focused on risk factors for antibiotic prescribing errors for which no systematic risk factors were found.

This study has some limitations. In order to audit antibiotic prescribing and its adequacy to renal function, dosages that did not follow the recommended guidelines were determined. However, it would have been important to assess the consequences of dosing errors in clinical practice. Concerning excess dosing, antibiotic modifications motivated by side effects were determined. However, the presence of side effects should have been assessed in every patient and not only in situations of antibiotic switch. Therefore, it is possible that adverse drug events related to prescribing errors were missed. Moreover, side effects should have been further characterized. In the case of under dosing, indices of therapeutic failure should have been searched.

Another important limitation was that neither the glomerular filtration rate nor the antibiotic serum concentration were measured, which would have been the gold standard, but being a retrospective study, this was not possible to obtain and, at the moment, only the serum levels of aminoglycosides and vancomycin can be assessed in our hospital.

As GFR was not directly measured, it was not possible to assess which equation was more accurate in estimating renal function in this group of very elderly patients. Thus, the present analysis was based solely on the comparison of estimated values.

Patients with acute illness frequently present altered pharmacokinetics either in absorption, distribution, metabolism and/or elimination, meaning that antibiotic dosing is challenging in this population and should be individualized. Since assessment of serum antibiotic levels for most antibiotics are not available, clinicians have to resort to other methods. The recommendation in acute kidney injury (AKI) is to use the trend in serum creatinine over several measurements – that is difficult to operate in a common ward and more feasible in high dependency or intensive care units, where the standard is the measure of creatinine clearance using its serum and urinary concentration, which is not possible for all hospitalized patients under antibiotic therapy and AKI. Therefore, dosage adjustments should be cautious and adjusted to the clinical scenario.

This study has a number of strengths. It included only very elderly patients, a particularly vulnerable segment of the population, in which adverse drug events are extremely common. Official dosing guidelines for renal impairment often disregard elderly patients as, in general, their inclusion in clinical studies is limited. Furthermore, this study only included antibiotics, a class of drugs widely used in clinical practice, associated with a high rate of adverse drug events. Finally, in order to ensure data was consistent, a large group of patients was studied.

CONCLUSION

In this population of very old patients there was an excellent correlation of CG with MDRD and CKD-EPI for different levels of renal impairment. The GFR calculated by MDRD and CKD-EPI equations overestimates creatinine clearance calculated by CG equation, and they estimate different things. Therefore, the use of the MDRD or CKD-EPI equations interchangeably with the CG equation in drug dosing cannot be advocated. Using the CG equation for drug dosing may be a safer and easier practice, especially in the very elderly. Also, given the high rate of antibiotic dosing errors documented, further studies should be conducted to investigate underlying causes of prescribing errors.

PROTECTION OF HUMAN AND ANIMAL SUBJECTS

The authors declare that the research procedures were performed according to the regulations of the institution's ethics committee and the Code of Ethics of the World Medical Association (Declaration of Helsinki).

PROTECTION OF HUMAN AND ANIMAL SUBJECTS CONFIDENTIALITY OF DATA

The authors declare that they have followed the protocols of their work center regarding the publication of data from patients.

CONFLICT OF INTEREST

No conflict of interest has been declared by any author.

FUNDING

No financial support was received by any author.

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Distribuição de Género em Cargos de Liderança na Área Médica em Portugal: O Exemplo das Candidaturas aos Órgãos da Ordem dos Médicos 2017-2019

Gender Distribution in Medical Leadership Roles in Portugal: The Example of Candidacy to Bodies of the Portuguese Medical Association 2017-2019

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Acta Med Port 2021 May;34(5):342-346 ▪ https://doi.org/10.20344/amp.12955

RESUMO

Introdução: A igualdade de género constitui um dos objetivos de desenvolvimento sustentável. Uma manifestação de desigualdade de género é a baixa participação de mulheres em cargos de liderança. Em Portugal, são escassos os estudos sobre a desigualdade de género na liderança na área médica. Assim, o presente trabalho pretendeu analisar a distribuição de género em candidaturas aos órgãos regionais da Ordem dos Médicos.

Material e Métodos: Foram extraídos da Revista da Ordem dos Médicos (número 175) os dados dos candidatos aos órgãos regionais da Ordem dos Médicos (mandato de 2017 - 2019). Obtiveram-se as percentagens de mulheres candidatas, globalmente, por lista, regiões e cargos. Calcularam-se razões observado-*versus*-esperado por secção regional e intervalos de confiança a 95% assumindo uma distribuição de Poisson. Foi realizada análise de sensibilidade, excluindo os candidatos a suplentes.

Resultados: Trinta e sete por cento dos candidatos eram médicas (variação por região: 29% - 51%). A nível nacional a razão observado-*versus*-esperado foi de 0,74 (intervalo confiança a 95%: 0,58; 0,92), principalmente influenciada pela razão da região Sul de 0,58 (intervalo confiança a 95%: 0,41; 0,80). Existiu uma predominância de mulheres nas candidaturas para suplentes e secretário (56% e 54% respetivamente).

Discussão: A diferença entre géneros é particularmente acentuada na região Sul, na frequência e tipo de cargos a que se candidatam. As razões apontadas na literatura relacionam-se com a maternidade, o papel social da mulher e perceções sobre o desempenho dos cargos de lideraça. Este estudo é limitado à análise de um tipo de liderança e um momento eleitoral, sendo necessárias análises mais abrangentes.

Conclusão: Houve menor participação do que o expectável por parte das médicas no processo eleitoral da Ordem dos Médicos. Quando participam, as mulheres tendem a fazê-lo em cargos de menor relevância ou com menos potencial para eleição (secretário ou suplente). É necessário aprofundar o estudo e introduzir medidas de combate à desigualdade de género em cargos de liderança.

Palavras-chave: Identidade de Género; Liderança; Portugal; Sexismo; Sociedades Médicas

ABSTRACT

Introduction: Gender equality is one of the sustainable development goals. Low participation of women in leadership roles is an example of gender inequality. In Portugal, there are few studies regarding gender inequality in medical leadership roles. Therefore, we aimed to analyse gender distribution of candidates to regional bodies of the Portuguese Medical Association.

Material and Methods: We extracted data from the candidates to the regional bodies of the Portuguese Medical Association (2017 - 2019 mandate) from the Association's magazine (issue number 175). We calculated the percentage of women candidates, overall and stratified by list, region and roles. We obtained observed-vs-expected ratios overall and by region, and respective 95% confidence intervals, assuming a Poisson distribution. Finally, we conducted a sensitivity analysis, excluding substitute candidates.

Results: Women accounted for 37% of the candidates (regional variation: 29% - 51%). The national observed-vs-expected ratio was 0.74 (95% confidence interval: 0.58; 0.92), mainly driven by the ratio from the South Region: 0.58 (95% confidence interval: 0.41; 0.80). Women ran mainly for alternate candidates and secretary positions (56% and 54% respectively).

Discussion: Gender differences were identified, particularly in the South, regarding the frequency and type of candidacy. Previous works have identified maternity, the social role of women and perceptions regarding the leadership roles as possible reasons to explain such differences. Our analysis is limited to specific leadership roles and an election moment; further studies should be pursued.

Conclusion: We identified a lower than expected participation of women in the elections for the Portuguese Medical Association. When they run, women are found mainly in less relevant positions or with less potential to be elected (secretary or alternate candidate). A deeper understanding and measures to fight gender inequality in leadership roles are required.

Keywords: Gender Identity; Leadership; Portugal; Sexism; Societies, Medical

INTRODUÇÃO

A igualdade de género é um dos valores fundadores da Declaração Universal dos Direitos Humanos e da União Europeia, sendo, desde os anos 90, um dos pontos altos da agenda europeia.[1,2] A importância de atingir a igualdade

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Recebido: 14 de outubro de 2019 - **Aceite:** 20 de janeiro de 2020 - ***First published*:** 09 de dezembro de 2020 - ***Online issue published*:** 03 de maio de 2021

de género é também contemplada nos objetivos de desenvolvimento sustentável das Nações Unidas, mais concretamente no objetivo número cinco.[3]

Uma das manifestações da desigualdade de género é a fraca participação das mulheres em cargos de liderança. Esta questão tem sido discutida com particular foco em cargos de liderança na área política e no setor económico.[1] Em Portugal, estudos realizados em empresas indicam que a representação das mulheres nos órgãos de gestão se encontra abaixo dos países nórdicos.[4] Um estudo das empresas que integram o PSI-20 demonstrou que em 2016, das 19 empresas analisadas, seis não tinham mulheres no conselho de administração, e a participação feminina máxima era de 33,3%.[5] Uma análise mais recente indica a baixa feminização em cargos de nomeação política em todas as áreas governativas.[6]

Estudos realizados nos Estados Unidos da América revelam que apenas 18% dos diretores executivos dos hospitais, 15% dos responsáveis de departamento das faculdades médicas e 16% dos diretores de faculdades médicas são mulheres. Estes valores verificam-se apesar de o número de graduados do sexo feminino ter vindo a aumentar, e metade ou mais dos estudantes que terminam a faculdade serem atualmente mulheres.[7] Em Portugal, a proporção de mulheres na profissão médica tem aumentado nas últimas décadas, com 40,2% de médicos do sexo feminino em 1991, 50,2% em 2010 e 55,3% em 2018.[8] Como tal, seria expectável começar a ver um maior número de cargos de liderança a serem ocupados por médicas. No entanto, tal como em outros países, esta tendência de maior percentagem de mulheres na medicina não se tem traduzido em maior percentagem de mulheres em cargos de liderança.[7,9,10] Também parece ser este o caso na escassa literatura que aborda esta área específica no nosso país. No final do século passado, apenas 20% dos docentes era do género feminino na Faculdade de Medicina da Universidade do Porto. Num dos grandes hospitais de Lisboa, 52% dos médicos eram mulheres, mas dos diretores de serviços apenas 17% eram mulheres.[11] Contudo, não são conhecidos estudos de abrangência nacional relativos à desigualdade de género em cargos de liderança na área médica (incluindo hospitais e faculdades médicas). A Ordem dos Médicos (OM) congrega atualmente todos os médicos a trabalhar em Portugal,[12] e, ainda que seja uma entidade nacional, está dividida estruturalmente em três secções regionais: Norte, Centro e Sul, encontrando-se as Regiões Autónomas incluidas nesta última.[12] Enquanto instituição democrática, a OM é liderada por estruturas constituídas por indivíduos eleitos após um processo eleitoral aberto a todos os médicos. Contudo, a função de liderança de maior destaque, a figura de bastonário, nunca foi ocupada por uma médica.[12] Dada a inexistência de estudos de âmbito nacional relativos à distribuição de género em cargos de liderança na área médica, o objetivo deste trabalho é descrever a distribuição por género das candidaturas às diferentes listas para os órgãos regionais das três secções da OM (Norte, Centro e Sul) para o triénio 2017-2019. Pretende-se, igualmente, identificar diferenças entre géneros nas candidaturas relativamente a posições dentro das candidaturas.

MATERIAL E MÉTODOS

Procedeu-se à extração dos dados para análise da Revista da Ordem dos Médicos nº. 175, de dezembro de 2016.[13] Foram recolhidos o nome de todos os candidatos, órgão e cargo a que se candidatavam, assim como a lista e secção regional pelo qual o faziam. O género dos candidatos foi identificado com base no nome. Nos casos em que existia dúvida relativamente ao género do candidato, foi usado o motor de busca Google para obter uma identificação de género através da pesquisa de fotografia do candidato e reconhecimento de traços fenotípicos caraterísticos de género. Com base na identificação de género, procedeu-se ao cálculo da percentagem de mulheres candidatas a nível nacional, por secção, por lista, e por cargo a que os indivíduos se candidatavam. Visto que os cargos apresentavam diferenças entre as várias listas, para a análise por cargo apenas se analisaram os cargos comuns a todas as listas.

De forma a estimar o que seria esperado de acordo com o número de médicas, foram calculadas razões observado-*versus*-esperado (O/E) por secção regional e intervalos de confiança a 95% assumindo uma distribuição de Poisson. Os valores observados foram os utilizados para calcular a proporção de candidatas. Os valores esperados foram obtidos aplicando a proporção de médicos do sexo feminino[8] ao número total de candidatos em cada secção regional. Dado que a proporção de médicos do sexo feminino tem vindo a aumentar, e é expectável que os candidatos tenham já alguma experiência, foram utilizadas duas proporções – a do ano de 2009 e de 2016. O número esperado com base de 2009 dá-nos o número de médicos do sexo feminino caso o conjunto de candidatos seguisse a distribuição de género existente em 2009. De igual modo, o número esperado com base em 2016 dá-nos o que seria expectável caso o conjunto de candidatos seguisse a distribuição de género existente em 2016. Uma razão inferior a 1 significa que existem menos candidatos do sexo feminino do que seria esperado de acordo com a distribuição de médicos por género, um valor de 1 corresponde ao valor esperado, e acima de 1 superior ao valor esperado.

Dado que os candidatos a suplentes têm uma menor possibilidade de ter desempenho efetivo do cargo, foram realizadas análises de sensibilidade excluindo os candidatos a suplentes. As análises foram conduzidas com recurso ao Microsoft Excel (versão 2016, Microsoft, Redmond, Washington, EUA) e R.[14]

Dado que foram utilizados apenas dados existentes no domínio público o trabalho não foi submetido para aprovação de Comissão de Ética.

RESULTADOS

Foi extraída informação relativa a 214 candidatos de todas as listas das três secções regionais. Destes, 78 eram

do sexo feminino (aproximadamente 37%). Relativamente às secções Norte, Centro e Sul, as percentagens de candidatos do sexo feminino foram 51%, 46% e 29%, respetivamente. A distribuição por listas, divididas por secção regional, encontra-se apresentada na Tabela 1, evidenciando que das seis listas apresentadas apenas uma tinha metade ou mais de mulheres.

Os resultados da análise das razões observados-*versus*-esperados são apresentados na Tabela 2. Verifica-se que o número de candidatas a nível nacional é inferior ao esperado, tendo em consideração a distribuição de médicas. No Norte, a distribuição é concordante com o esperado enquanto que em Lisboa o número de candidatas é quase metade do esperado. Os resultados são semelhantes considerando a distribuição de médicas em 2009 e 2016. Quando são retirados os candidatos a suplentes, as razões diminuem em todos os grupos.

Na Tabela 3 é apresentada a percentagem de candidatas por posição. Nos cargos identificados como presidente (Mesa da Assembleia Regional, Conselho Regional e Conselho Fiscal Regional) existia um candidato do sexo feminino, num total de 18 candidatos. De forma semelhante, para a posição de vice-presidente de lista, 33% dos candidatos eram mulheres. No que diz respeito ao cargo de tesoureiro, apenas uma candidatura (17%) apresentava mulheres. Num total de seis mandatários e seis delegados de lista, apenas existiu um nome de mulher em cada uma destas funções. No caso da Secção Regional Sul, nenhuma mulher surge como mandatária, delegada ou candidata a presidente de órgão. Por outro lado, no que diz respeito às posições de secretário e de suplente para os diferentes órgãos, 56% e 54% dos candidatos eram mulheres.

DISCUSSÃO

Este estudo constitui a primeira caracterização conhecida da desigualdade de género em situação de candidaturas a cargos de liderança na área médica em Portugal. Os resultados apresentados demonstram uma menor participação de médicas no processo eleitoral do que o esperado, considerando o número de médicas. Esta diferença torna-se ainda mais relevante quando retiramos candidaturas a cargos suplentes.

A diferença entre géneros é particularmente acentuada na região Sul, sendo o número de candidatas cerca de metade do número esperado. Contudo, é de realçar que na Secção Regional Norte, o aparente melhor resultado se deve a uma lista ter uma elevada percentagem de candidatas. Esta lista incluía o aumento do número de mulheres em posições efetivas na sua missão de campanha eleitoral.[13] A aparente diferença geográfica deve também ser interpretada com precaução, dado os números analisados serem pequenos e por isso terem grande variabilidade. Estudos futuros poderão analisar outros exemplos de cargos de liderança e aprofundar a análise em termos de distribuição geográfica.

Em relação às diferenças de percentagens de mulheres candidatas por cargos a que se candidatam, verificou-se uma predominância de candidatos homens a assumir posi-

Tabela 1 – Candidatos do género feminino envolvidas no processo eleitoral por secção regional e lista (total e excluindo as candidaturas a cargos suplentes)

Secção regional	Lista	Candidatos do género feminino % (n, T)	Candidatos do género feminino, excluindo candidaturas a suplentes % (n, T)
Norte	1	29 (7/24)	25 (5/20)
	2	76 (16/21)	71 (12/17)
	Total	51 (23/45)	46 (17/37)
Centro	3	46 (16/35)	41 (11/27)
Sul	4	33 (15/45)	30 (11/37)
	5	36 (16/45)	37 (14/38)
	6	18 (8/44)	11 (4/36)
	Total	25 (39/134)	26 (29/111)
Total	-	37 (78/214)	33 (57/175)

T: total de candidatos para cada grupo

Tabela 2 – Razões observado-*versus*-esperado com e sem suplentes, nos anos de 2009 e 2016 a nível nacional e pelas três secções regionais (Norte, Centro e Sul)

	O/E 2009		O/E 2016	
Região	Com suplentes	Sem suplentes	Com suplentes	Sem suplentes
Nacional	0,74 (0,58; 0,92)	0,66 (0,50; 0,85)	0,67 (0,53; 0,84)	0,60 (0,45; 0,78)
Norte	1,05 (0,66; 1,57)	0,94 (0,55; 1,51)	0,92 (0,58; 1,38)	0,85 (0,50; 1,36)
Centro	0,94 (0,54; 1,53)	0,85 (0,42; 1,51)	0,89 (0,51; 1,44)	0,79 (0,39; 1,41)
Sul	0,58 (0,41; 0,80)	0,52 (0,35; 0,74)	0,54 (0,39; 0,74)	0,48 (0,32; 0,69)

Tabela 3 – Candidatos do género feminino envolvidos no processo eleitoral por posição e por região

Posição*	Secção Regional	Candidatos do género feminino % (n,T)
Mandatário	Norte	0 (0/2)
	Centro	100 (1/1)
	Sul	0 (0/3)
	Total	17 (1/6)
Delegado	Norte	50 (1/2)
	Centro	0 (0/1)
	Sul	0 (0/3)
	Total	17 (1/6)
Presidente	Norte	20 (1/5)
	Centro	0 (0/3)
	Sul	0 (0/7)
	Total	7 (1/15)
Vice-presidente	Norte	50 (2/4)
	Centro	50 (1/2)
	Sul	17 (1/6)
	Total	33 (4/12)
Tesoureiro	Norte	0 (0/2)
	Centro	0 (0/1)
	Sul	33 (1/3)
	Total	17 (1/6)
Secretário	Norte	83 (5/6)
	Centro	33 (1/3)
	Sul	44 (4/9)
	Total	56 (10/18)
Vogais	Norte	50 (8/16)
	Centro	71 (5/7)
	Sul	30 (7/23)
	Total	42 (20/46)
Suplentes	Norte	75 (6/8)
	Centro	63 (5/8)
	Sul	44 (10/23)
	Total	54 (21/39)

*: Apenas se apresentam as posições com candidatos em todas as listas pelo que o somatório difere do total de candidatos.
T: total de candidatos para cada grupo

ções de liderança, enquanto existe um maior predomínio de mulheres a concorrer a cargos de menor exposição (como secretário) ou menor possibilidade de desempenho efetivo (suplente da lista). Existe evidência de maior predisposição para criticar detentores de cargos em posições a que o seu género não é tipicamente associado.[15] Se considerarmos que cargos de liderança não estão tradicionalmente associados ao género feminino, tal pode indicar que, para além de maiores dificuldades em atingir este tipo de posições, as mulheres poderão sentir-se como foco de crítica, optando por escolher posições de menor exposição ou envolvimento menos ativo.

Para além do acima referido, entre as razões apontadas na literatura como possíveis explicações para uma menor participação das mulheres em posições de liderança encontram-se aspetos relacionados com o papel social da mulher: (i) a maternidade, sobretudo nos seus anos iniciais; (ii) a imagem social de priorização da família para as mulheres[10,16,17]; (iii) as mulheres continuarem a dedicar mais tempo às tarefas domésticas do que os seus companheiros.[7] Para além do papel na maternidade e nas tarefas domésticas, está descrito que as mulheres poderão ter um menor interesse em assumir posições de liderança por perceções associadas a estes cargos (e.g. possível afastamento da medicina[9] e sobrevalorização de desafios associados a estes).[18] Para atingir maior igualdade de género em posições de liderança, algumas organizações médicas estão a divulgar exemplos de liderança por mulheres e a alterar políticas institucionais relativas à maternidade, para facilitar a conciliação da mesma com o exercício profissional.[9,10] Outra possível intervenção será a implementação de esquemas de mentoria.[10,16] Embora estes aspetos requeiram medidas concertadas a vários níveis de atuação e fora do âmbito do presente trabalho, consideramos que os resultados agora apresentados contribuem para a discussão do papel das mulheres na liderança na área médica e das medidas a implementar para dar resposta à desigualdade existente.

Este estudo apresenta várias limitações que devem ser consideradas. Verifica-se a não completa sobreposição das secções da OM com as regiões obtidas a nível de NUTS II. Contudo, dada a extensão limitada da zona de não-sobreposição e a magnitude dos resultados encontrados é pouco expectável que esta limitação tenha enviesado os resultados de forma relevante. Por outro lado, este estudo apenas considerou uma eleição para alguns dos corpos da OM, refletindo por isso uma imagem limitada da situação a nível nacional, num período eleitoral específico. Este exemplo foi selecionado devido à disponibilidade pública de dados para o realizar e constitui, graças à inexistência de estudos prévios, um primeiro contributo na caracterização da situação de desigualdade de género nos cargos de liderança na área médica, a nível nacional. Uma caracterização mais detalhada da situação e a compreensão dos motivos que a causam serão aspetos a considerar em estudos futuros. Para além disso, dada a recente obrigatoriedade de apresentação de listas candidatas mais paritárias,[19] será também relevante observar de que forma esta condicionante se reflete na constituição das listas a ser apresentadas.

CONCLUSÃO

Há uma menor participação do que o que seria expectável por parte das médicas nos processos eleitorais da OM, com significância estatística a nível nacional e na Secção Regional do Sul. Quando participam, as mulheres tendem a estar mais presentes em cargos de menor relevância, ou com menor potencial para eleição (e.g. secretário ou suplente). Estes resultados indicam a necessidade de uma maior compreensão desta problemática e medidas para o combate à desigualdade de género em cargos de liderança.

PROTECÇÃO 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 revista em 2013.

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

Este projeto não recebeu qualquer apoio financeiro.

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International Consensus on Antinuclear Antibody em Portugal

International Consensus on Antinuclear Antibody Patterns in Portugal

ARTIGO ORIGINAL

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Acta Med Port 2021 May;34(5):347-354 ▪ https://doi.org/10.20344/amp.13121

RESUMO

Introdução: A pesquisa de autoanticorpos em células HEp-2 através de imunofluorescência indireta é o teste padrão atualmente aceite como a ferramenta central para o diagnóstico das doenças autoimunes sistémicas. O *International Consensus on Antinuclear Antibody* (ANA) *Patterns* tem como objetivo principal alcançar um consenso na nomenclatura e na descrição dos diferentes padrões morfológicos de anticorpos antinucleares. Este trabalho tem como objetivo ampliar o projeto do *International Consensus on* ANA *Patterns* de forma a estabelecer um consenso em Portugal para a sua nomenclatura, procurando contribuir para a harmonização no diagnóstico autoimune e promover a qualidade diagnóstica nas doenças reumáticas sistémicas autoimunes.

Material e Métodos: Os laboratórios participantes identificaram cada designação de padrão citoplasmático e nuclear do *International Consensus on* ANA *Patterns* (incluindo o código padrão anti-célula), e fizeram corresponder a cada uma a respetiva nomenclatura portuguesa em uso. Os resultados foram agregados e serviram de base ao trabalho de harmonização da nomenclatura. Seguiram-se reuniões de consenso, num processo iterativo até à redação de uma proposta final consensualizada.

Resultados: A concordância prévia entre laboratórios era superior a 75% para 23 do total de 29 padrões anti-célula. O grau em que cada laboratório está alinhado com a referência internacional do *International Consensus on* ANA *Patterns* varia entre 22,1% e 100%. Foi possível elaborar uma versão consensualizada da nomenclatura do *International Consensus on* ANA *Patterns* para Portugal.

Discussão: Existia uma boa base de consenso para a nomenclatura do *International Consensus on* ANA *Patterns*, mas com diferenças importantes em algumas das traduções da terminologia. O estudo realça a necessidade de colaboração entre laboratórios para uma descrição inequívoca dos resultados laboratoriais.

Conclusão: Este trabalho mostra o potencial positivo da colaboração entre laboratórios para gerar consensos que contribuam para a melhoria do diagnóstico e acompanhamento dos doentes.

Palavras-chave: Anticorpos Antinucleares/análise; Portugal; Técnica Indireta de Fluorescência para Anticorpo/métodos

ABSTRACT

Introduction: Screening for autoantibodies in HEp-2 cells by indirect immunofluorescence is currently accepted as the gold-standard test for the diagnosis of systemic autoimmune diseases. The main objective of the International Consensus on ANA Patterns is to achieve a consensus on the nomenclature and description of antinuclear antibody morphological patterns. This work aims to build on the International Consensus on ANA Patterns project to establish a nomenclature consensus in Portugal, thus contributing to harmonization in autoimmune diagnosis and promoting diagnostic quality in autoimmune systemic rheumatic diseases.

Material and Methods: Participating laboratories identified all the nuclear and cytoplasmic pattern designations in the International Consensus on ANA Patterns (including the anti-cell pattern code), and matched them with the corresponding Portuguese nomenclature in use. The results were aggregated and used as a foundation for nomenclature harmonization work. Consensus meetings followed an iterative process, until a final consensual proposal was drafted.

Results: Prior agreement between laboratories was over 75% for 23 of the total 29 anti-cell patterns. The degree to which each laboratory is aligned with the International Consensus on ANA Patterns international reference ranges from 22.1% to 100%. It was possible to write a consensual version of the International Consensus on ANA Patterns nomenclature for Portugal.

Discussion: There was a good consensus basis for the nomenclature in the International Consensus on ANA Patterns, despite relevant differences with some translations. The study highlights the need for collaboration among laboratories towards an unambiguous description of laboratory results.

Conclusion: This study shows that there is good potential for collaboration between laboratories in order to produce the consensus needed to improve diagnosis and patient follow-up.

Keywords: Antibodies, Antinuclear/analysis; Fluorescent Antibody Technique, Indirect/methods; Portugal

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Recebido: 18 de novembro de 2019 - **Aceite:** 17 de fevereiro de 2020 - ***First published*:** 02 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

INTRODUÇÃO

A pesquisa de autoanticorpos em células HEp-2 através da técnica de imunofluorescência indireta (IFI), tem sido utilizada desde 1950, altura das primeiras descrições feitas por Coons e Kaplan.[1] Tornou-se o teste padrão quando migrou dos tecidos animais para as células epiteliais humanas HEp-2 e é atualmente aceite como a ferramenta central para o diagnóstico das doenças autoimunes sistémicas.[2]

Em 2013, um grupo de peritos internacionais (especialistas de laboratório, cientistas e clínicos), elaborou um conjunto de recomendações para a correta avaliação e interpretação de autoanticorpos celulares, historicamente conhecidos como anticorpos antinucleares (ANA), identificando a imunofluorescência indireta como o método de referência para o *screening* de ANA. Desde esse momento, a deteção de anticorpos orientada para elementos nucleares e não nucleares passou a ser designada como ANA,[2] ou HEp-2 IFI.[3]

Em 2006, Alan Wiik afirmou, no artigo *Guidelines for antinuclear antibody testing*, que a terminologia ANA tem sido usada para todos os anticorpos celulares que podem ser visualizados através da IFI no substrato HEp-2,[4] e que apesar da célula conter milhares de proteínas diferentes, poucas têm propriedades autoantigénicas. Subsequentemente, os ANA podem ser divididos em cinco grupos: i. os que reconhecem organelos do nucleoplasma, ii. nucléolo, iii. antigénios da membrana celular, iv. aparelho mitótico e v. citoplasma.[4] Os diferentes tipos de ANA geram padrões diferentes e individualmente característicos nas células HEp-2, dependendo da localização celular e das propriedades do antigénio alvo presente na amostra.

Em 2014, foi criada, em São Paulo, no Brasil, a iniciativa ICAP (*International Consensus on Antinuclear Antibody (ANA) Patterns*), decorrente do 12º Encontro sobre Autoimunidade e Autoanticorpos (IWAA). Esta iniciativa foi organizada por membros do Comité de Padronização dos Autoanticorpos (ASC), que integra o Comité de Avaliação da Qualidade e Padronização da União Internacional das Sociedades de Imunologia, este último associado à Organização Mundial de Saúde (OMS). O comité ICAP tem como objetivo principal alcançar um consenso na nomenclatura e na descrição dos diferentes padrões morfológicos ANA, com detalhes altamente variáveis quando observados por IFI em células HEp-2.[5] Outro objetivo importante é alcançar uma harmonização na forma como os resultados dos testes ANA são reportados,[6] obtida através da descrição dos padrões e sub-padrões, aos quais são atribuídos códigos

Tabela 1 – Antigénios-alvo e doenças associadas para os padrões nucleares

Padrão nuclear (ICAP)	Código	Antigenos associados	Doenças associadas
Homogéneo	**AC-1**	dsDNA, nucleossomas, histonas	SLE, lúpus induzido por drogas, artrite idiopática juvenil
Mosqueado	**AC-2, 4, 5**	hnRNP, U1RNP, Sm, SS-A/Ro (Ro60), SS-B/La, RNA polimerase III, Mi-2, Ku	MCTD, SLE, SJ, DM, sobreposição SSc/PM
Mosqueado fino denso	**AC-2**	DFS70/LEDGF	Raro em SLE, SjS, SSc
Mosqueado fino	AC-4	SS-A/Ro (Ro60), SS-B/La, Mi-2; TIF1Y, TIF1β, Ku, RNA helicase A, Proteína de replicação A	SjS, SLE, DM, Sobreposição SSc/PM
Mosqueado grosseiro	AC-5	hnRNP, U1RNP, Sm, RNA polimerase III	MCTD, SLE, SSc
Centrómero	**AC-3**	CENP-A/B (C)	SSc cutânea limitada, CBP
Pontos nucleares discretos	**AC-6, 7**		
Múltiplos pontos nucleares	AC-6	Sp100, PML proteínas, MJ/NXP-2	CBP, SARD, PM/DM
Raros pontos nucleares	AC-7	p80-coilina, SMN	SjS, SLE, SSc, PM, indivíduos assintomáticos
Nucleolar	**AC-8 ,9, 10**		
Nucleolar homogéneo	AC-8	PM/Scl-75, PM/Scl-100, Th/To, B23/ nucleofosfomina, nucleolina, No55/SC65	SSc, sobreposição SSc/PM
Nucleolar aglomerado	AC-9	U3-snoRNP/fribrilarina	SSc
Nucleolar ponteado	AC-10	RNA polimerase I, hUBF/NOR-90	SSc, SjS
Envelope nuclear	**AC-11, 12**		
Membrana nuclear linear	AC-11	Laminas A, B, C, ou proteínas associadas a laminas	SLE, SjS, artrites seronegativas
Membrana nuclear ponteada (complexo poro-nuclear)	AC-12	Proteínas do complexo poro nucleares (i.e., gp210)	CBP
Pleomórfico	**AC-13, 14**		
Pleomórfico (tipo PCNA)	AC-13	PCNA	SLE, outras condições
Pleomórfico (tipo CENP-F)	AC-14	CENP-F	Cancro, outras condições

SLE: lúpus eritematoso disseminado; MCTD: doenças mistas do tecido conjuntivo; SjS: síndrome de Jorgen; DM: dermatomiosite; Sobreposição SSc/PM: síndrome de sobreposição entre esclerodermia/poliomiosite; SSc: esclerodermia; SSc cutânea limitada: esclerodermia na forma cutânea limitada; CBP: colangite biliar primária; SARD: doenças autoimunes reumáticas sistémicas; PM: poliomiosite; PM/DM: poliomiosite/dermatomiosite

padrão anti-célula (AC) no intervalo de AC-1 a AC-29, classificados em três categorias de manchas: i. padrão nuclear, ii. padrão citoplasmático e iii. padrão mitótico. A iniciativa tem partilhado o seu trabalho na internet, com traduções em inglês, francês, italiano, espanhol, holandês, mandarim e português (de Portugal e do Brasil), disponíveis em www.anapatterns.org.

Consenso internacional atual

Padrões nucleares

Os padrões nucleares são definidos como qualquer coloração dos núcleos das células HEp-2 em *interfase* HEp-2. A nomenclatura para os padrões nucleares é baseada principalmente na reatividade observada no nucleoplasma (e.g. homogéneo ou mosqueado) e nos subcomponentes nucleares reconhecidos (e.g. centrómero ou nucleolar). Os padrões nucleares incluem padrões homogéneo, mosqueado, centrómero, pontos nucleares discretos, nucleolar, membrana nuclear e padrões pleomórficos. O *Dense Fine Speckled* 70 (DFS70) pertence ao grupo mosqueado. O padrão do centrómero pertence aos pontos nucleares discretos, mas recebe o seu próprio grupo devido ao seu padrão característico e ocorrência frequente num determinado contexto clínico. Os grupos nucleares de padrões estão ainda divididos em subgrupos, como fino ou grosseiro, múltiplos ou raros pontos nucleares, nucleolar homogéneo, aglomerado ou ponteado; membrana nuclear linear ou ponteada e padrões pleomórficos semelhantes a *Proliferating Cell Nuclear Antigen* (PCNA) ou *Centromere Protein F* (CENP-F). Esta classificação do padrão nuclear fornece informações sobre os prováveis antigénios-alvo e, assim, possíveis indicações da doença (Tabela 1). A título de exemplo, o padrão homogéneo surge em reações com componentes da cromatina, como DNA de cadeia dupla, histonas e/ou nucleossomas. Estes autoanticorpos estão associados ao LES, lúpus induzido por drogas e artrite idiopática juvenil. Outras reações nucleares podem ajudar os clínicos a delimitar a DMTC, SjS, ES, PM, DM, CBP ou outras doenças autoimunes. Os padrões mistos podem ocorrer quando mais de um autoanticorpo estiver presente na amostra dos doentes, como autoanticorpos para ambos os centrómeros (nucleares) e mitocôndrias (citoplasmáticas), que co-ocorrem frequentemente com CBP.

Padrões citoplasmáticos

Os padrões citoplasmáticos são definidos a partir de qualquer coloração do citoplasma HEp-2. A nomenclatura é primariamente baseada na reatividade observada no citoplasma (e.g. filamentoso ou granular) e na estrutura citoplasmática reconhecida (e.g. anéis e bastonetes). Os cinco principais padrões citoplasmáticos incluem os filamentosos, granular, reticular/do tipo mitocondrial (AMA), polar/do tipo Golgi e anéis e bastonetes. O padrão filamentoso é ainda subdividido em linear, fibrilar e segmentar, enquanto o padrão granular é subcategorizado em grânulos isolados, fino denso e fino. Os autoanticorpos citoplasmáticos de diferentes especificidades encontram-se numa variedade de doenças (Tabela 2), incluindo DMTC, PM, DM, LES, ES,

Tabela 2 – Antigénios-alvo e doenças associadas para os padrões citoplasmáticos

Padrão nuclear (ICAP)	Código	Antigenos associados	Doenças associadas
Fibrilar	**AC-15, 16, 17**		
Linear/ actina	AC-15	Actina, miosina não muscular MCTD	MCTD, hepatite crónica ativa, cirrose hepática, miastenia gravis, doença de Crohn, CBP, hemodiálise a longo prazo, raro em SARD, outro que não seja MCTD
Filamentoso/ microtúbulos	AC-16	Vimentina, citoqueratinas	Infeções ou condições inflamatórias, hemodiálise a longo prazo, doença hepática alcoólica, SARD, psoríase, controlos saudáveis
Segmentar	AC-17	Alfa-actina, vinculina, tropomiosina	Miastenia gravis, doença de Crohn, colite ulcerosa
Mosqueado	**AC-18, 19, 20**		
Grânulos isolados	AC-18	SGW182, Su/Ago2, Ge-1	CBP, SARD, condições neurológicas e autoimunes
Fino granular denso	AC-19	PL-7, PL-12, proteína ribossomal P	"Síndrome anti-sintetase", PM/DM, SLE, SLE juvenil, SLE neuropsiquiátrico
Fino granular	AC-20	jo-1/histidil-tRNA sintetase	Síndrome anti-sintetase, PM/DM, SSc limitado, derrame pleural idiopático
Reticular/AMA	**AC-21**	PDC-E2/M2, BCOADC-E2, OGDC-E2, Subunidade alfa E1 do PDC, E3BP/proteína X	Comum em CBP, SSc, raro em outras SARD
Polar (tipo Golgi)	**AC-22**	Giantina/macrogolgina, golgina-95/GM130, golgina-160, golgina-97, golgina-245	Raro em SjS, SLE, RA, MCTD, GPA, ataxia cerebelar idiopática, degeneração cerebelar paraneoplásica, infeções virais
Anéis e bastonetes	AC-23	IMPDH2, outras	Pacientes com HCV post-IFN/ terapia com ribavirina, raro em SLE, Hashimoto e indivíduos saudáveis

MCTD: doenças mistas do tecido conjuntivo; CBP: colangite biliar primária; SARD: doenças autoimunes reumáticas sistémicas; PM/DM: poliomiosite/dermatomiosite; SLE: lúpus eritematoso disseminado; SSc: esclerodermia; SSc: esclerodermia forma cutânea limitada; SjS: síndrome de Sjörgen; RA: artrite reumatóide; GPA: granulomatose com poliangiite; HCV post-IFN: hepatite C pós-interferon

Tabela 3 – Antigénios-Alvo e doenças associadas para os padrões mitóticos

Padrão nuclear (ICAP)	Código	Antigenos associados	Doenças associadas
Centrossoma	AC-24	Pericentrina, nineína, Cep250, Cep110, enolase	Raro em SSc, fenómeno de Raynaud, infeções (viral e micoplasma)
Fuso mitótico	AC-25	HsEg5	Raro em SjS, SLE, outras SARD
Fuso mitótico (NuMA-1)	AC-26	Centrofilina	SjS, SLE, outras
Ponte Intercelular	AC-27	Aurora cinase B, CENP-E, MAS-2, KIF-14, MKLP-1	Raro em SSc, fenómeno de Raynaud, malignidade
Envelope cromossómico	AC-28	Histona H3 modificada, MCA-1	Raro no lúpus eritematoso discóide, leucemia linfocítica crónica, SjS, e polimialgia reumática

SSc: esclerodermia; SjS: síndrome de Sjörgen; SLE: lúpus eritematoso disseminado; SARD: doenças autoimunes reumáticas sistémicas

CBP, doença de Crohn, colite ulcerosa e *miastenia gravis*. Os padrões citoplasmáticos devem ser descritos nos resultados dos doentes e não reportados como ANA negativos.

Padrões mitóticos

Os padrões mitóticos são definidos como padrões associados aos domínios celulares claramente relacionados com a mitose. Os padrões mitóticos incluem o centrossoma, o fuso mitótico com o subpadrão do aparelho mitótico nuclear (NuMA-1), a ponte intercelular e o envelope cromossómico. Alguns padrões mitóticos (e.g., centrossoma) não estão associados exclusivamente à mitose, mas exibem características muito distintas nas células mitóticas. Os anticorpos mitóticos são ocorrências raras em doenças como a ES, LES, SjS e fenómeno de Raynaud (Tabela 3).

Confirmação dos resultados do teste por IFI

Os resultados positivos no teste de ANA por IFI devem ser confirmados através de testes específicos adicionais, usando técnicas diferentes, como *immunoblot multiplex* ou *enzyme-linked immunosorbent assay* (ELISA) (Fig. 1).

Perspetivas

A iniciativa do ICAP lançou as bases para a criação de uma nomenclatura harmonizada e para a melhoria da descrição dos resultados dos testes ANA. Existem, naturalmente, questões pendentes para serem abordadas em edições futuras, que incluem a classificação de padrões compostos e mistos (e.g., topoisomerase I (Scl-70)), a inclusão de padrões raros, ou se os anticorpos citoplasmáticos e mitóticos devem ser classificados como positivos para ANA ou reportados separadamente. A otimização das estratégias de confirmação também terá de ser analisada. O consenso é um processo contínuo que se espera que amadureça para um padrão global que incorpore contribuições de laboratórios e de clínicos de todo o mundo. Outra contribuição importante para a harmonização dos ANA é o uso crescente de *software* de reconhecimento de padrões nos laboratórios. A automação da avaliação IFI aumenta a consistência entre diferentes laboratórios e aumenta a velocidade e a eficiência do procedimento de avaliação. Adicionalmente, o *software* também pode ser adaptado, à medida que as normas que orientam a interpretação evoluem.

Devido ao facto dos ANA surgirem numa grande variedade de doenças autoimunes sistémicas, incluindo lupus sistémico eritematoso (LSE), doença mista do tecido conjuntivo (DMTC), síndrome de Sjörgen (SjS), esclerose sistémica (ES), polimiosite (PM), dermatomiosite (DM) e colangite biliar primária (CBP), sendo um critério importante para diagnosticar e discriminar estas doenças, consideramos a padronização e a harmonização no diagnóstico autoimune

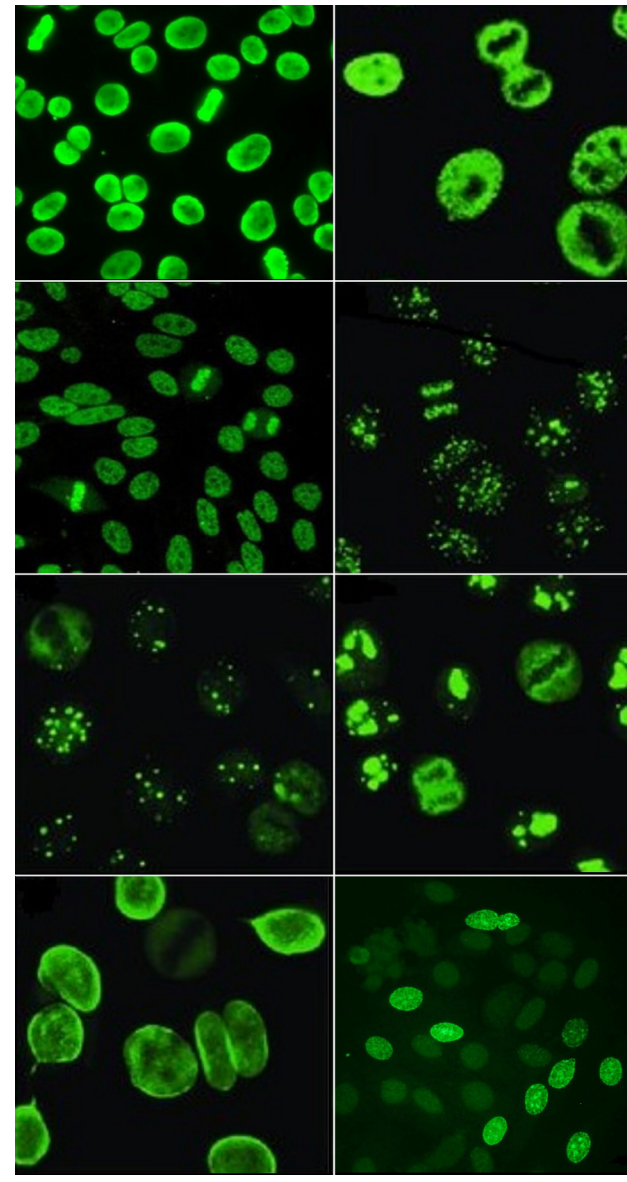

Figura 1 – Algoritmo para pesquisa reflexa de autoanticorpos guiada pelos padrões nucleares

um marco para a qualidade diagnóstica nas doenças reumáticas sistémicas autoimunes.

Além da participação neste grupo de trabalho e das traduções publicadas, um grupo de peritos Portugueses decidiu ampliar o projeto do ICAP de forma a estabelecer um consenso em Portugal para a sua nomenclatura com vista a eliminar as atuais discrepâncias na descrição de resultados, e a permitir uma melhoria tanto na qualidade do diagnóstico como na comunicação entre os profissionais envolvidos nos processos de diagnóstico e tratamento.

MATERIAL E MÉTODOS

Para este trabalho criámos um grupo de consenso que incluiu médicos e farmacêuticos a trabalhar na área da Medicina Laboratorial em nove locais diferentes de Portugal, com vasta experiência no teste por IFI e padrões ANA. Do total, seis são laboratórios públicos (hospitais ou hospitais universitários) e os três restantes são privados, selecionados devido à sua capacidade e vasta experiência com o teste IFI em células HEp-2.

Pedimos a todos os laboratórios participantes para identificarem cada designação de padrão citoplasmático e nuclear do ICAP (incluindo o código AC), com a nomenclatura Portuguesa correspondente em uso, para a qual não havia consenso ou referência prévia.

Antes da primeira reunião de consenso, agregámos e enviámos os resultados de todos os laboratórios para o grupo de trabalho, num relatório com a estatística descritiva. Foi também descrita a taxa de concordância para cada padrão, permitindo que todos os participantes avaliassem o seu nível de consenso e identificassem a terminologia mais comumente utilizada antes da segunda fase deste trabalho.

Seguiram-se várias reuniões de consenso tendo por base o primeiro relatório, num processo iterativo apoiado por documentos circulados por correio eletrónico, até à redação de uma proposta. Após o acordo respeitante à nomenclatura em português, foi concluída uma versão final para o consenso do ICAP em Portugal, com a concordância dos nove laboratórios para todas as designações citoplasmáticas e nucleares, listadas em baixo.

Os autores excluíram a necessidade de fazer um pedido de aprovação deste estudo em sede de comissão de ética, por este não envolver doentes ou a utilização de informação privada ou sensível.

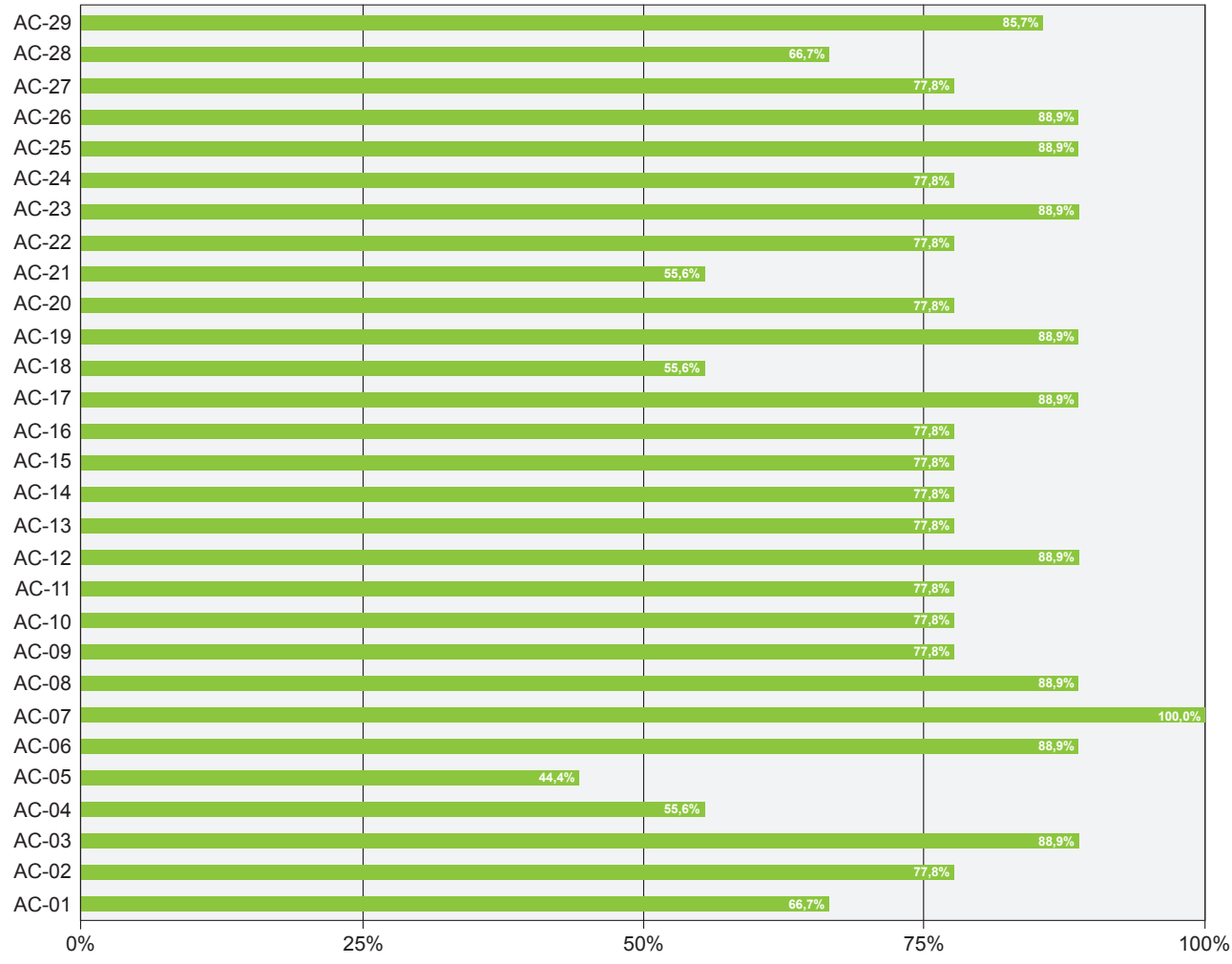

Figura 2 – Concordância da nomenclatura para cada padrão AC, entre os laboratórios. As barras indicam o nível de concordância entre laboratórios para a nomenclatura usada em cada padrão AC.

RESULTADOS

Globalmente, a concordância entre os laboratórios portugueses é alta, com uma concordância inferior a 75% (Fig. 2), à exceção de seis padrões AC. Não há padrões com concordância no intervalo do primeiro quartil e há um padrão no segundo quartil. Vinte e três padrões (79,3%), estão dentro do intervalo do último quartil. Para os AC referentes aos padrões mitóticos, o nível mais baixo de concordância é de 66,7%, enquanto o nível mais alto é de 88,9%. Apenas um padrão nuclear (AC-07) reuniu 100% de concordância entre laboratórios. Este resultado é obtido no mesmo grupo (padrões nucleares), onde podemos observar o único nível de concordância abaixo de 50% (AC-05), e onde a faixa de concordância também é maior entre os três grupos (44,4% - 100%). Os padrões citoplasmáticos variam entre 55,6% a 88,9%, mas a grande maioria dos níveis de concordância verifica-se acima de 75%.

Para além dos níveis de concordância em relação à nomenclatura, foi também avaliada a homologia entre os laboratórios antes do processo de consenso (Fig. 3). Verificou-se que apesar dos níveis altos de concordância global para os padrões de AC no país, o grau em que cada laboratório estava alinhado com a referência internacional do ICAP variava consideravelmente.Apenas dois laboratórios apresentaram um nível de concordância inferior a 75%. Todos os outros (n = 7) apresentaram uma concordância acima dos 75%.

No final do processo, anteriormente descrito na metodologia, foi elaborada uma lista com a nomenclatura acordada traduzida para português, como base de consenso para todos os laboratórios participantes (Tabela 4).

DISCUSSÃO

Os resultados mostram uma concordância acima dos 75% para 23 dos 29 padrões AC, confirmando que, anteriormente ao nosso estudo, já existia uma boa base de consenso para o ICAP no nosso país. Este consenso é de alguma forma similar a estudos de âmbito nacional no universo da avaliação da qualidade, no binómio que inclui o teste utilizado e a forma de descrever os resultados.[7] No entanto, encontrámos diferenças em traduções da terminologia usada entre os diversos laboratórios, com impacto na forma como os resultados são relatados, um fenómeno anteriormente identificado e amplamente discutido.[8-10]

Outra dimensão relevante dos nossos resultados está associada à evidência de diferenças na nomenclatura utilizada para o conjunto de todos os padrões AC, comparada com a referência internacional do ICAP, antes do processo de consenso. O grau de concordância variou entre os 24% e os 100%, o que poderá ter impacto na correta interpretação de resultados no contexto da partilha de dados entre instituições, justificando, anteriormente, processos similares de consenso de âmbito internacional.[5]

Uma das limitações deste estudo é a ausência de investigação sobre os fatores que podem ter influenciado os níveis de homologia entre os laboratórios, incluindo a localização geográfica, a cultura e a estrutura organizacional dos laboratórios, e o trabalho anterior com o ICAP. Estes fatores não foram abordados aqui devido ao âmbito específico deste trabalho e à complexidade metodológica envolvida nessa avaliação, e devem ser objeto de uma futura investigação. Outra limitação é o número de laboratórios envolvidos. Apesar dos exemplos de processos de consenso similares serem internacionais,[5] com universos que têm como unidade de estudo países e não laboratórios, consideramos como princípio positivo o aumento do número de laboratórios participantes nos processos de consenso. Aumentará, assim, a probabilidade de maior impacto a médio e a longo prazo.

Este estudo permitiu evidenciar a importância da adoção de terminologia de consenso na emissão de resultados dos ANA e destacar a importância de trabalhos multicêntricos, diminuindo os riscos associados à falta de harmonização, anteriormente identificada.[11]

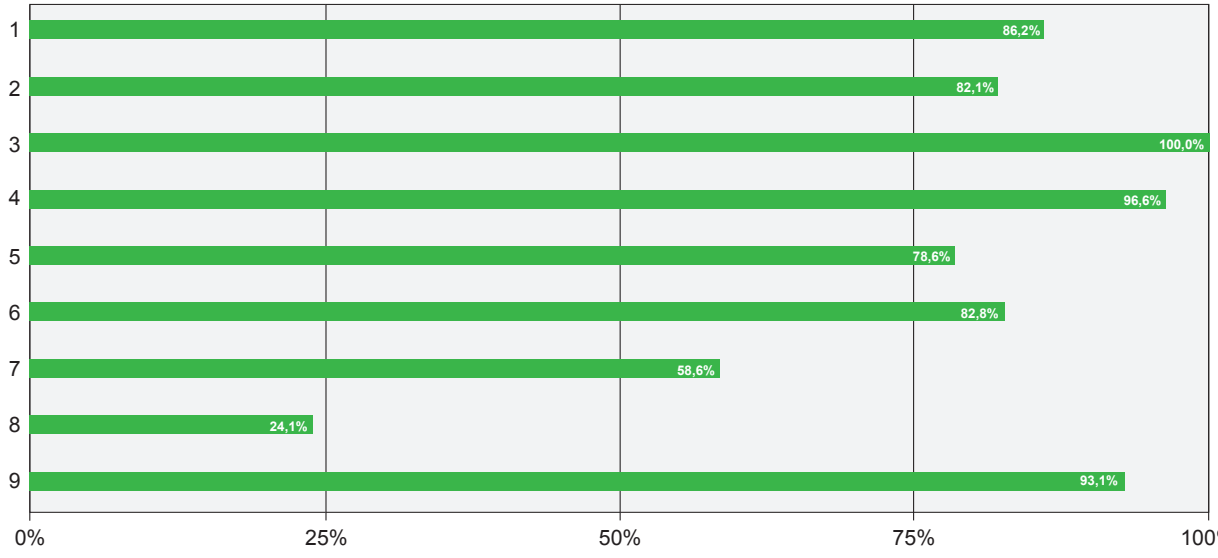

Figura 3 – Homologia da nomenclatura, por laboratório. As barras indicam o nível de concordância com a nomenclatura de todos os padrões AC, por laboratório, antes do processo de consenso.

Tabela 4 – Nomenclatura original em inglês e tradução final de consenso para os padrões AC

	Pattern	Padrão (consenso para Portugal)
AC-01	*Nuclear homogeneous*	**Nuclear homogéneo**
AC-02	*Nuclear dense fine speckled*	**Nuclear mosqueado fino denso**
AC-03	*Centromere*	**Centrómero**
AC-04	*Nuclear fine speckled*	**Nuclear mosqueado fino**
AC-05	*Nuclear large/coarse speckled*	**Nuclear mosqueado grosseiro**
AC-06	*Multiple nuclear dots*	**Múltiplos pontos nucleares**
AC-07	*Few nuclear dots*	**Raros pontos nucleares**
AC-08	*Homogeneous nucleolar*	**Nucleolar homogéneo**
AC-09	*Clumpy nucleolar*	**Nucleolar aglomerado**
AC-10	*Punctate nucleolar*	**Nucleolar ponteado**
AC-11	*Smooth nuclear envelope*	**Membrana nuclear linear**
AC-12	*Punctate nuclear envelope*	**Membrana nuclear ponteada (complexo poro-nuclear)**
AC-13	*PCNA-like*	**Pleomórfico (tipo PCNA)**
AC-14	*CENP-F-like*	**Pleomórfico (tipo CENP-F)**
AC-15	*Cytoplasmic fibrillar linear*	**Citoplasmático filamentoso linear**
AC-16	*Cytoplasmic fibrillar filamentous*	**Citoplasmático filamentoso fibrilar**
AC-17	*Cytoplasmic fibrillar segmental*	**Citoplasmático filamentoso segmentar**
AC-18	*Cytoplasmic discrete dots/GW body-like*	**Citoplasmático granular (grânulos isolados)**
AC-19	*Cytoplasmic dense fine speckled*	**Citoplasmático granular fino denso**
AC-20	*Cytoplasmic fine speckled*	**Citoplasmático granular fino**
AC-21	*Cytoplasmic reticular/AMA*	**Citoplasmático reticular (tipo mitocondrial)**
AC-22	*Polar/Golgi-like*	**Citoplasmático polar (tipo Golgi)**
AC-23	*Rods and rings*	**Citoplasmático anéis e bastonetes**
AC-24	*Centrosome*	**Centrossoma**
AC-25	*Spindle fibers*	**Fuso mitótico**
AC-26	*NuMA-like*	**Fuso mitótico (NuMA-1)**
AC-27	*Intercellular bridge*	**Ponte intercelular**
AC-28	*Mitotic chromosomal coat*	**Envelope cromossómico**
AC-29	-	**Nuclear granular (tipo topoisomerase I/ ScL-70)**

Um acordo mais abrangente e consensual para todas as terminologias significa uma melhoria substancial na forma como os laboratórios contribuem para o processo de diagnóstico, bem como na descrição inequívoca dos resultados.

CONCLUSÃO

Este trabalho demonstra o potencial positivo da colaboração entre laboratórios para gerar consensos que contribuem para a melhoria do acompanhamento dos doentes. O uso e a aceitação dos padrões do ICAP em Portugal só serão possíveis se a tradução para o português for aceite por um grande número de laboratórios e se existir o envolvimento alargado dos médicos, que são os principais utilizadores dos resultados laboratoriais. Deverá existir, como próximo passo, um plano de disseminação e discussão da informação agora 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.

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

Este projeto não recebeu qualquer apoio financeiro.

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The Impact of the COVID-19 Pandemic on Children's Health in Portugal: The Parental Perspective

O Impacto da Pandemia COVID-19 na Saúde Infantil em Portugal: O Relato dos Pais

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Acta Med Port 2021 May;34(5):355-361 ▪ https://doi.org/10.20344/amp.14805

ABSTRACT

Introduction: The COVID-19 pandemic poses unprecedented challenges for healthcare services and has led to changes in the usage pattern of the pediatric population. We aimed to describe the impact of COVID-19 on children's health, wellbeing, and access to medical care in Portugal.

Material and Methods: We conducted a cross-sectional study through an anonymous online survey via social media. The collected data refers to a period between the 16th of March and the 17th of May 2020.

Results: We obtained responses to the survey on 19 745 children. Of the previously scheduled outpatient consultations, 54.2% were postponed by healthcare institutions and 21.6% of planned vaccinations were missed. Parents expressed concerns regarding psychological, social, and physical consequences for their children due to the pandemic.

Discussion: The observed reduction of pediatric emergency department visits and the postponement of outpatient consultations and vaccine administrations are potentially harmful for non-COVID patients. The current pandemic and the imposed social distance might have an important negative impact on the mental health of children.

Conclusion: Further studies are necessary to fully comprehend the outcomes of the decreased access to medical care, as well as the collateral damage for children beyond the clinical aspects of the pandemic. Defining strategies regarding the urge to vaccinate children and not postpone urgent evaluations should be a public health priority.

Keywords: Child; Coronavirus Infections; COVID-19; Health Care Quality, Access, and Evaluation; Health Impact Assessment; Pandemics; Pediatrics

RESUMO

Introdução: A pandemia COVID-19 constitui um desafio sem precedentes para os serviços de saúde e conduziu a alterações no padrão de utilização dos recursos pela população pediátrica. Procurámos descrever o impacto da pandemia COVID-19 na saúde infantil e no acesso à saúde em Portugal.

Material e Métodos: Realizámos um estudo retrospetivo, recolhendo dados através da aplicação de um inquérito anónimo *online* nas redes sociais. Os dados referem-se ao período entre 16 de março e 17 de maio de 2020.

Resultados: Obtivemos respostas ao inquérito relativas a 19 745 crianças. Da análise às respostas, concluímos que 54,2% das consultas previamente agendadas foram adiadas pelas instituições de saúde e 21,6% das vacinações previstas não se realizaram. Os pais expressaram preocupação quanto às consequências psicológicas, sociais e físicas da pandemia nos seus filhos.

Discussão: A reduzida utilização dos serviços de urgência pediátricos, bem como a não realização de consultas e vacinações previamente agendadas é potencialmente lesiva para os doentes não-COVID. A pandemia e o isolamento social imposto poderão causar um impacto negativo na saúde mental das crianças.

Conclusão: Estudos adicionais são necessários para melhor compreender as consequências da diminuição do acesso à saúde, bem como os efeitos psicológicos, sociais e físicos nas crianças. A definição de estratégias para incentivar a vacinação e o não adiamento de avaliações médicas urgentes deveriam ser prioridades de Saúde Pública.

Palavras-chave: Avaliação do Impacto na Saúde; COVID-19; Criança; Infecções por Coronavírus; Pandemia; Pediatria; Qualidade, Acesso e Avaliação da Assistência à Saúde

INTRODUCTION

The novel coronavirus SARS-CoV-2, causative agent of COVID-19, emerged in December 2019 in the city of Wuhan, China, and has since spread worldwide. The World Health Organization declared COVID-19 to be a pandemic on the 11th of March 2020.[1] The first case of the disease in Portugal was diagnosed on the 2nd of March and until the end of May there were 1799 children and adolescents (0 - 19 years old) diagnosed with COVID-19.[2] Most published scientific articles focus on COVID-19 in adults, and, based on current knowledge, the virus seems to cause milder symptoms and have lower fatality rates in the pediatric population.[3–8]

The current pandemic poses new challenges for the healthcare workforce as well as for patients, potentially leading to changes in medical care usage patterns[9]. Concerns have been raised regarding the consequences for non-COVID patients due to decreased access to medical care both in adults[10,11] as in children,[12–14] as visits to emergency departments (ED) have dropped significantly.[9,12,15–19] Medical resources have been redistributed to meet the needs of this health emergency, with most non-urgent appointments being postponed. There is some evidence of potentially harmful consequences of these measures such as reductions in vaccination coverage compared to the same period in previous years.[20,21]

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Recebido: 07 de setembro de 2020 - **Aceite:** 05 de março de 2021 - ***First published*:** 26 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

Confinement in the household for a long period of time while being deprived from school, outdoor activities and contact with family-members and friends, has been challenging for children and their parents during the pandemic. The psychological, social and physical consequences due to social distancing are yet to be determined.[22–24]

This study aims to describe the impact of the pandemic on the use of healthcare services by the pediatric population and to assess the perspective of parents regarding the consequences for their children's health and wellbeing.

MATERIAL AND METHODS

We conducted a cross-sectional study, with data being collected through an anonymous online survey on social media. The survey consisted of an original non-validated questionnaire. Only fully completed surveys could be submitted, and participants could quit at any time. The survey was available for submission between the 1st of May and the 17th of May 2020, the day before the official reopening of kindergartens in Portugal after the first lockdown.

We accepted responses from parents with at least one child or adolescent (0 to 17 years and 364 days old) living in Portugal. Parents were asked to answer questions of mixed type (quantitative and qualitative), including multiple choice questions, dropdown questions, Likert scales and short-answer questions, concerning the period between the official school closure by the Portuguese government (March 16th) and the day of the submission of the survey.

Socio-demographic characterization included the child's district of residence, nationality, and age, as well as the maternal and paternal ages and educational level.

We collected information regarding the use of healthcare services during the COVID-19 pandemic, namely symptoms presented by the child (fever, cough, dyspnea, nausea or vomiting, diarrhea, otalgia, odynophagia, headache, urinary complaints, injuries following trauma, others), if he/she was taken to an emergency department (ED), whether the parents' choice of postponing or not visiting the ED would have been different if there was no pandemic and the number of hospital admissions and invasive medical interventions performed on the child (blood drawing for testing, intravenous or intramuscular medication, surgical procedure, others) during the stated period.

Pandemic-related information was gathered by assessing whether the child was part of a high-risk group for COVID-19 according to the guidelines of the Portuguese Directorate-General of Health[25] and complemented by the local hospital's criteria (newborn, prematurity, asthma, bronchopulmonary dysplasia, diabetes, heart failure, chronic liver disease, chronic kidney disease, active malignant disease, inflammatory bowel disease, sickle cell disease, pharmacological immunosuppression, institutionalized child), and parental degree of concern of their child contracting the virus in a Likert scale from 1 (not at all concerned) to 5 (extremely concerned).

Consequences of COVID-19 on the child's health and access to medical care were assessed through questions concerning the attendance of scheduled medical appointments, vaccinations of the national immunization program and neonatal metabolic screening (options being no scheduling, carried out in person, conducted virtually, cancelled/postponed by the family, cancelled/postponed by the healthcare institution or doctor), as well as the parental perception of negative consequences of the pandemic on their child's health on a Likert scale from 1 (strongly disagree) to 5 (strongly agree), complemented by a non-mandatory question characterizing the negative consequences observed. All other questions in the survey required a mandatory response.

We analyzed the data using frequencies and percentages for categorical variables. Counts and percentages were used to describe survey participants. Median values and interquartile range were reported for quantitative variables. Significant associations were evaluated by applying the Pearson's chi-squared test (χ^2), Mann-Whitney U-test (U), Kruskal-Wallis test (H) and the Spearman's correlation coefficient (rs) when appropriate, using SPSS 20®. Significance for all the results was defined as $p < 0.05$.

The study was approved by the Ethics Commitee of Hospital Beatriz Ângelo.

RESULTS

We obtained 12 390 responses to the survey, regarding 19 745 children. No participants were excluded from the study.

Socio-demographic characteristics of the participants are depicted in Table 1. The mean age of children in the study was 6.29 years (SD = 4.84).

As far as the usage of healthcare services during the pandemic is concerned, 20.6% of parents reported that at least one of their children was ill during the designated period. The most frequently reported symptoms were fever (49.3%), cough (34.9%) and odynophagia (21.9%). Among the 2552 children that were reportedly ill, 31.8% were taken to an ED. When questioned, 33.9% of parents who visited the ED believed they would have gone earlier and 16.0% more often to the ED if it was not for the pandemic. Among the inquired whose children were ill and did not visit the ED, 22.8% admitted they would have visited the ED if there was no pandemic. The children's presentation of symptoms during the designated period was not significantly associated with the parental degree of concern towards the virus (U = 12 338 909.5, $p > 0.05$). During the stated period, 1.0% of children in the survey were hospitalized and 3.2% underwent invasive interventions. There were no significant differences in hospitalization rates or invasive interventions between children whose parents stated they would have come earlier (would have come earlier: 19.0%; would not have come earlier: 21.9%; $\chi^2 = 2.184$, $p > 0.05$) or more often (would have come more often: 21.5%; would not have come more often: 21.4%; $\chi^2 = 0.001$, $p > 0.05$) to the ED in comparison with other children.

Concerning pandemic-related information, almost half of parents (49.6%) stated that they were extremely concerned

Table 1 – Socio-demographic characteristics of the participants

Socio-demographic characteristics	n (%) of respondents (n = 12 390)
District of residence	
Aveiro	332 (2.7)
Beja	120 (1.0)
Braga	821 (6.6)
Bragança	49 (0.4)
Castelo Branco	84 (0.7)
Coimbra	306 (2.5)
Évora	145 (3.4)
Faro	416 (3.4)
Guarda	62 (0.5)
Leiria	305 (2.5)
Lisboa	6207 (50.1)
Portalegre	68 (0.5)
Porto	1240 (10.0)
Santarém	321 (2.6)
Setúbal	1381 (11.1)
Viana do Castelo	101 (0.8)
Vila Real	64 (0.5)
Viseu	178 (1.4)
Região autónoma dos Açores	58 (0.5)
Região autónoma da Madeira	131 (1.1)
Age of children	
0 - 2 years	5413 (27.4)
3 - 6 years	5963 (30.2)
7 - 11 years	4831 (24.5)
12 - 17 years	3538 (17.9)
Nationality of chidren	
Portuguese	12 240 (98.8)
Other nationalities	150 (1.2)
Maternal age	
< 20 years	14 (0.1)
20 - 29 years	1136 (9.2)
30 - 39 years	6360 (51.3)
40 - 49 years	4421 (35.7)
> 50 years	444 (3.6)
NA	15 (0.1)
Paternal age	
< 20 years	1 (0.0)
20 - 29 years	678 (5.5)
30 - 39 years	5475 (44.2)
40 - 49 years	5071 (40.9)
> 50 years	1115 (8.9)
NA	50 (0.4)
Maternal educational level	
Primary school (1st to 9th grade)	776 (6.2)
Secondary school (10th to 12th grade)	2293 (18.5)
Bachelor's degree or equivalent	6846 (55.3)
Master's or Doctoral degree	2475 (20.0)
Paternal educational level	
Primary school (1st - 9th grade)	2020 (16.2)
Secondary school (10th - 12th grade)	3066 (24.7)
Bachelor's degree or equivalent	5436 (43.9)
Master's or Doctoral degree	1868 (15.1)

NA: not applicable

(5 on the Likert scale) with the possibility of their child contracting the novel coronavirus (Fig. 1). Only 1.4% of respondents considered not to be to be concerned at all (1 on the Likert scale). Regarding the high-risk groups for COVID-19, 18.1% of children in our study were included in at least one of the groups, mainly due to asthma (9.6%), followed by prematurity (5.1%) and being newborn (1.8%). During the designated period, children in a high-risk group presented with symptoms significantly more often compared to other children but did not attend the ED in significantly higher rates (Table 2). There was a significant association between belonging to a high-risk group and undergoing an invasive intervention or hospitalization (Table 2), with the odds being 3.44 times higher if the child had a risk factor compared to if he or she did not. Being included in a high-risk group was also significantly associated with a higher level of parental concern for their child contracting the virus (high-risk group: Mdn = 5.00, IQR = 4.00 - 5.00; no risk group: Mdn = 4.00, IQR = 3.00 - 5.00; U = 9 640 774, $p < 0.001$).

Regarding the consequences of COVID-19 on children's health and access to medical care, 48.3% of responders had a medical appointment previously scheduled for their child during the stated period. Of these 5984 scheduled appointments, 21.7% were carried out in person, 10.9% were conducted virtually (e.g., by telephone), 13.3% were cancelled at the request of the family, while 54.2% of appointments did not take place due to postponement or cancellation by the healthcare institution or doctor (Table 3). Parents' perception of a negative impact of the pandemic on their child was significantly impacted by the way medical appointments were conducted during this period [H(3) = 40.334, $p < 0.01$]. Compared to when consultations were carried out in person, there was no significant difference in parental perception when they were cancelled by the family itself (U = 494 987.5, $p > 0.05$). However, when appointments were conducted virtually (virtual appointments: Mdn = 2.00, IQR 1.00 - 3.00; appointments in person: Mdn = 1.00, IQR = 1.00 - 3.00; U = 389 571.5, $p < 0.01$) or cancelled/postponed by the healthcare institution (appointments cancelled by healthcare institution: Mdn = 2.00, IQR 1.00 - 3.00; appointments in person: Mdn = 1.00, IQR = 1.00 - 3.00; U = 1 874 389, $p < 0.001$), the parental perception of a negative impact was significantly higher.

Concerning the vaccination appointments scheduled for vaccines included in the national immunization program, 22.2% (2747 children) had a vaccine administration scheduled during the designated period. While 78.4% were vaccinated according to plan, 21.6% (594 children) missed their vaccination – 11.6% due to family preference and 10.0% due to postponement or cancellation by the healthcare institution (Table 3).

The neonatal metabolic screening (heel prick test) was planned for 2.9% of children included in the survey, 1.4% of whom did not take place (five newborns) – one of them by choice of the family and four because of cancellation by the healthcare institution (Table 3).

Nearly half of parents (48.7%) strongly disagreed that

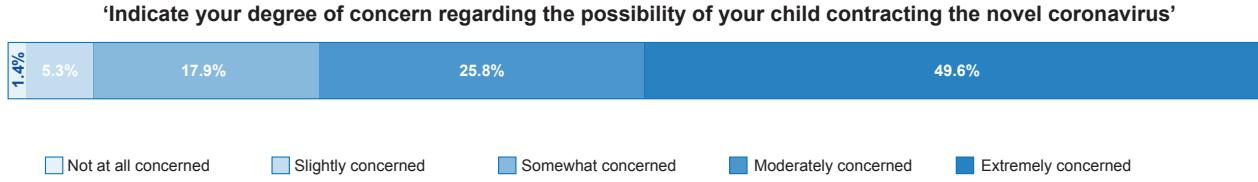

Figure 1 – Results of a Likert scale question used in the survey

the social distancing imposed by the pandemic affected their children's' health negatively (1 on the Likert scale), while only 4.4% strongly agreed there were negative health consequences (5 on the Likert scale). When asked to characterize these consequences in a non-mandatory question, 2517 parents described the negative effects observed in their children. Parental concerns included psychological consequences (47.2%) such as anxiety, the most reported negative outcome (417 children), as well as behavioral and emotional changes; social consequences (33.6%) comprising social isolation, decreased outdoor time and increased screen-time; health related issues (27.0%), namely the loss of medical appointments and therapies considered essential; and physical health (20.6%) including reduction of physical activity, weight increase and changes in eating and sleeping habits. There was a significant positive correlation between parental degree of concern towards the virus and the conviction of the pandemic and social distancing measures having a negative impact in their children's health (rs = 0.054, $p < 0.001$).

DISCUSSION

This study aims to describe the consequences of the COVID-19 pandemic on children's health and use of medical care in Portugal. We gathered information concerning around 1% of the Portuguese pediatric population, according to the national data of 2019.[26]

The COVID-19 pandemic contributed to changes in health-behaviors of the pediatric population including a reduction in the use of healthcare services, as one can see by the rate of parents in our study who claim they would have visited the ED earlier, more often, or instead of other medical services for their children's symptoms if there was no pandemic. Changes in access to healthcare can also be demonstrated by the reduction of visits to the ED observed in several countries.[9,12,16,17,19] The quasi simultaneous beginning of the pandemic with the decrease of ED visits seems to underline the association between the two events.[9] Multiple factors seem to be involved in this change in the pattern of ED use. On one hand, children confined in the household tend to develop less acute infections and traumatic injuries compared to when contacting with other children in school and extracurricular activities.[9,12] The natural reduction in the reasons that motivate visits to the ED is not outbalanced by children with COVID-19 seeking medical care, since most of them have mild symptoms and are treated at home, with no need for hospital admission.[5,27] Nevertheless, socially isolated children continue to get ill with occasional acute infections, trauma and acute presentations or exacerbations of chronic conditions, which might lead to the need for medical observation. Parental concern about their children being exposed to COVID-19, reported to be extremely high in almost half of the parents in this study, might contribute to the reluctance of bringing their children to an ED, as has been suggested by other studies.[9,12,15] Some authors have pointed out the fear of "bothering the doctor" who is in the front line against COVID-19 as well as the fear of overburdening the healthcare system as an additional obstacle for

Table 2 – Comparison between children who belong to a high-risk group and children who do not

	n (%) of respondents		*p*
	Risk group (n = 2241)	**No risk group** (n = 10 149)	
Symptoms presented*	600 (26.8)	1952 (19.2)	< 0.001
ED visits*	190 (31.7)	621 (31.8)	NS
History of invasive interventions or hospitalization*	178 (7.9)	250 (2.5)	< 0.001

ED: emergency department; NS: not significant. * Presented as percentage, statistical analysis using Pearson's chi-squared test.

Table 3 – Outcome of scheduled medical appointments, vaccinations, and neonatal screenings

Scheduled appointments	n (%) of respondents			
	Carried out in person	**Carried out virtually**	**Cancelled/ postponed by the family**	**Cancelled/ postponed by the healthcare institution**
Medical appointment (n = 5984)	1298 (21.7)	651 (10.9)	793 (13.3)	3242 (54.2)
Vaccination (n = 2747)	2153 (78.4)	-	320 (11.6)	274 (10.0)
Neonatal screening (n = 357)	352 (98.6)	-	1 (0.3)	4 (1.1)

seeking medical care.[10] Reports show that the delayed access to medical care has led to negative consequences in children's health, including fatal outcomes.[12,13] A recently published study also showed that the decreased access to healthcare was one of the contributing factors to the excess mortality rates reported in the Portuguese population since the beginning of the pandemic, although the group under 55 years old did not contribute to the observed increase.[15] Our study did not show a significant association between parents who opted to postpone or not visit the ED and negative health consequences such as increased number of invasive interventions, hospital admissions, or fatal outcomes. This might suggest that, apart from all the explanations above, there is a baseline overuse of emergency care in non-pandemic times and that children's symptoms could be handled by other healthcare services, namely the primary care setting. This is supported by the fact that Portugal is the country with the highest use of emergency services per capita in the Organization for Economic Cooperation and Development (OECD),[28] representing significant numbers of inadequate use of this resource.[9] Nevertheless, the potential danger of delayed access to medical care should not be overlooked and could impact the health of pediatric populations in both the short and long-term.

Regarding the postponement or cancellation of non-urgent medical appointments, our study shows that most scheduled consultations did not take place during the designated period, mainly by government-imposed measures or decisions from healthcare providers. A major concern is that the reduction of preventive medical care might be detrimental for non-COVID patients, especially those with chronic diseases or belonging to vulnerable groups.[29] In the long term, this collateral effect of the pandemic may lead to a rise in hospital admissions, healthcare-costs and contribute to the overload of healthcare facilities already crowded with COVID-patients.[29] The significant association between medical appointments either carried out virtually or cancelled/postponed by healthcare services and parental perception of negative outcomes for their children underlines how the decision of how consultations are carried out could have a damaging impact on children's health and contribute further to parental fear of accessing healthcare, thus aggravating the reluctance in seeking medical assistance.

The decline in vaccination coverage during the pandemic is particularly important, with 21.6% of the scheduled vaccinations in our study being missed. During the month of April 2020, the vaccine administrations within the Portuguese national immunization program dropped to almost half the numbers of the previous year[20] and data from several countries points to similar potentially harmful health behaviors,[21,23] posing an increased risk of outbreaks of vaccine-preventable diseases. Considering neonatal metabolic screening, which intends to diagnose genetic diseases that benefit from early treatment, five tests in our study were missed, representing 1.4% of newborns in the study. According to the national data available, neonatal screening coverage in Portugal reaches 99.5%,[30] meaning the rate in our study poses a 2.8-fold increase in missed screenings.

Looking at the consequences of the COVID-19 pandemic on the health and wellbeing of children and adolescents, it becomes clear that a major threat for this population might lie beyond the clinical aspects of the pandemic.[31] Parents in our study expressed several apprehensions in different areas of development of their children.

Countries worldwide have opted for school closures in order to reduce the transmission of the virus, although the effectiveness of this measure is not entirely clear.[32] The closure of schools creates enormous challenges, starting with restrictions to the learning process for children all over the world. It also seems to pose a risk of aggravating the widening gap between children of high and low-income families, since poorer households might have limited resources such as computers or internet access to maintain online learning provided by some schools.[23] Furthermore, some of these children rely on school meals for adequate nutrition or washing facilities for adequate hygiene.[31] Other vulnerable groups especially affected by school closures include children with special educational needs and disabilities, to whom the lack of daily routines and appropriate stimuli can cause significant disruption to the wellbeing . The fact that these children are missing their medical appointments and therapy sessions constitutes a risk for setbacks in their development and progression of essential skills,[22] and is a worry expressed by parents in our study.

Other outcomes reported by parents in our study have to do with the reduction of physical activity, increased weight, change in eating and sleeping habits as well as increased sedentary activities and screen-time, as has been described by other authors.[24,31] The disruption of daily routines and the acquired sedentary behaviors might exacerbate childhood obesity,[33,34] and the establishment of unhealthy habits in the long-term can compromise future cardiovascular and musculoskeletal health.[31] Furthermore, physical activity contributes positively to mental health, and can be used as a coping mechanism when facing challenges such as pandemics, leading to reduction of anxiety and depression levels.[34–36]

Mental health seems to be a major concern for parents in our study, with anxiety being the most frequently expressed preoccupation. Reasons for anxiety during pandemics include the fear of infection, frustration, boredom, lack of interaction with family members and friends, increased incidence and severity of domestic violence, abuse, and child neglect,[22,23] and the aforementioned school closures and reduction of physical activity.[37] Facing a worldwide pandemic with extraordinary and sudden routine disruptions poses a challenge for children's resilience and coping mechanisms, and yet mental health seems to be at risk of being overlooked and not prioritized.[38] When comparing post-traumatic stress responses in children who were quarantined during pandemics and others who were not, the mean scores for post-traumatic stress disorders were found to be four times higher in children who were quarantined.[39] The long-term effects of these unprecedented social distancing measures

on children's mental health is yet to be determined, and the possible psychological costs should be taken into consideration when imposing these measures.[22,37]

There are some limitations to our study. Information was gathered via parental recall, which might introduce bias for various reasons, including subjective perception and accuracy of memory. The fact that parents with more than one child filled a single questionnaire for all their children might hinder the analysis of data, especially when concerning vaccination coverage. By collecting data through an online survey, our inquiry might not have reached the social fringes, since internet access is not equally accessible to all social strata. Additionally, the dissemination of the survey through social media poses a risk of biased selection of participants, excluding non-users of those networks. Moreover, Portuguese districts were not portrayed in a representative proportion, with over-representation of major cities. The fact that the study was conducted for a brief period potentially biased the responses according to the pandemic-related events during the designated period.

CONCLUSION

In summary, the impact of the COVID-19 pandemic on children's health includes a change in the use of healthcare services as well as psychological, social, and physical consequences pointed out by parents that should not be overlooked. The future course of the pandemic is uncertain, as is the reorganization of medical services to face this challenge. Future studies to be carried out will be necessary in order to better understand the consequences of decreased ED visits, allowing for interventions to address potentially negative health outcomes. Efforts should be made to clearly communicate the recommendation of not postponing urgent medical evaluations to patients. Simultaneously, safety conditions must be ensured in healthcare facilities to minimize the risk of exposure to the novel coronavirus to a minimum, protecting both patients and healthcare workers and restoring confidence in seeking medical care. It should be a public health priority to compel parents to vaccinate their children and create pathways to allow vaccination without risk of COVID-19 exposure. Psychological, social, and physical consequences for children and adolescents risk being overlooked during the pandemic and should be assessed in further depth in order to set strategies to minimize potentially negative outcomes, especially in the most vulnerable populations.

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 of Hospital Beatriz Ângelo and by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENCIALITY

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

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Biological Therapy in Patients with Rheumatoid Arthritis in a Tertiary Center in Portugal: A Cross-Sectional Study

Artrite Reumatóide em Doentes Submetidos a Terapêutica Biológica num Centro Terciário de Referenciação em Portugal: Um Estudo Transversal

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Acta Med Port 2021 May;34(5):362-371 ▪ https://doi.org/10.20344/amp.13605

ABSTRACT

Introduction: Clinical outcomes in rheumatoid arthritis have greatly improved with therapeutic advances. Despite the availability of substantial clinical trial evidence, there is a lack of real-life data. The aim of this study was to assess disease status and quality of life in an outpatient population treated with biological disease-modifying anti-rheumatic drugs.

Material and Methods: Cross-sectional study recalling all patients ever treated in our unit with biological disease-modifying anti-rheumatic drugs. Clinical and demographic data, compliance, disease activity, functional status, joint deformities, and comorbidities were documented, and patients queried on occupational status, education, marital status and generic health related quality of life questionnaires.

Results: Recall was attended by 77 of the original 94 patients. At recall, median age was 63 years old, 82% of the patients were female and the median disease duration was 12 years. Biological therapy was started at a median of four years following disease onset. According to the disease activity score (DAS28), the percentage of patients with high, moderate, low disease activity or remission changed from 50, 45, 0 and 5 (pre-therapy) to 11, 37, 25 and 26 at recall, respectively; functional status was significantly improved. Seventy-five per cent of the patients retained the original treatment with good compliance. Lower Short Form-36 domain scores accompanied a low EQ-5D-3L score. Deceased patients (n = 6) had a lower estimated 10-year survival rate. In this group, biological therapy was discontinued at a higher frequency during follow-up.

Discussion: A high disease activity and a high HAQ disability index characterized most patients at pre-bDMARD onset.

Conclusion: Despite therapy switches and regular follow-up, a significant percentage of patients still presented with moderate disease activity, functional impairment and a poor health-related quality of life.

Keywords: Arthritis, Rheumatoid/drug therapy; Biological Products/therapeutic use; Biological Therapy; Quality of Life

RESUMO

Introdução: Avanços no tratamento da artrite reumatóide contribuiram para uma evolução favorável. Apesar de evidências substanciais provenientes de ensaios clínicos, são menos conhecidos os dados provenientes da vida real. O objetivo do estudo foi caracterizar a doença e a qualidade de vida em doentes sob fármacos biotecnológicos.

Material e Métodos: Trata-se de um estudo transversal com recolha de dados clínicos relativos à adesão terapêutica, atividade da doença, capacidade funcional, deformidades articulares, comorbilidades e questionários de qualidade de vida relacionada com a saúde, estado civil, situação profissional e escolaridade.

Resultados: Foram recrutados 77 doentes do grupo original de um total de 94. A mediana da idade foi 63 anos, 82% do sexo feminino e início de biológico cerca de quatro anos após o início da doença, com uma mediana de duração de 12 anos. De acordo com o *Disease Activity Score* (DAS28), a percentagem de doentes com atividade alta, moderada, baixa ou em remissão mudou, respectivamente, de 50, 45, 0 e 5 pré- biológico para 11, 37, 25 e 26 na altura da re-avaliação, com melhoria funcional. Setenta e cinco por cento dos doentes mantiveram o tratamento original com boa adesão. Pontuações mais baixas do *Short Form-36* associaram-se a uma baixa pontuação no EQ-5D-3L. No grupo de doentes que viriam a falecer (n = 6), foi observada uma menor esperança de vida aos 10 anos, assim como uma maior discontinuação da terapêutica biológica.

Discussão: Pré-biológico, uma elevada percentagem dos doentes apresentava elevada atividade da doença e incapacidade funcional.

Conclusão: Não obstante ajustes terapêuticos e seguimento regular, uma percentagem significativa de doentes mantinha atividade moderada e limitação funcional com baixa qualidade de vida relacionada com a saúde.

Palavras-chave: Artrite Reumatoide/tratamento farmacológico; Biológicos/uso terapêutico; Qualidade de Vida; Terapia Biológica

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Recebido: 14 de fevereiro de 2020 - **Aceite:** 11 de agosto de 2020 - ***First published*:** 10 de fevereiro de 2021 - ***Online issue published*:** 03 de maio de 2021

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease predominantly characterized by chronic inflammation of synovial joints. Without appropriate therapy the disease almost inevitably leads to severe joint deformities, particularly of the hands, chronic pain and suffering, disability, inability to work, poor quality of life and early mortality.[1] Chronic glucocorticoids and non-steroidal anti-inflammatory drugs used from the 1950´s failed to control disease and had too many associated side-effects, often life-threatening.[2] The era of innovative medicines occurred in the late 1990's with the focus shifting to a treat to target–based approach (T2T), with new treatment paradigms, including early diagnosis and intensive management. This was made possible through the use of biological disease-modifying anti-rheumatic drugs (bDMARD) in addition or as an alternative to synthetic disease-modifying anti-rheumatic drugs (sDMARD).[3-5] The first biological therapies to be developed in rheumatology were tumor necrosis factor inhibitors (TNFi) for patients who did not respond to treatment with sDMARDs.[4,6] Most importantly, the therapeutic judgment has to take into account co-morbidities (such as heart failure and infectious risk), past history of neoplasia and ideally identify those with a high risk of relapse.[6] Currently, there is a much wider therapeutic armamentarium ranging from membrane receptor agonists or antagonists (Fc-CTLA4, CD20) to anti-cytokine (Il-6, IL-17) and JAK kinase inhibitors.[7]

Despite advances, there are still no easily available biomarkers to establish a personalized treatment plan at the time of disease onset or diagnosis. Similarly, during follow-up, most therapeutic decisions frequently remain empirical. This is the case when tentatively adapting the chosen therapy to a personalized optimal dose and regimen, but also when prescribing co-therapies or switching to another bDMARD when the treatment is inefficient or associated with intolerance or adverse events. Furthermore, therapies may be ineffective (wrong target) or become neutralized due to their immunogenicity. Of note, in Portugal, these therapies are entirely state subsidized and are associated with a significant societal cost.

Clinical assessment of disease activity, progression and remission are robust and quantitative,[8] as are indicators of a patient's quality of life. In this study we aimed to assess every single patient with RA that ever received biological therapy in our unit and answer some very simple questions that nevertheless remain at the core of the management of these patients. Are our patients free of deformities? Are they able to work and do they lead productive lives? Have they retained their original therapies? Was a switch required? Was therapy interrupted and for what reason? Have they suffered important side-effects? Do they suffer from important co-morbidities? Have we lost patients to follow-up? Are they alive?

MATERIAL AND METHODS

Study design and population

This is a cross-sectional study that took place in an outpatient care setting between December 2017 and May 2018. We only included patients that were on biological therapy for at least three months. All patients fulfilled the American College of Rheumatology 1987[9] and 2010[10] revised criteria for the classification of rheumatoid arthritis (RA) and were aged 18 years and over. Our unit´s database allowed us to identify 94 patients with RA that started biological therapy (bDMARD) from January 2002 (date of first bDMARD treatment in the unit) to December 2017. At the time of recall, seven patients were lost to follow-up, six patients had died, and four refused to participate in our study. Overall, the recall involved 77 patients. Each patient underwent a physical examination, recording of disease activity and hand joint deformities and was requested to complete a questionnaire regarding demographic and social characteristics as well as generic health related quality of life (HR-QoL) questionnaires validated for Portugal. Demographic and clinical data was also extracted from the medical records. The Charlson Comorbidity index[11] which predicts 10-year survival in patients with multiple comorbidities was calculated for all patients at the onset of bDMARD therapy and at the time of recall. Pharmacy refill information was obtained for every patient under self-administered biological therapy. The study was registered at EuroQol Group website (14th July 2013) and collaboration was obtained from Professor Pedro Lopes Ferreira (24th January 2015). The study protocol was approved by the hospital Ethics Committee (process 183/2015) and the *Comissão Nacional de Protecção de Dados* (3886/2016).

Therapeutic approach

In the latter years, a T2T approach was followed according to recommendations.[5] When a TNFi patient was intolerant to methotrexate, failed to reach at least low disease activity or presented with poor prognostic signs, a switch was performed, to rituximab, tocilizumab or abatacept, depending on prior medical history and comorbidities and also according to marketing authorizations and ministry of health re-imbursement policies at the time. Rituximab was administered at the dose of 1 g, two weeks apart, with the exception of one patient with Sjögren´s syndrome that received 375 mg/m^2 – four doses, weekly. Prednisolone was tapered and discontinued whenever possible.

Disease activity and deformities

Disease activity was measured by Disease Activity score 28-erythrocyte sedimentation rate [DAS28-ESR][12] defined as follows: high disease activity (HDA) > 5.1; moderate disease activity (MDA) ≥ 3.2 and ≤ 5.1; low disease activity (LDA) ≥ 2.6 and < 3.2; remission < 2.6. DAS28-ESR was routinely recorded at clinic visits. In a subset of patients, at recall, the attending physician counted the number of wrist and hand deformities per patient.

Health assessment questionnaire

The functional status was measured by the health assessment questionnaire (HAQ). The HAQ consists of eight categories which evaluate the patient's difficulty with activities of daily living over the past week. The questionnaire consists of 41 total items: 20 specific activities are grouped into eight functional categories with each category given a single score equal to the maximum score of their component activities, 13 additional questions on the use of assistive devices, and eight additional questions assessing help received from others using a scale 0, 1, 2 or 3. The patient's responses were recorded on a scale from zero (no disability) to three (completely disabled).[13-16]

Patient compliance

Compliance was determined by the proportion of days covered (PDC) for the index biological drug during the 12-month follow-up period. Non-compliance of self-administered biologics (etanercept adalimumab, golimumab and tocilizumab) was defined as proportion of days covered < 80% during the post index period.[17] Patient compliance was obtained by using pharmacy refill information for the duration of one year prior to recall visit. Patients were considered non-compliant with medication when less than 80% of prescriptions were collected from the pharmacy. Patients under intravenous medication (rituximab, tocilizumab, infliximab, and abatacept) were considered compliant since in our Unit qualified nurses perform administration of biologics in a Day Hospital.

Health related quality of life

HR-QoL, defined as those aspects of quality of life that directly or indirectly relate to health, a concept that includes physical, psychological, and social domains, was measured through the short form (SF-36) health survey and the EuroQoL Group 5D-3L (EQ-5D-3L).

SF-36 is a 36-item, patient-reported survey consisting of eight scaled scores, which are the weighted sums of the questions in their section. Some questions have an inverted scale. After each scale is directly converted into a 0 - 100 scale, the lower the score the higher the disability. In other words, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight dimensions are: vitality (V), physical functioning (PF), bodily pain (BP), general health perceptions (GH), physical role functioning (RP), emotional role functioning (RE), social role functioning (SF) and mental health (MH). Scoring algorithms allow for aggregation of scores from the eight SF-36 subscales in two distinct scores: a physical component summary (PCS) and a mental component summary (MCS). In the present study, SF-36 was analysed according to the norms for the Portuguese population.[18,19]

Each patient was asked to report their socio-demographic characteristics (age, gender, marital status) and complete the EQ-5D-3L in order to self-report their own health in a five-dimension descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each attribute has three levels: no problems, some problems, and severe problems, resulting in 243 possible health states, the best of which corresponds to a score of one. Each health state was then assigned an index value by applying scores from national Portuguese preference weights (tariffs) using a validated model,[20,21] Patients were asked to provide a score on a visual analogue scale (VAS) ranging from endpoints 0 for the 'worst imaginable health state' to 100 for the 'best imaginable health state'.

Statistical analysis

According to the normality of their sampling distributions, continuous variables were recorded as means (± standard deviation) or medians (IQR1 - IQR3). Dichotomous variables were examined by frequency distribution, recorded as percentage, and comparisons were made using the chi-square test or Fisher's exact test for independent samples. The *t* test was used for comparison between normally distributed variables. For continuous data that were not normally distributed, the Wilcoxon Signed Rank test was used to compare paired means and the Mann-Whitney *U* test for comparisons between independent samples. Correlations between continuous variables were analysed with Pearson's correlation coefficient. A *p* value below 0.05 was considered statistically significant. Analyses were performed using SPSS version 23 software.

RESULTS

Initial patient cohort: demographic and clinical features

Overall, 94 patients started bDMARD in their fifth decade of life, after a median disease duration of four years (Table 1). Most patients were female with no differences between the types of bDMARD regarding age and gender distribution (Appendix 1, Table 1; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Rheumatoid factor or anti-CCP antibodies were positive in 81% of the patients. Methotrexate (MTX) - median dose 20 mg per week and corticosteroids - median dose prednisolone (PDN) equivalent 10 mg/day had failed to control disease activity in 87% and 66% of patients, respectively. Treated dyslipidemia (51%) and arterial hypertension (41%) were frequently documented, 19% of patients suffered from chronic anxiety, 16% were smokers and 10% were obese. The median of the estimated 10-year survival using the Charlson comorbidity index was 90%.

Recall patient cohort: demographic and clinical features

Recruitment was achieved in 77 patients, mostly between 47 and 66 years of age (Table 2). Regarding professional status almost half of the sample was retired (49%) and 10.5% unemployed. The majority (40.8%) only had four years of schooling; 11% had completed 12 years of schooling and 17% underwent university education. Only 17% were single.

Over two thirds (79%) of patients remained on bDMARD

Table 1 – Baseline demographic and clinical characteristics

	Original cohort	Recall cohort
Number of patients	94	77
Male:female	19:75	14:63
Caucasian, n (%)	86 (91)	71 (92)
Age (y), median (IQR)	50 (42 – 57)*	63 (55 – 71)
Age (y) bDMARD started, median (IQR)	56 (47 – 62)	56 (49 – 61)
Disease duration (y) from time of diagnosis to first bDMARD, median (IQR)	4 (1 – 9)	4 (1 – 9)
Either or anti-CCP/RF positive, n (%)	76 (81)	61 (79)
Anti-CCP/RF negative, n (%)	18 (19)	16 (21)
Prior to bDMARD:		
Prednisolone, n (%)	62 (66)	57 (74)
Prednisolone equivalent mg/day, median (IQR)	10 (5 – 12)	10 (5 – 10)**
Methotrexate, n (%)	82 (87)	73 (95)
Methotrexate mg/day, median (IQR)	20 (15 – 20)	20 (13 – 20)
Pre-bDMARD DAS 28 – ESR, median (IQR)	5.31 (4.51 – 6,29)	5.060 (4.500 – 5.998)
Number of patients for which DAS available	75	62
- high disease activity (HDA) > 5.1, n (%)	52 (46)	31 (50)
- moderate disease activity (MDA) ≥ 3.2 and ≤5.1, n (%)	30 (40)	28 (45)
- low disease activity (LDA) ≥ 2.6 and < 3.2, n (%)	0	0
- remission < 2.6, n (%)	3 (4)	3 (5)
Pre-bDMARD HAQ, median (IQR) initial n=33; recall n=27	2.00 (1.47 – 2.53)	2.00 (1.44 – 2.49)
On bDMARD, n (%)	94 (100)	61 (79)
bDMARD:		
Infliximab, n (%)	3 (3)	1 (1,5)
Etanercept, n (%)	55 (59)	31 (51)
Adalimumab, n (%)	14 (15)	5 (8)
Golimumab, n (%)	2 (2)	2 (3)
Rituximab, n (%)	6 (6)	6 (10)
Tocilizumab, n (%)	14 (15)	15 (25)
Abatacept, n (%)	0	1 (1.5)
Comorbidities:		
Benign tumors, n (%)	2 (1)	0
Malignancy	6 (6)	2 (2)
Active smoking, n (%)	12 (16)	11 (14)
Dyslipidemia, n (%)	48 (51)	41 (53)
Arterial hypertension, n (%)	39 (41)	33 (43)
Obesity, n (%)	9 (10)	8 (10)
Chronic anxiety/depression disorder, n (%)	18 (19)	14 (18)
Charlson Comorbidity index at time bDMARD started, median (IQR)	2 (2 – 3)	2 (2 – 3)
Estimated 10-year survival at the time bDMARD started, median (IQR)	90 (77 – 90)	90 (77 – 90)

* age at diagnosis
** dose not known in six females and two males

(n = 61), and most were on etanercept and tocilizumab; 75% remained on the original bDMARD with an adequate compliance (Table 3). Approximately one fifth of patients stopped bDMARD (n = 16), mostly due to infection but also because of primary or secondary failure or deliberately due to subjectively controlled disease activity. One third of patients (n = 22) switched from the original bDMARD, and eight patients required further switches. Up to three and four switches occurred in single patients. After bDMARD onset, MTX use reduced from 95% to 22% (p = 0.002, chi square test between frequencies). Likewise, steroid use significantly decreased from 74% to 30% (p < 0.001, chi square test

Table 2 – Age distribution, professional situation, schooling, marital status and socio-economic status at recall*

Age range (y) (n = 77)	n (%)
27 - 36 y	1 (13)
37 – 46 y	5 (6.5)
47 – 56 y	17 (22.1)
57 – 66 y	26 (33.8)
≥ 67 y	28 (36.3)
Professional situation*	
Employed	21 (27.6)
Unemployed	8 (10.5)
Retired	37 (48.7)
Student	2 (2.6)
Stay at home parent	6 (7.9)
Other	2 (2.6)
Schooling*	
Cannot read or write	1 (1.3)
Can read and write but no schooling	3 (3.9)
First 4 years	31 (40.8)
First 6 years	4 (5.3)
First 9 years	15 (19.7)
Completed schooling (12 years)	9 (11.8)
University degree	13 (17)
Marital status*	
Single	13 (17.1)
Married	43 (56.6)
Divorced	11 (14.5)
Widow	9 (11.8)

* missing information in one patient

between frequencies), halving the prednisolone equivalent dose to a median of 5 mg/day. Of note, the frequency of steroid use was slightly higher in those patients that discontinued bDMARD. Approximately 40% of patients presented hand deformities, but the median number of deformities per patient was generally low. Dyslipidemia (53%) and arterial hypertension (43%) were equally distributed among the participants but chronic anxiety (18%), smoking (14%) and obesity (10%) were only registered in females. The original age difference between males and females was no longer present, with no other difference between genders concerning demographic features, disease duration from diagnosis to recall, onset of first bDMARD and follow-up. Unlike before, the Charlson comorbidity index was now higher in men than women, estimating a lower 10-year survival for the former (p = 0.019) (Appendix 1, Table 2; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

At recall, DAS28-ESR and HAQ were significantly lower when compared to the pre-bDMARD values, both with a p value < 0.001 (Wilcoxon Signed Rank test). However, the median DAS28-ESR of 3.2 (IQR 2.390 – 3.950) was borderline between low and moderate disease activity and the median HAQ-DI index was 1.310 (IQR 0.500 – 1.810), indicative of mild to moderate disability. Additionally, at recall, there was no significant difference in DAS28-ESR or HAQ when comparing patients on bDMARD with patients off bDMARDs (p = 0.917 and 0.975, respectively - Mann Whitney-U test). Of note, the pre-bDMARD HAQ could only be obtained for 28 of the 77 patients at recall.

Recall patient cohort: health related quality of life outcomes

Lower scores on the SF-36 reflect poorer HR-QoL, particularly affecting the physical domains, general health perception and vitality in our patient cohort (Fig. 1). Due to missing values, the SF-36 physical (PCS) and mental component summaries (PCS) could only be calculated for 44 subjects with mean values of 37.7 ± 9.5 and 46.5 ± 11.6, respectively. Regarding EQ-5D-3L (Table 3), the mean calculated score and VAS were 0.45 (± 0.3) and 60.64 (± 22.1), respectively. There were no significant differences in the EQ-5D-3L domains between men and women (Appendix 1, Table 2; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Moderate yet significant correlations were found between PCS, MCS and EQ-5D-3L mean score and VAS (Appendix 1, Table 3: see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

Full data regarding professional status are shown in Appendix 1, Table 4 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Unemployed patients (n = 7) had a significantly lower EQ-5D Portuguese tariff when compared to employed patients (n = 19) (p = 0.012, T-test), with a similar age; even though not significantly, unemployed patients had higher DA28, HAQ and number of deformities in comparison to the latter.

Demographic, clinical and therapeutic characterization of patients who died or were lost to follow-up

Patients lost to follow-up were younger than the group as a whole, emigrated or returned to their country of origin or followed their physician to another hospital (Table 4). The estimated 10-year survival rate at the time of first biological therapy was significantly different between the deceased patients and the recall group (p = 0.006) with median values of 65 (29 – 77) and 90 (77 - 90), respectively (Appendix 1, Table 5: see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

DISCUSSION

Our unit is dedicated to the treatment of patients with systemic autoimmune diseases including RA. We officially started treating RA patients with biological therapy in 2002, with our first patient ongoing regular follow-up since treatment onset. With a median age of 50 years, our patients presented a high disease activity (median DAS28 of 5.30)

Figure 1 – Health-related quality of life using the SF-36 health survey. Values are shown for each dimension: physical functioning (PF), role limited by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limited by emotional problems (RE), and mental health (MH).

and a high HAQ disability index (median of 2.00) despite sDMARD therapy, at pre-bDMARD onset. These indices are known to be inter-related and known to predict irreversible damage, physical and work disability and mortality.[22,23]

In our cohort, a high-risk group of patients, with a potentially productive work-life, initiation of bDMARD occurred at a median of four years after RA onset. A recent meta-analysis of 36 randomized clinical trials comparing the standard doses of the five anti-TNF inhibitors combined with MTX with MTX monotherapy described trial participants with a mean age varying from 48.4 to 60.7 years and a mean duration of disease from 0.2 to 11 years,[24] effectively meaning that the median therapeutic delay of four years, in our patient population, is probably not that prolonged when compared to others. Lack of access to specialist care may significantly contribute to the therapeutic delay. The Portuguese register Reuma.pt provides longitudinal information for over 7000 patients with RA at a national level.[25] Patients' access to biologics in RA stood at 7% in 2010 (12 percentage points below the average of the selected European countries)[26] having tripled from 2007 to 2012.[27] Low education, on the other hand, may contribute to poor health literacy (40.8% of our patients only had four years of schooling) but of note, the latter has also been found to be relatively common among those with a high level of education.[28]

Due to the retrospective nature of our study we are unable to assess the degree of irreversible joint damage already present at the time bDMARD was started and which might have been prevented through earlier treatment. At recall, 22 of 54 patients presented hand deformities but the

Table 3 – Disease duration, therapy, disease activity, functional status and EQ-5D-3L at recall

Number of patients	77
Disease duration (y) from diagnosis to recall, median (IQR)	12 (7 – 18)
Duration of follow-up from onset of bDMARD to recall, median (IQR)	7 (4 – 9)
Continued bDMARD by recall, n (% of 77)	61 (79)
Last bDMARD:	
Etanercept, n (%)	31 (51)
Adalimumab, n (%)	5 (8)
Tocilizumab, n (%)	15 (25)
Infliximab, n (%)	1 (1,5)
Rituximab, n (%)	6 (10)
Golimumab, n (%)	2 (3)
Abatacept, n (%)	1 (1.5)
Retained original bDMARD, n (%)	46 (75)
Compliance with bDMARD over the past year (n = 56)	45 (80)
Had discontinued bDMARD by recall, n (% of 77)	16 (21)
Reason for discontinuation:	
1. Primary failure to bDMARD, n (%16)	2 (13)
2. Secondary failure to bDMARD, n (%16)	2 (13)
3. Infection, n (% 16)	6 (38)
4. Neoplastic disease, n (% 16)	1 (6)
5. Remission, n (% 16)	3 (19)
6. Other, n (% 16)	2 (13)
Retained original bDMARD, n (% of 61)	46 (75)
Switched bDMARD, n (% of 61)*	22 (36)
1. Once, n (% 22)	14 (64)
2. Twice, n (% 22)	6 (27)
3. Thrice, n (% 22)	1 (5)
4. Fourth, n (% 22)	1 (5)
Compliance with bDMARD over the past year (n = 56)	45 (80)
Methotrexate, n (% of 77)	17 (22)
Methotrexate dose mg/week, median (IQR)	15 (10 – 20)
Steroids, n (% of 77)	23 (30)
Prednisolone equivalent mg/day, median (IQR)	5 (5 – 10)
Steroids plus bDMARD, n (% of 61)	16 (26)
Steroids having discontinued bDMARD, n (% of 16)	7 (43)
Deformities, n (%) – 54 patients evaluated	22 (41)
Deformities/patient, median (IQR)**	0.5 (0 – 2.25)
Recall HAQ, median (IQR) n = 77	1.310 (0.500 – 1.810)
Recall DAS 28 – ESR, median (IQR) n = 72	3.200 (2.390 – 3.950)
- high disease activity (HDA) > 5.1, n (%)	8 (11)
- moderate disease activity (MDA) ≥ 3.2 and ≤ 5.1, n (%)	27 (37)
- low disease activity (LDA) ≥ 2.6 and < 3.2, n (%)	18 (25)
- remission < 2.6, n (%)	19 (26)
EQ-5D 3L (n = 76)	
Mobility, mean (SD)	1.72 (0.51)
Personal care, mean (SD)	1.65 (0.58)
Usual activities, mean (SD)	1.76 (0.59)
Pain and unwell, mean (SD)	1.97 (0.57)
Anxiety and depression, mean (SD)	1.72 (0.72)
EQ-5D 3L Visual Analogue scale (VAS), mean (SD)	60.64 (22.07)
EQ-5D 3L score – Portuguese tariff, mean (SD)	0.45 (0.3)

* 5 patients switched and then stopped
** Missing information in 23 patients

highest number of deformities per patient was 2.25. Remission or LDA as determined by DAS28 was found in 51% of patients. Disappointingly, 37% of patients presented with moderate and 11% with high disease activity. Even though significantly lower, the HAQ disability index continued to reveal severe functional disabilities.

After a median duration of seven years, most patients (79%) remained on bDMARD, retaining the original medication (etanercept). Discontinuation of bDMARD occurred primarily due to infection (38%) followed by treatment failure (26%). Our data contrasts with that of the Rheumatic Diseases Portuguese Register (Reuma.pt) of bDMARD treated patients after 13 years of prospective follow-up. In the latter, a higher frequency of patients (50%) discontinued their first bDMARD mainly due to treatment failure (55%) with a much lower frequency of infections (4%).[29] Of note, in those patients who died, the Charlson co-morbidity index was significantly higher at treatment onset and bDMARD was discontinued more frequently than in the recall group.

Table 4 – Demographic and clinical characterization of deceased patients or lost to follow-up

Characteristics	
Alive but lost to follow-up, n (% of 94)	7 (7)
- Female:Male	5:2
- Went to live abroad, n	4
- Followed at another hospital in Portugal, n	3
- Age (y) bDMARD started, median (IQR)	44 (36 – 54.5)
- Patient age (y) at the time lost to follow-up, median (IQR)	47 (39 – 60)
- Disease duration (y) from time of diagnosis to first bDMARD (median ± IQR)	2 (1 – 4)
- Disease duration (y) at the time lost to follow-up, median (IQR)	4 (3 – 5)
- Either or anti-CCP/RF positive	5
- Anti-CCP and RF negative	2
- Charlson comorbidity index at the time bDMARD started, median (IQR)	1 (1 – 2)
- % Estimated 10 year survival at the time bDMARD started, median (IQR)	96 (86.5 – 96)
- bDMARD:	
- Etanercept, n; later switch to rituximab, n	4; 1
- Tocilizumab, n	1
- Infliximab switched to abatacept, n	1
Death, n (% of 94)	6 (6)
- Female:Male	3:3
- Cause of death unknown	3
- Cause of death known:	
- Pneumocystis pneumonia	1
- Pulmonary tuberculosis	1
- Stroke	1
- Age (y) bDMARD started, median (IQR)	60 (57 – 63)
- Age (y) at time of death, median (IQR)	66 (61 – 67)
- Disease duration (y) from time of diagnosis to first bDMARD (median ± IQR)	7 (3 – 11)
- Disease duration (y) at time of death (median ± IQR)	16 (8 – 21)
- Either or anti-CCP/RF positive, n (%)	7 (100)
- Charlson comorbidity index at time bDMARD started, median (IQR)	3.5 (3 – 4.75)
- % Estimated 10 year survival at time bDMARD started, median (IQR)	65 (29 – 77)
On methotrexate and bDMARD at time of death (n=2):	
- Etanercept, n	1
- Adalimumab, n	1
Off bDMARD at time of death (n=4):	
- Previous etanercept, n	2
- Previous adalimumab, n	1
- Previous rituximab, n	1

When compared with the frequencies of employed Portuguese people (pordata.pt - 2017), of which the majority have been through more than four years of schooling, our group of patients may have been at a disadvantage. On the other hand, the mean national age for retirement in Portugal in 2018 was 62.6 years, corresponding to the median age of our patients. Not surprisingly, at recall, almost 50% of our patients were pensioners. The median age of the unemployed patients (57.5 years) was nearing retirement age, but it should be noted that despite bDMARD therapy, they had the highest disease activity, functional impairment and the lowest EQ-D5-3L score. This is in line with a recent Portuguese study that recalled a similarly high HAQ value for unemployed albeit younger RA patients.[30]

The mean EQ-5D-3L score calculated with the Portuguese tariff was 0.45 (± 0.3), effectively placing our RA patients at a low score regarding HR-QoL. Interestingly, baseline mean EQ-5D-3L and HAQ scores for a Greek population of RA patients were 0.57 and 0.75, (our scores being 0.45 and 1.3) respectively. In this respect, higher HR-QoL scores clearly correlated with a lower functional impairment as measured by HAQ.[31] We nevertheless believe that our therapeutic strategies have provided benefit as shown by a decrease in disease activity and improvement in the disability index.

We consider the following limitations: due to the retrospective nature of the study we could not assess H-QoL indices from baseline and as such could not attempt to verify both the efficacy of particular drug regimens or compare them and evaluate how many patients became work-disabled due to disease. As bDMARD therapy was started late in the course of disease, we cannot assess if those who started early had clinical improvement compared with patients with a delayed onset of therapy. Moreover, the dynamic nature of RA therapy cannot be reflected in this cross-sectional design. After recall, some of the patients who had moderate or high disease activity were switched to alternative therapies that proved effective; other patients that were controlled subsequently lost response.

CONCLUSION

The use of bDMARD provided therapeutic benefit as reflected by a significant decrease in DAS28, HAQ and steroid use. There were few hand joint deformities per patient. The presence of comorbidities had an impact on mortality. Most patients retained the original bDMARD, few switches were required and the main cause for bDMARD interruption was infection. Nevertheless, the mean EQ-5D-3L scores were low, indicating a poor HR-QoL, the smaller impact on the mental component domains of SF-36 possibly reflecting less suffering. Earlier onset of therapy may have prevented deformities and residual irreversible functional incapacity. Increased literacy, access to healthcare and new therapeutic choices can be expected to contribute to earlier diagnosis and remission and improved overall outcomes in the years to come.

ACKNOWLEDMENTS

Secretarial Assistance: Ana Martins

Medical care: Nuno Riso for prior coordination and long-standing commitment to the Unit.

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 2013 Helsinki Declaration of the World Medical Association.

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.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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C3 Glomerulonephritis Associated with Monoclonal Gammopathy of Renal Significance

Glomerulonefrite C3 Associada a Gamopatia Monoclonal de Significado Renal

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Acta Med Port 2021 May;34(5):372-377 ▪ https://doi.org/10.20344/amp.13823

ABSTRACT

Introduction: Monoclonal gammopathy of renal significance (MGRS) is described as a hematologic condition characterized by nephrotoxic monoclonal proteins produced by a non-malignant B-cell or plasma cell clone. Nevertheless, MGRS can cause serious renal lesions, leading to high morbidity. In C3 glomerulonephritis, a monoclonal protein can cause renal damage indirectly. Acting as an autoantibody, the protein cannot be detected in the kidney biopsy, promoting the dysregulation of the alternative pathway of the complement system.

Material and Methods: This non-systematic review was based on a comprehensive search in databases and scientific journals, such as PubMed, Nature Reviews Nephrology and Kidney International, including the terms 'C3 Glomerulonephritis' and 'Monoclonal gammopathy of renal significance'. We review the pathophysiology, presentation, diagnosis, differential diagnosis and treatment of C3 glomerulonephritis associated with MGRS.

Discussion: With the increasing understanding of the complex interaction between monoclonal gammopathy and renal damage, such as C3 glomerulonephritis, it becomes clear that an early recognition is crucial, as Ig-directed therapy might improve outcomes. In this context, and in order to maximize the chance of a correct diagnosis, renal biopsy is mandatory to determine the exact nature of the lesion, and the severity of renal disease.

Conclusion: It is important to make an early diagnosis of MGRS-associated C3 glomerulonephritis in order to prevent not only the progression to a hematological malignancy, but also end-stage renal disease.

Keywords: Glomerulonephritis; Monoclonal Gammopathy of Renal Significance

RESUMO

Introdução: A gamopatia monoclonal de significado renal (MGRS) é descrita como uma doença hematológica caracterizada pela existência de proteínas monoclonais nefrotóxicas produzidas por um clone não maligno de células B ou plasmócitos. A MGRS pode causar lesões renais graves, levando a elevada morbilidade. Na glomerulonefrite C3, a proteína monoclonal pode causar indiretamente lesão renal. A proteína atua como auto-anticorpo, não sendo detetada na biópsia renal, promovendo a desregulação da via alternativa do complemento.

Material e Métodos: Esta revisão não sistemática foi baseada numa pesquisa abrangente com recurso a base de dados e revistas científicas, como a PubMed, *Nature Reviews Nephrology* e *Kidney International*, utilizando os termos 'Glomerulonefrite C3' e 'Gamopatia monoclonal de significado renal'. Apresentamos uma revisão da fisiopatologia, apresentação clínica, diagnóstico, diagnóstico diferencial e tratamento de glomerulonefrite C3 associado a MGRS

Discussão: Com a crescente compreensão da complexa interação entre a gamopatia monoclonal e a lesão renal, como é exemplo a glomerulonefrite C3, torna-se claro que um reconhecimento precoce é crucial, dado que a terapia dirigida à Ig pode melhorar o resultado. Neste contexto, para maximizar a probabilidade de um diagnóstico correto, uma biópsia renal é necessária para determinar a natureza exata da lesão e a severidade da doença renal.

Conclusão: É importante realizar um diagnóstico precoce de glomerulonefrite G3 associada a MGRS de modo a prevenir não apenas a progressão para uma neoplasia hematológica, mas também para doença renal terminal.

Palavras-chave: Gamopatia Monoclonal de Significado Renal; Glomerulonefrite

INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell disorder. The prevalence in the general population is about 0.7% and increases with age, to 3.2%, 5.3% and 7.5% in people older than 50 years, 70 years and 85 years, respectively. It is also estimated to be more prevalent in men (4.0%) compared to women (2.7%).[1]

MGUS is defined by monoclonal immunoglobulin (Ig) below 3 g/dL, plasma cells in the bone marrow below 10%, and the absence of signs or symptoms related with multiple myeloma (MM) (CRAB: hypercalcemia, renal insufficiency, anemia and bone lesions) or other lymphoproliferative malignancies.[2] It is a pre-malignant precursor, with a progression rate to MM or related malignant neoplasm of 1% per year, and this annual risk of progression is not affected by age or duration of the pre-malignant precursor.[3]

As a pre-malignant disorder, treatment of MGUS is not recommended until progression to MM.

However, the recognition of potential renal involvement led to the revision of the therapeutic approach, not previously considered.[4]

The term 'monoclonal gammopathy of renal significance'

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Recebido: 31 de março de 2020 - **Aceite:** 16 de junho de 2020 - ***First published*:** 05 de abril 2021 - ***Online issue published*:** 03 de maio de 2021

(MGRS) was introduced in 2012 and updated in 2017 by the International Kidney and Monoclonal Gammopathy Research Group (IKMG). Nowadays, MGRS is described as a hematologic condition characterized by nephrotoxic monoclonal proteins, produced by a non-malignant B-cell or plasma cell clone, that does not meet any hematologic criteria for therapy targeting the underlying clonal disorder.[5] The prevalence of MGRS is around 0.32% and 0.53% in people older than 50 and 70 years old, respectively.[6]

MGRS can be associated with a variety of renal disorders. However, no renal lesion is specific of any hematologic disorder. The nephrotoxic monoclonal immunoglobulin (Ig) or fragment can affect any structure in the renal parenchyma, and the pattern of renal lesion is mostly determined by the intrinsic structural and physicochemical characteristics of the monoclonal protein (intact monoclonal immunoglobulins or immunoglobulin light chains), rather than by the rate of production, and clone features.[5,7] On the other hand, the kidneys receive approximately 20% of the cardiac output, and have a unique environment where its chemical properties might change the monoclonal protein making it more toxic, and therefore, making kidneys more susceptible to damage.[8,9] There are essentially two types of mechanisms of renal injury based on the detection of monoclonal protein: direct and indirect. The most important mechanism is the direct one, characterized by the presence of monoclonal Ig deposits, which can be formed by the full or parts of the monoclonal immunoglobulin (heavy or light chains) or by various products of aggregation.[5] In the indirect mechanism, there are no Ig deposits, and monoclonal Ig acts as an autoantibody, dysregulating the alternative pathway of the complement system.

The best example of a MGRS-associated disorder with absent or scant monoclonal Ig deposition is C3 Glomerulopathy, more precisely C3GN and Dense Deposits Disease (DDD).[6,10]

In fact, a high proportion (reaching 65.1%) of patients older than 50 years of age with the diagnosis of C3 glomerulopathy have detectable levels of serum monoclonal Ig, which means a prevalence of monoclonal Ig in this group 16 times higher compared with the general population (4.2%).[1,11]

C3 glomerulopathy is a histopathological diagnosis which encompasses a group of rare renal diseases affecting about 1 to 2 per million people worldwide and is characterized by dysregulation of the alternative pathway of the complement system, leading to complement C3 deposition in the glomerulus, with sparse immunoglobulin deposition. Additionally, terminal pathway dysregulation might also occur, especially in C3GN.[10,12]

This abnormal control of the alternative pathway may be driven by acquired or genetic changes. Genetic causes are less frequent and include mutations that result either in loss of function in genes responsible for regulatory proteins or in gain of function in activator proteins. Acquired factors include the presence of autoantibodies towards regulatory proteins. The most common are the C3 nephritic factors, which stabilize C3 convertase, increasing its half-life, but other autoantibodies have been identified such as C5 nephritic factors (which target C3bBbC3b), C4 nephritic factors (towards C4b2a), factor H and factor B autoantibodies.[10,13]

In this review we are going to focus on C3GN associated with MGRS.

MATERIAL AND METHODS

We performed a comprehensive search in databases and scientific journals, such as PubMed, Nature Reviews Nephrology and Kidney International, including the terms 'C3 Glomerulonephritis' and 'Monoclonal gammopathy of renal significance' until December 2019. A total of 58 articles were initially selected, with subsequent exclusion of 28 (language not in English, and/or inclusion of glomerulonephritis other than C3GN). We present a review of the pathophysiology, presentation, diagnosis, differential diagnosis, and treatment of C3GN associated with MGRS.

Diagnostic approach

Presentation

The typical presentation of C3GN is a nephritic syndrome, characterized by edema, hematuria, proteinuria, azotemia and hypertension, with high risk for the development of end-stage renal disease (ESRD).

C3GN is a rare disease that affects children and adults, and C3GN associated with MGRS is even more exceptional.

MGUS increases with age, being around 3.2% in people older than 50 years old and reaching approximately 31.2% for patients with C3GN with the same age group.[1,14]

Therefore, patients aged more than 50 years with features of C3GN on renal biopsy, should be evaluated for the presence of a monoclonal gammopathy.

Renal biopsy

A renal biopsy is mandatory to assess the diagnosis. It is indicated for clarification of the etiology of a nephritic syndrome, as well as in cases of MGUS with suspected renal involvement, for instance because of the presence of isolated proteinuria or nephritic syndrome.

Moreover, renal biopsy provides valuable additional information such as the severity of the renal damage, through the activity and chronicity of the lesions observed.[15] This procedure remains essential even in patients with advanced renal disease in whom renal transplantation is intended, since the disease recurs in the allograft in the absence of control of the underlying clone.[16]

On light microscopy, C3GN usually shows a membranoproliferative pattern but can also show mesangial proliferative glomerulonephritis. The electron microscopy (EM) offers valuable supplementary information, regarding the structure of the deposits and their location. In C3GN, it typically reveals ill-defined electron dense deposits in the subendothelial space, subepithelial space and/or mesangium. This procedure is critical for the distinction of the

other forms of C3 glomerulopathy associated with MGRS, the DDD, which shows highly electron dense 'sausage like' deposits that segmentally infiltrate the glomerular basement membrane lamina densa.[7]

Interestingly, humps are common in both, C3GN and DDD on light microscopy.[7]

The immunofluorescence microscopy is positive for granular C3 deposits, of at least two orders of magnitude more intense than any other immune reactants but negative for Ig (either heavy or light chains), and components of the classical or lectin pathways (particularly of C1q and C4). This pattern is known as glomerulonephritis with dominant C3.[10,12,15]

Laser microdissection and mass spectrometry are useful to confirm the presence of C3 deposition, especially C3dg, which is a breakdown product, as well as small amounts of C5, C6, C7, C8, C9 and the complement factor-H-related proteins (FHR1-FHR5). Moreover, it confirms the absence of Ig.[10,12,15]

Complement evaluation

Investigation of the complement system should be done in all patients with a renal biopsy that is suggestive of C3GN.

As a result of the uncontrolled activation of the alternative pathway and C3 glomerular deposition, the serum level of C3 can be decreased and C3 breakdown products elevated (Fig. 1). The serum level of C4 is frequently normal but might be low in some patients. In addition, factor B and factor H might also be low.[15]

As a result of the terminal pathway dysregulation that could also occur in C3GN, serum C5 and C5b-9 levels might be low and elevated, respectively. However, these measures imply a sophisticated and difficult technique that is not widely available.[15]

Since complement dysregulation can be driven by both acquired and genetic factors, a detailed assessment of these forms is crucial.

As acquired drivers, C3 and C5 nephritic factors are the most frequent in C3GN. In addition, both factor H and factor B autoantibodies, as well as C4 nephritic factors should also be tested by functional assays of complement activity, especially if C3GN associated with MGRS is suspected.[11] C3 nephritic factors exist approximately in 50% of patients with C3GN, but can also appear in healthy individuals, as well as in other glomerulopathies.[11] Therefore, even though it can act as a driver, it might not be sufficient to cause the disease, highlighting the relevance of screening other possible drivers.[17]

Genetic screening is indicated for the assessment of the etiology of C3GN. Nevertheless, concomitant genetic factors are infrequent in C3GN associated with MGRS, reaching approximately only 7% of patients.[18]

It should particularly include mutations in the complement regulatory protein factor H, I, and CD46. Furthermore, in patients with negative C3 nephritic factor, complement factor H mutations should not be missed as well.[12]

Conversely, gain of function mutations in activators proteins (factor B and C3), are infrequent.[12]

Screening for monoclonal immunoglobulin

In C3GN associated with MGRS, the monoclonal Ig can be a trigger, and might act as an autoantibody against alternative pathway regulating proteins, acting as C3 nephritic factor or a factor-H antibody.[14] With this in mind, screening for monoclonal Ig must be done, especially in patients over 50 years old. The screening includes serum and urine

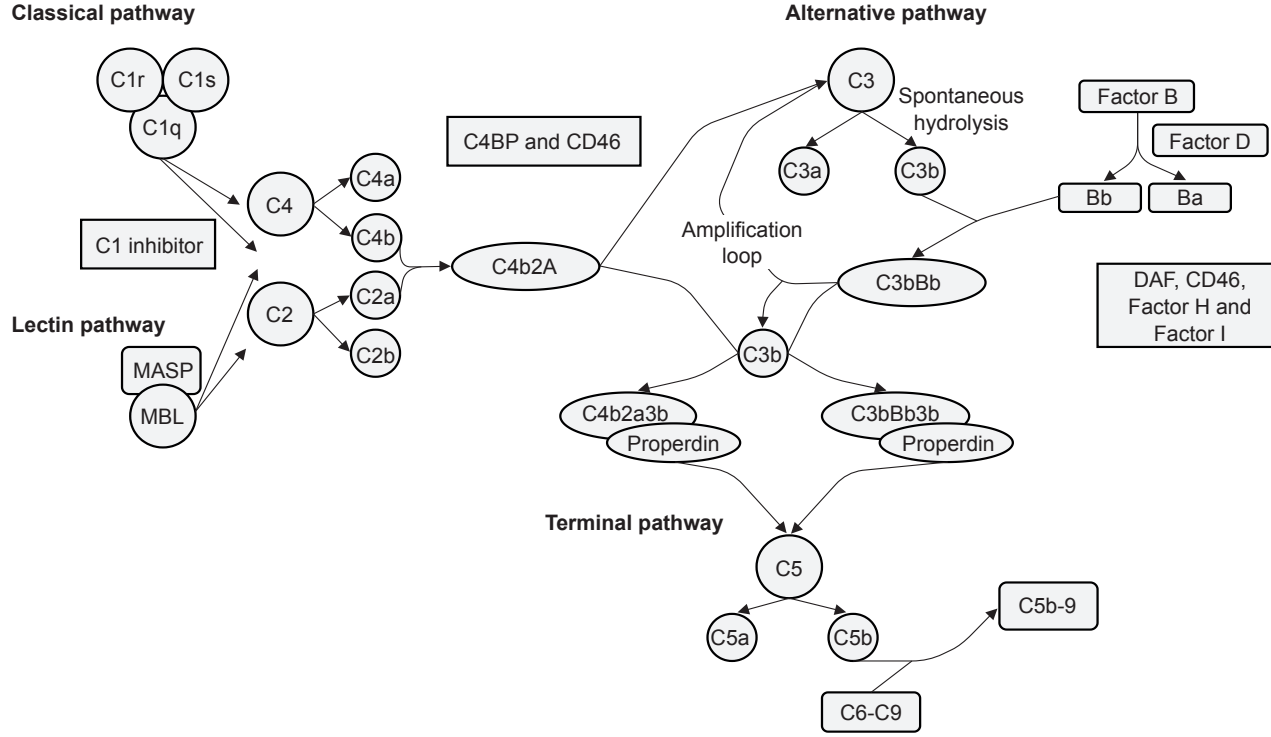

Figure 1 – Complement cascade

protein electrophoresis, immunofixation electrophoresis, as well as serum-free light chain (sFLC) immunoassay.[3,14,19] Serum protein electrophoresis is an inexpensive and rapid technique that allows the quantification of the M-component, which is important for the diagnosis, and for the evaluation of treatment response. However, it may not detect low levels of monoclonal Ig, a presentation not uncommon in MGRS.[20] On the other hand, only free light chains are filtered by healthy glomerulus, and consequently urine protein electrophoresis is the least sensitive test. Despite that, it may help to identify the pattern of renal injury through the detection of the level of total protein, albumin and globular proteins, details that can be important for the diagnosis and treatment monitoring.[5,21] Serum and urine immunofixation are more sensitive to detect small clones, contributing to a more precise evaluation of the treatment response. The serum FLC assay has high sensitivity and uses polyclonal antibodies specific to epitopes (which are only uncovered when light chains are free) in order to measure kappa, lambda lights chains, and its ratio. If the value of the ratio falls outside of the normal range, that can be due to the overproduction of one of the FLC, and therefore a monoclonal FLC is identified. Moreover, if the glomerular filtration rate is decreased, the serum concentration of FLC will increase, widening the ratio estimates. In order to increase the specificity, without losing sensitivity, adapted reference range values should be used.

Time-of-flight mass spectrometry and urinary exosomes are two new techniques with the ability to detect a very low amount of monoclonal Ig and distinguishing nephrotoxic from non-nephrotoxic monoclonal lights chains, respectively. [20]

Clonal identification

After the documentation of the monoclonal protein, the next step should be the identification and characterization of the clonal population of cells. In all patients a detailed hematologic evaluation should be carried out. This evaluation requires a sample of bone marrow, peripheral blood, as well as lymph nodes in some cases. The bone marrow biopsy or aspiration are usually enough to detect the clone. The type of underlying clone can be easily identified by morphological assessment. Nevertheless, additional studies may be necessary to complement the evaluation. On bone marrow biopsy, immunohistochemical staining for CD138 or CD5, CD10 and CD20 allows the identification of plasma cells and B cells population, respectively. Fluorescence in situ hybridization (FISH) can demonstrate restricted production of the monoclonal Ig, and flow cytometry can also be helpful in bone marrow aspirates, lymph nodes or peripheral blood. If no plasma cell clone is found on bone marrow or the paraprotein is IgM, further imaging studies to find the B-cell clone should be performed, which include conventional radiography, computer tomography scan (CT) of the chest, abdomen and pelvis and/ or 18-fludeoxyglucose positron emission tomography (PET)/CT. Any suspicious lymph nodes found should undergo a biopsy.[5,7,22,23] Furthermore, clone identification and characterization are critical not only in terms of diagnosis, but also in terms of therapeutic approach.

Diagnostic challenges

Besides the differential diagnosis between DDD and C3GN, provided by EM findings, other conditions should be excluded.

Post-infectious glomerulonephritis (PIGN) is a common misleading diagnosis.[24]

About 30% of PIGN can have isolated C3 deposits with no Ig, particularly during the late stage. But distinction from C3GN can be made as the clinical and laboratory findings of PIGN are self-limited, with normalization usually within 8 weeks of resolution of the infection.[10] Therefore, progressive renal impairment, persistent hypocomplementemia, hematuria and proteinuria after 12 weeks should raise the suspicion of C3GN, and a repeat renal biopsy is required. Of note, some studies suggest that some cases of PIGN might take longer to resolve, and are classified as 'atypical'. Furthermore, when an infection occurs, it can act as a trigger to the alternative pathway, which normalizes with the resolution of the infection. However, in patients with a defect of the alternative pathway, the infection may unmask or exacerbate this abnormality, and consequently the clinical and laboratory features may have a slower rate of resolution. In these cases, an overlap between C3GN and 'atypical' PIGN in biopsy findings might be found, underlining the importance of a detailed evaluation of the clinical history to achieve the correct diagnosis.[24]

Approximately 5% - 10% of patients with monoclonal gammopathy in whom renal biopsy shows a C3GN will, in fact, have a membranoproliferative glomerulonephritis with masked monoclonal deposits.[23] In order to avoid misdiagnosis, all patients diagnosed with C3GN associated with monoclonal gammopathy should undergo a pronase immunofluorescence.[25] This technique uses a paraffin-embedded tissue with an antigen-retrieval step by pronase digestion, which helps to unmask monoclonal deposits. In spite of being more sensitive as an unmasking technique, it has poor sensitivity for grading C3 staining intensity when compared with immunofluorescence on frozen tissue.[25,26] Along with no masked Ig deposits on pronase immunofluorescence, the absence of C4d staining can also be helpful to exclude immune complex glomerulonephritis.[10,27]

In conclusion, the diagnosis of C3GN associated with MGRS is a diagnosis of exclusion that requires a renal biopsy, albeit with some pitfalls for misdiagnosis. Achieving the right diagnosis requires a high index of suspicion during all the steps of the evaluation.

Treatment

The best treatment for C3GN associated with MGRS has not been established. However, after the diagnosis of C3GN, all patients require renoprotective treatment, adequate nutrition, and modification of unhealthy lifestyle behaviors. Renoprotective treatment includes angiotensin-converting enzyme inhibitors or angiotensin-receptor

blockers as first-line therapy for proteinuria and hypertension, and lipid-lowering agents in case of dyslipidemia. Nevertheless, this treatment may not be sufficient to prevent ESRD. However, in addition to immunosuppressant treatment, it contributes to better renal outcomes.

Despite the absence of specific guidelines for the treatment of C3GN associated with MGRS, there is some evidence that Ig-target therapy is useful in delaying the progression of renal disease, highlighting the correlation between the reduction of monoclonal Ig and better renal outcomes.[7,11] Moreover, successful treatment favors the risk reduction of recurrence of C3GN after renal transplantation. Treatment should be initiated even in patients with advanced renal disease, as long as kidney transplantation is being considered.[21] The type and nature of monoclonal protein is important for the selection of Ig-targeted agent, but the clinician also has to take into account histological features of C3GN (balance between active and chronic lesions), renal function, and potential toxicity, which can preclude some of them.[28]

Bortezomib is a proteasome inhibitor preferred in MGRS with no need of dose adjustment in patients with chronic kidney disease (CKD), including in patients on dialysis. By itself, bortezomib can achieve a response rate between 30% and 50%, and when associated with dexamethasone and cyclophosphamide, the rate can increase up to 94%.[8,22] A clone with high expression of CD20, particularly a B cell clone, rituximab, an anti-CD20 monoclonal antibody, is a drug not to be overlooked, and full doses can also be given in CKD without the need for dose adjustments.[22] Among cytotoxic therapies, cyclophosphamide and melphalan, whose target are both plasma and B cells, are also optimal choices in MGRS. The first one is used more often, and is typically given at full doses, without hematologic stem cell toxicity. Melphalan is usually considered in candidates for autologous stem cell transplantation, but it requires dose adjustment in patients with CKD stage ≥ 3. Another option is bendamustine. Thalidomide is an immunomodulatory drug with activity against plasma and B cells, albeit with potential neurotoxicity.[29] Despite activity against B cells, purine analogs should be avoided due to the need of renal dose adjustment, and high risk for the development of adverse effects.[22,28] Furthermore, in patients with a plasma cell disorder, autologous stem cell transplant can be beneficial as a complementary therapy, helping to achieve a deeper and sustained or even a complete hematological response, which is essential to reduce the risk of recurrence, particularly after renal transplant.[21]

As a consequence of the lack of standardized therapies, treatment options should be carefully evaluated in each case in terms of risk/ benefit ratio.[28] Nevertheless, patients should be followed-up regularly by a nephrologist and a hematologist not only to prevent progression of renal damage, but also to detect early recurrence of monoclonal gammopathy and potential progression to a hematologic malignant disease, like MM.[30]

DISCUSSION

The best example of a case of MGRS-associated disorder without deposits of monoclonal Ig is C3GN, where monoclonal protein causes renal damage indirectly through continuous activation of the alternative pathway of the complement system. This glomerulonephritis typically presents with hematuria, proteinuria, and renal impairment. Besides a careful anamnesis, physical examination and biochemical tests, a renal biopsy is required not only to determine the nature and severity of the lesion, but also to confirm the diagnosis. Immunofluorescence microscopy must show a predominant C3 staining, and EM findings are essential to differentiate C3GN from DDD. Complement evaluation should also be done in all patients, and should include measurement of complement proteins, genetic testing, screening for autoantibodies and functional assays of complement activity. In this evaluation, C3 serum levels are typically low because of the dysregulation of the alternative pathway, C5 and C5b-9 serum levels might be low and elevated respectively, as a result of the uncontrolled activation of the terminal pathway that can also occur.

Given the evidence that the incidence of monoclonal gammopathy in the general population increases with age, particularly in C3GN where it reaches a significant proportion in patients older than 50 years, screening for monoclonal Ig is highly recommended, and clonal identification should follow monoclonal protein documentation. Pronase immunofluorescence should also be done to exclude unmasked Ig deposits, in order to avoid misdiagnosis with other membranoproliferative glomerulonephritis, specifically those that are immune complex mediated.

There are no standardized guidelines for treatment, and effective therapy requires an individualized approach, evaluating the risk/benefit ratio. Besides general renoprotective measures, treatment should focus on the hematologic disease given the correlation between hematologic response and renal outcomes, in addition to the prevention of recurrence after renal transplantation.

CONCLUSION

C3GN associated with MGRS is a diagnosis of exclusion, requiring a high index of suspicion during all the steps of evaluation. Clinical awareness is required in order to provide an early diagnosis, avoid delays in treatment initiation, and improve outcomes.

CONFLICTS OF INTEREST

The authors declare they have no conflict of interest.

FUNDING SOURCES

No funding was received for this study.

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Antibody Negative Autoimmune Encephalitis: A Case Report

Encefalite Autoimune Sem Anticorpo Identificado: Um Relato de Caso

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Acta Med Port 2021 May;34(5):378-382 ▪ https://doi.org/10.20344/amp.13793

ABSTRACT

Encephalitis is characterized by inflammation of the brain. Literature describes autoimmune as one of the most common aetiology of non-infectious encephalitis. Given the similarities in clinical, imagological and laboratory findings with viral encephalitis and due to the wide variety of clinical features, the diagnosis is rather challenging and therefore physicians need an increased clinical suspicion to make the correct diagnosis. We report a case of a 35-year-old male with no past medical history that presented with two episodes of autoimmune encephalitis in a 6-month period. Despite having the typical clinical presentation and imagological findings consistent with autoimmune encephalitis, this case had negative results for antibodies, which delayed the diagnosis. It is essential to highlight the importance of considering the hypothesis of autoimmune aetiology on the differential diagnosis of all patients presenting with clinical and magnetic resonance imaging results suggestive of probable encephalitis, regardless of the negative antibodies results. This case clearly depicts the difficulties of diagnosing and treating an autoimmune encephalitis. The main goal of this case report is to increase awareness towards early diagnosis to promptly implement a specific treatment that has proven to improve the outcome and prognosis.
Keywords: Autoantibodies; Encephalitis/diagnosis; Encephalitis/diagnostic imaging; Immunotherapy

RESUMO

A encefalite é caracterizada por inflamação cerebral. A literatura descreve a etiologia autoimune como uma das causas mais frequentes de encefalite não infeciosa. Dadas as semelhanças dos resultados laboratoriais e imagiológicos com a encefalite viral, e devido a uma extensa variedade de manifestações clínicas, o diagnóstico é desafiante, pelo que os médicos precisam de maior suspeita clínica realizarem um diagnóstico correto. Relatamos o caso de um indivíduo de 35 anos, do sexo masculino, sem antecedentes pessoais de relevo, que apresentou dois episódios de encefalite autoimune num período de seis meses. Não obstante uma apresentação clínica e imagiológica típica de encefalite autoimune, o doente apresentava resultados negativos para anticorpos, o que atrasou o diagnóstico. É importante considerar a hipótese de etiologia autoimune no diagnóstico diferencial de todos os pacientes que apresentem sintomas clínicos ou resultados de ressonância magnética nuclear sugestivos de provável encefalite, independentemente da presença ou ausência de anticorpos. Este caso retrata claramente as dificuldades de diagnóstico e tratamento de uma encefalite autoimune. O principal objetivo deste relato de caso é salientar a importância do diagnóstico precoce, que permite implementar rapidamente uma terapêutica específica, e demonstrou melhorar o prognóstico e suavizar as consequências da doença.
Palavras-chave: Autoanticorpos; Encefalite/diagnóstico; Encefalite/diagnóstico por imagem; Imunoterapia

INTRODUCTION

Encephalitis is characterized by inflammation of the brain. The literature describes autoimmune encephalitis as one of the most common types of non-infectious encephalitis (data from northern Europe shows that autoimmune encephalitis comprises almost 20% of all cases of encephalitis).[1] The most common form of autoimmune encephalitis (AIE) is the type associated with antibodies against the *N*-methyl-D-aspartate receptor (NMDAR). A study showed that the frequency of this AIE surpassed the frequency of any individual viral cause of encephalitis in young individuals.[2] Encephalitis characterized by antibodies against leucine-rich, glioma-inactivated 1 (LGI1) is the second most frequent AIE.[3]

AIE may present a range of clinical features including behavioural changes, impaired memory and cognition, psychiatric symptoms, involuntary movements, altered level of consciousness and seizures. Tumours (paraneoplastic) and infections (parainfectious) are frequent triggers of encephalitis.[1,4]

Because of the similarities in the clinical, imaging and laboratory findings with viral encephalitis, the diagnosis of AIE is rather challenging and physicians require increased awareness and clinical acumen to make the correct diagnosis.

AIE was not described until 2007 because of the lack of specific clinical symptoms, laboratory, and magnetic resonance imaging (MRI) results.[5] When these three parameters are combined, as shown in this case report, the diagnosis of definite AIE can be made, enabling specific therapeutic interventions that if performed at an early stage can significantly improve the outcome.[6]

It is important to acknowledge that patients with AIE may present seronegative cerebrospinal fluid (CSF) and therefore antibody testing is not pathognomonic.

CASE PRESENTATION

A 35-year-old healthy male, without any significant past medical history presented at the emergency department

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Recebido: 25 de março de 2020 - **Aceite:** 21 de julho de 2020 - ***First published*:** 31 de dezembro de 2020 - ***Online issue published*:** 03 de maio de 2021

(ED) in January 2019 with behaviour disturbances in the previous five days and speech disturbances in the previous twenty-four hours. There was a suspicion that he had a seizure before coming to the ED. No sphincter incontinence or tongue biting was noticed. In the previous five days, he had been experiencing periods of confusion, sweating, and fainting sensation from which he spontaneously recovered. There was no prior history of seizures, loss of consciousness, or drug use. Simultaneously, he had an unintentional weight loss of 10 kg in eight months, anorexia, and vomiting.

Physical examination was normal. On neurological examination, he was awake and presented global aphasia (non-fluent speech, he was unable to repeat words or to follow commands), without any other focal neurologic deficits. There were no meningeal signs. Brain computed tomography (CT) was normal. The electroencephalography (EEG) revealed a probable complex partial status epilepticus (frequent left frontotemporal paroxysmal activity). The MRI showed a hyperintense signal on T2-weighted/FLAIR on the medial left temporal lobe (Fig. 1).

CSF showed pleocytosis (47 cells) with mononuclear predominance and elevated proteins (67 mg/dL). The suspicion of a seizure combined with the MRI hyperintense signal on the left temporal lobe was suggestive of herpes simplex encephalitis (HSE).[7]

He was first treated with phenytoin 750 mg IV for reversal of status epilepticus and then started a 21-day cycle of acyclovir 750 mg 8/8 hours for presumed HSE. The microbiological study of CSF was unremarkable [polymerase chain reaction (PCR) with both negative serology and bacteriological study – *HSV-1*, *HSV-2, HHV-3,* Epstein-Barr virus, cytomegalovirus, *HHV-6, HHV-7, HHV-8* negative]. Lumbar puncture was not repeated, but lumbar puncture (LP) was performed three days after onset of symptoms. Blood cultures were also negative. He experienced considerable improvement with medication (recovery of normal behaviour and speech) and besides experiencing persecutory delusions while in the hospital, he was released with sporadic speech disorder and without full recovery of cognitive functions. There was a reversal of the imaging changes after treatment.

In July, six months later, he presented in the ED with behavioural and speech changes associated with right hemiparesis in the past 24 hours. His wife mentioned episodes of mental confusion and speech changes since his previous hospitalization. He also showed sudden impairment of consciousness (not reactive to stimuli), right arm clonic movements, and oculocephalic deviation to the right. He received antiepileptic treatment with slight improvement. The EEG was consistent with a complex partial status epilepticus (left temporal paroxysmal activity). Since the status epilepticus was refractory to the antiepileptic medication administered in the ED, he was transferred to the intensive care unit (ICU).

The brain CT showed a hypodensity in the left frontoparietal region. The MRI showed a hyperintense T2/Flair signal in the left frontoparietal and occipital region (Fig. 2). The lumbar puncture performed on the same day of the hospitalization showed CSF with mildly elevated proteins (71 mg/dL), mononuclear cells (25 cells) negative bacteriological examination, negative serologies, and negative cytology for neoplastic cells. The LP was repeated and showed clear and colourless CSF with mononuclear cells (seven cells)

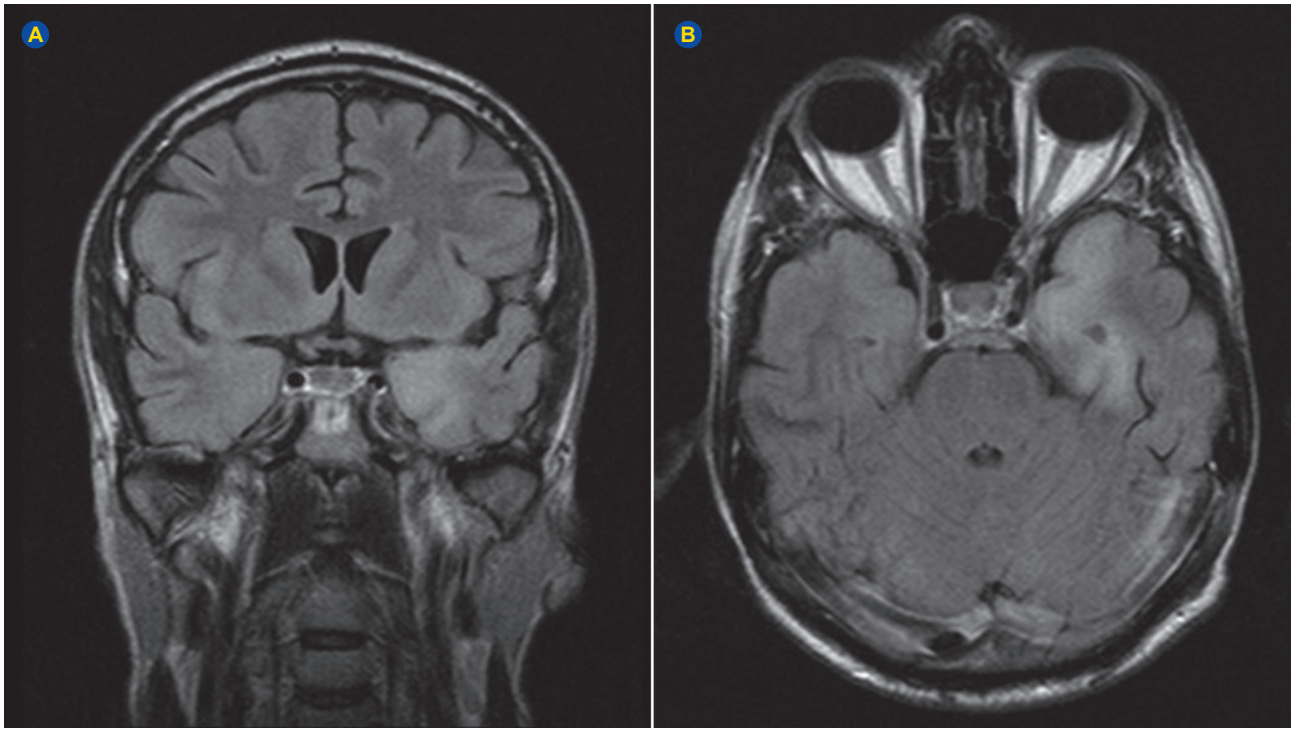

Figure 1 – MRI in February 2019 showed hyperintense signal on T2/FLAIR on the medial left temporal lobe in coronal and axial planes, respectively

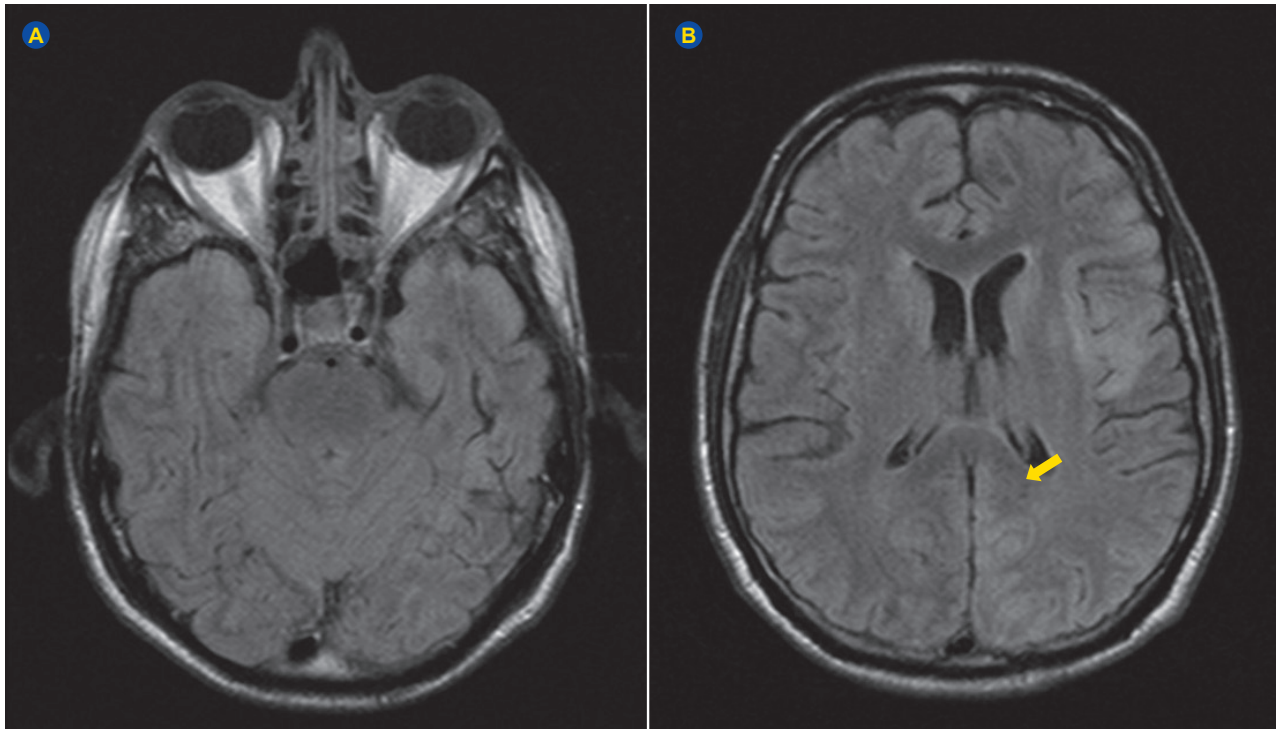

Figure 2 – MRI in July 2019 showed no changes on the previous lesion site (medial left temporal lobe) and showed hyperintense T2/FLAIR signal in the left frontoparietal and occipital region

and proteins (0.7 mg/dL), negative serology, bacteriological, and mycological examination. The autoimmune study was negative for anti VGKC, anti-NMDAR, anti-GABAa-R, anti-GABAb-R, anti-LGI1, anti- Ma2/Ta, anti-GAD, anti-MAG, anti-Hu and anti- CV2 (immunoblotting and indirect immunofluorescence assay) The diagnostic study in blood culture, urine culture and CSF (PCR) was negative for HSV-1, *HSV-2, HHV-3,* Epstein-Barr virus, cytomegalovirus, *HHV-6, HHV-7, HHV-8,* Enterovirus, *Treponema pallidum*, HBV, HIV, HTLV, Mycobacterium tuberculosis, *Borrelia burgdorferi*, tick-borne encephalitis virus (TBEV), *Anaplasma phagocytophilum*, *Ehrlichia chaffeensis/ Ehrlichia muris*, human polyomavirus 2 (JC), polyomavirus BK.

To exclude paraneoplastic causes, a thoracoabdominal pelvic CT scan was performed, with no relevant alterations.

In the ICU he was treated first with a 5-day cycle of high-dose methylprednisolone with a progressive reduction in oral dose associated with a 5-day cycle of immunoglobulin. Simultaneously, he also received a 21-day cycle of acyclovir. He was also treated for a urinary tract infection with amoxicillin and clavulanic acid. He progressively showed some slight improvements in speech and motor functions (ability to follow commands, articulate words, and phrases, improved spatial and self-orientation), with successful treatment of the complex partial status epilepticus. The patient was released in August with antiepileptic medication (levetiracetam, lacosamide, and clobazam) and periodic appointments to assess the mental status and investigate a possible paraneoplastic cause.

On a follow-up clinic in November, although maintaining normal speech and motor functions, he had a clear limitation in time, spatial, and self-orientation and showed considerable memory loss with implications in daily life activities. He presented a score of five in the Montreal Cognitive Assessment (MoCA).

DISCUSSION

This case presents the challenges of diagnosing AIE, since the patient, despite having the typical clinical presentation and imaging findings consistent with AIE, had negative results for antibodies in blood and CSF. Such cases can be misdiagnosed as viral encephalitis. This case report highlights the importance of considering the hypothesis of autoimmune aetiology on the differential diagnosis of all patients presenting with clinical and MRI results suggestive of probable encephalitis regardless of the negative antibody results. Confirmatory antibody testing should be required, but a negative result does not exclude the diagnosis, especially if other possible causes are excluded. The diagnostic criteria for the different types of AIE were published by Graus *et al* in 2016.

The hypothesis of autoimmune encephalitis after herpes simplex encephalitis (post-herpetic anti-NMDA encephalitis) should be considered. In fact, a prospective observational study showed that 27% of patients present with AIE after HSE. These patients developed neuronal antibodies (100%), usually within two months after treatment of HSE.[8,9]

Therefore, the clinical findings do not completely substantiate this hypothesis as the results for infection by herpesviruses were negative and there were no antibodies for NMDA receptors or neuronal antigens in the CSF. Therefore, this case, and according to the criteria mentioned

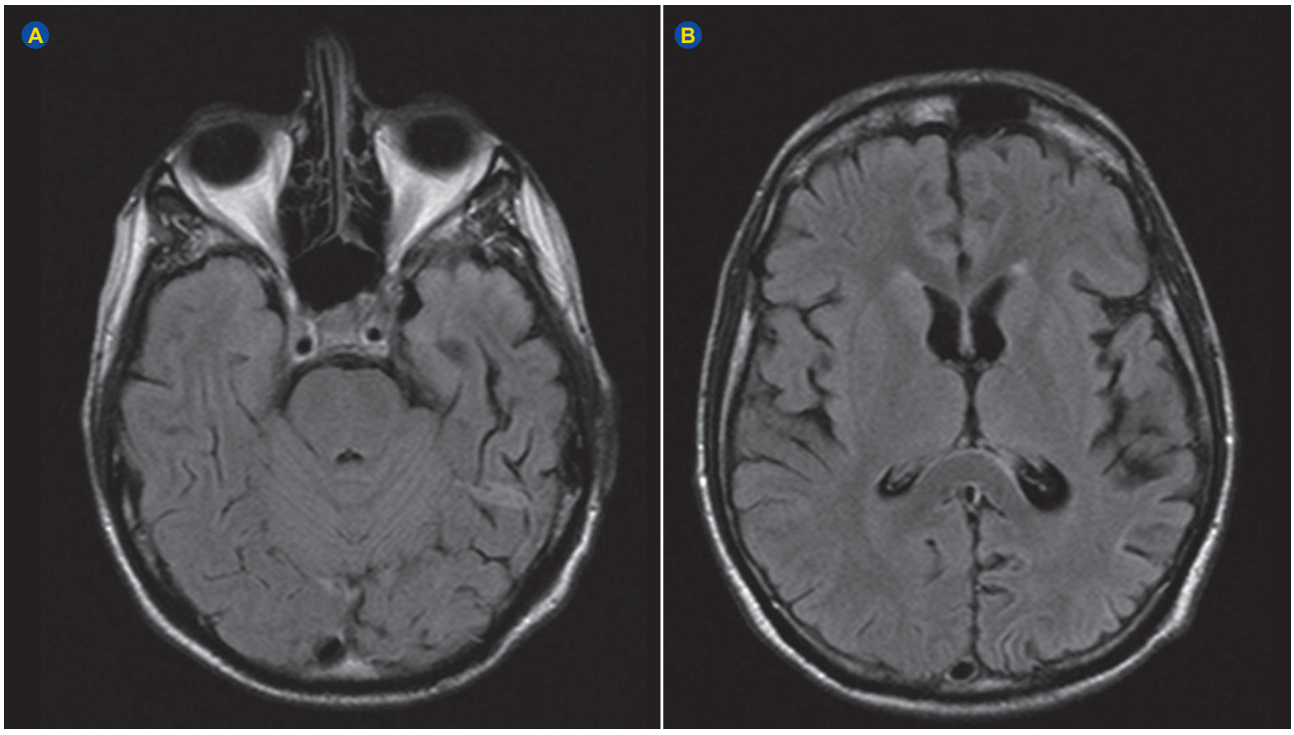

Figure 3 – MRI in August 2019 showed reversal of imaging changes with increased peripheral cortical sulci, probably due to post encephalitis brain atrophy

Table 1 – Diagnostic criteria for negative-antibody probable encephalitis

1. Rapid progression (less than 3 months) of working memory deficits, altered mental state or psychiatric symptoms;
2. Exclusion of known syndromes of autoimmune encephalitis (e.g. ADEM typical limbic encephalitis)
3. Absence of antibodies in serum and CSF, and at least two of the following criteria: • MRI findings suggestive of autoimmune encephalitis • CSF pleocytosis or CSF-specific oligoclonal bands or elevated CSF IgG index • Brain biopsy showing inflammatory infiltrates and excluding other causes
4. Exclusion of alternative etiologies
Only if all of the four criteria have been met, diagnosis can be made

ADEM: acute disseminated encephalomyelitis; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid

above, presents a probable diagnosis of antibody negative AIE.[10] Noteworthy, this is the best available diagnosis concerning this case, and is not a definitive one.

This case report presents limitations, particularly the fact that not all commercially available antibodies were tested (for example anti-RI, anti-Yo, anti-CASPR2, anti-AMPA) and the screening in cells/tissues samples would be necessary for the definitive diagnosis of antibody negative autoimmune encephalitis.

Currently, the guidelines for diagnosis suggest that a complete antibody panel (intracellular, surface antigen and ion channels) should be done if there is a suspicion of AIE.[11]

Treatment for probable encephalitis is frequently given empirically prior to the results. In this case, acyclovir was given empirically for presumed HSE. The same reasoning can be used, prior to antibody results, with probable AIE, because clinical presentation and treatment response of antibody negative cases does not differ significantly from definitive AIE. Therefore, in suspected patients of AIE based on probable diagnosis, starting first line therapy, which consists of methylprednisolone, IVIG and/or plasmapheresis (there is no strong evidence of a difference in efficacy between IVIG and plasmapheresis), is recommended. First line immunotherapy can be given sequentially if no improvement is shown.[6,12] In the absence of response, second line therapy should be started with rituximab or cyclophosphamide.[6,12] The treatment should not be delayed since the evidence suggests early immunotherapy is associated with favourable outcomes and better prognosis.[1,11,12]

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 2013 Helsinki Declaration of the World Medical Association.

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.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Intoxicação por Lítio após Cirurgia Bariátrica: Um Caso Clínico

Lithium Intoxication after Bariatric Surgery: A Case Report

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Acta Med Port 2021 May;34(5):382-386 ▪ https://doi.org/10.20344/amp.12868

RESUMO

A cirurgia bariátrica é uma opção terapêutica no tratamento da obesidade em doentes cuidadosamente selecionados, com perturbação psiquiátrica. Cerca de metade dos doentes referenciados para cirurgia bariátrica têm diagnosticada, pelo menos, uma perturbação mental, estando a maioria medicada com psicofármacos. Este procedimento pode alterar significativamente a biodisponibilidade dos fármacos e o lítio não é exceção. Contudo, apesar da absorção parecer diminuir na maioria dos fármacos, no caso do lítio existe um elevado risco de toxicidade. Neste artigo, descreve-se o caso de uma doente de 44 anos com um quadro de intoxicação por lítio após cirurgia bariátrica. Realizou-se uma revisão dos casos clínicos descritos na literatura de toxicidade ao lítio pós-cirurgia bariátrica e apresentam-se potenciais soluções clínicas preventivas. É essencial uma maior consciencialização das alterações na absorção dos psicofármacos pós-cirurgicos, particularmente no caso do lítio. Recomenda-se fortemente uma monitorização, de forma mais regular, pós-cirúrgica clínica e laboratorial dos níveis séricos de lítio.

Palavras-chave: Cirurgia Bariátrica; Lítio/efeitos adversos; Lítio/intoxicação

ABSTRACT

Bariatric surgery is a therapeutic option to treat obesity in (carefully selected) patients with psychiatric disorders. About half of the patients referred for bariatric surgery have a diagnosis of (at least one) mental disorder and most of them are treated with psychotropic drugs. This procedure may modify the bioavailability of drugs and lithium is no exception. However, although absorption seems to decrease in most drugs, in the case of lithium, there is a high risk of toxicity. In this article, we describe the case of a 44-year-old female patient with lithium intoxication after bariatric surgery. We conducted a review of the published clinical cases in the scientific literature about lithium toxicity after bariatric surgery, and we propose potential preventive clinical solutions. It is essential to increase awareness of changes to the absorption of psychotropic drugs in the post-surgery period, particularly in the case of lithium. Regular postoperative clinical and laboratory monitoring of lithium serum levels is strongly recommended.

Keywords: Bariatric Surgery; Lithium /adverse effects; Lithium/poisoning

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Recebido: 24 de setembro de 2019 - **Aceite:** 13 de novembro de 2019 - ***First published*:** 16 de setembro de 2020- ***Online issue published*:** 03 de maio de 2021

INTRODUÇÃO

A cirurgia de *bypass* gástrico tornou-se, nas últimas décadas, um tratamento cada vez mais frequente da obesidade.[1] A obesidade é uma doença crónica com múltiplas consequências médicas, sendo que para alguns doentes, dieta e exercício físico, bem como a utilização de fármacos psicotrópicos não associados a aumento de peso, não são uma opção suficiente ou viável.[2] São muitos os fatores que podem contribuir para a obesidade, sendo que no caso de pessoas com perturbação mental, o aumento de peso pode estar associado a alterações no estilo de vida (sedentarismo pela avolia, anedonia e isolamento social), alterações da dieta habitual (hiperfagia para pseudocompensação do humor, ou alterações da preferência alimentar), a efeitos adversos dos psicofármacos, entre outros.[3] A cirurgia bariátrica apresenta-se, nestes doentes, como uma alternativa de tratamento da obesidade e consequentes comorbilidades médicas.[2]

A prevalência de pelo menos uma perturbação psiquiátrica em doentes referenciados para cirurgia bariátrica é significativa (62,2%), sendo frequente a perturbação depressiva e/ou perturbação de ingestão compulsiva. O tratamento psicofarmacológico é comum, principalmente com antidepressivos.[3] Dado que a cirurgia bariátrica provoca alterações anatómicas e fisiológicas que poderão ter impacto na absorção dos fármacos, é essencial para os clínicos conhecerem quais as consequências na farmacocinética dos mesmos após este procedimento cirúrgico.[4]

O lítio é um dos tratamentos de primeira linha na perturbação afetiva bipolar e com eficácia comprovada em outras doenças mentais. Porém, a sua janela terapêutica é estreita e a sua farmacocinética sofre modificações após a cirurgia bariátrica que implicam um acompanhamento multidisciplinar.

Neste caso clínico, descreve-se o caso de uma doente com perturbação afetiva bipolar, estabilizada há vários anos com lítio, que é admitida por um quadro clínico compatível com intoxicação grave ao lítio, um mês após *bypass* gástrico. Apresenta-se também uma revisão da escassa literatura existente sobre os mecanismos subjacentes, desafios e potenciais soluções.

CASO CLÍNICO

Mulher de 44 anos com antecedentes médicos de perturbação afetiva bipolar, diabetes *mellitus* tipo II, dislipidémia, hipertensão arterial e obesidade mórbida, tendo sido submetida um mês antes da observação em serviço de urgência (SU) a uma cirurgia bariátrica (técnica de *bypass* gástrico Roux-en-Y). Na observação em SU apresentava um quadro clínico com uma semana de evolução de agravamento progressivo, caracterizado por confusão mental,

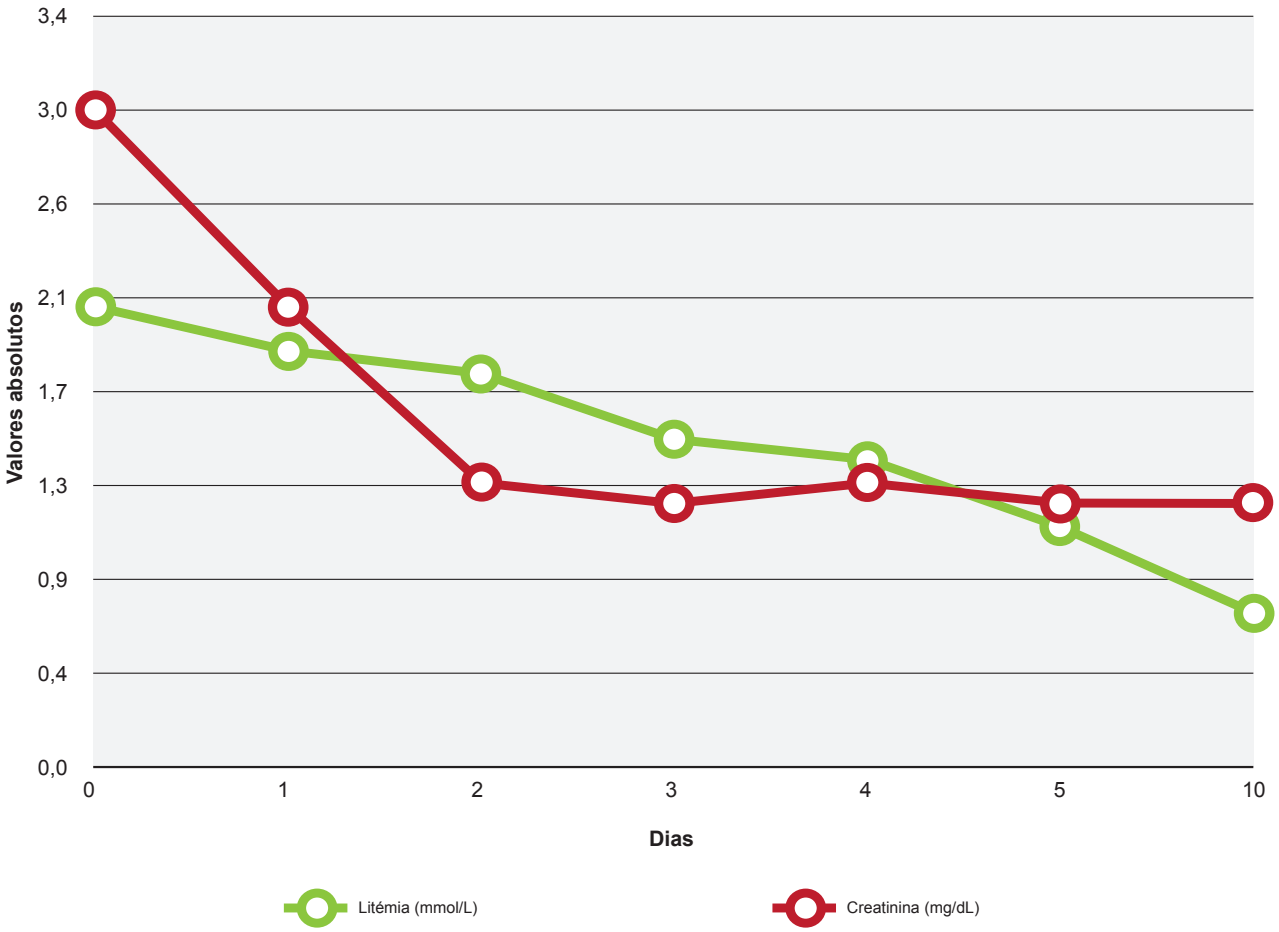

Figura 1 – Evolução dos valores de litémia e função renal, após suspensão de lítio e fluidoterapia

fadiga persistente, fraqueza muscular marcada, tremores exuberantes dos membros superiores, dificuldades na coordenação motora, náuseas e diarreia. A medicação psicotrópica habitual diária, revista seis meses antes, seria quetiapina 300 mg, fluoxetina 20 mg, lorazepam 5 mg e carbonato de lítio 600 mg de libertação prolongada (litémia habitual 0,7 mmol/L, terapêutica crónica há oito anos). No exame físico apresentava-se hemodinamicamente estável, apirética, salientando-se no exame neurológico sumário ataxia e hiperreflexia. A doente encontrava-se obnubilada, desorientada no tempo e espaço, com atenção captável mas facilmente dispersável e marcada perseveração ideativa, incapaz de colaborar na realização do restante exame mental. Analiticamente, salientava-se insuficiência renal aguda (creatinina 3,0 mg/dL, ureia 130 mg/dL) e hiponatrémia (128 mEq/L).

Após doseamento de litémia, que se apresentava em níveis de 2,1 mmol/L (toxicidade > 1,5 mmol/L), assumiu-se quadro de intoxicação por lítio e foi internada no serviço de Medicina Interna. Optou-se por abordagem conservadora inicial (suspensão de lítio e hidratação por fluidoterapia), que se manteve pela rápida e progressiva melhoria clínica e analítica, em cinco dias, como verificado na Fig. 1.

Por manutenção de níveis de creatinina no limite superior normal (valores de referência: 0,6 a 1,1 mg/dL) e dificuldade na depuração total de lítio, optou-se pela não reintrodução do fármaco, com manutenção de humor eutímico e sem oscilações da energia vital.

DISCUSSÃO

A cirurgia bariátrica provoca alterações anatómicas e fisiológicas que poderão ter impacto na absorção oral dos fármacos. Os procedimentos que provoquem mal-absorção (*bypass* e derivação biliopancreática) têm maior impacto na farmacocinética dos fármacos, destacando-se como alterações farmacocinéticas características a redução da acidez gástrica, a redução do volume e motilidade do estômago, esvaziamento gástrico e trânsito intestinal acelerados.[4]

Um estudo *in vitro*, mostrou que a dissolução de fármacos estaria reduzida em 10 de 22 psicofármacos testados, porém no lítio, esta taxa estaria aumentada em mais de 200%.[5, 6]

O lítio é rápida e totalmente absorvido no estômago e intestino proximal. É hidrofílico e não se liga a proteínas, não sofre metabolização, sendo excretado pelo rim praticamente na totalidade. Níveis séricos entre os 0,6 e 1,0 mmol/L são considerados terapêuticos na pperturbação afetiva bipolar (doses mais altas, entre 1,0 e 1,2 mmol/L, estão indicadas para tratamento e prevenção da mania aguda), sendo considerados tóxicos quando acima de 1,5 mmol/L (toxicidade ligeira: 1,5 - 2,5 mmol/L; toxicidade moderada: 2,5 - 3,5 mmol/L; toxicidade grave: > 3,5 mmol/L).[7,8] Os sintomas de toxicidade associada ao lítio são descritos na Tabela 1.[7]

Dentro dos fatores de risco principais para toxicidade temos: interações medicamentosas (anti-inflamatórios não esteroides, diuréticos e IECA/ARA), idade avançada, doença crónica e dose total diária de lítio.[9]

A intoxicação por lítio, nestes casos, é essencialmente provocada pelas reduções de volume de água e massa corporal: a redução de aporte líquido provoca desidratação e, consequente lesão renal aguda, diminuindo a depuração de lítio; no caso particular do carbonato de lítio, o menos solúvel de todos os sais de lítio, tais alterações levam à sua acumulação e absorção prolongada; verifica-se também que, no geral, doentes obesos apresentam aumento da capacidade de depuração de lítio.[10-15]

Neste caso clínico, optou-se por uma abordagem

Tabela 1 – Manifestações clínicas da intoxicação por lítio[6]

Neuropsiquiátricas	Tremor, apatia, sonolência, agitação, disartria, ataxia, nistagmo, movimentos coreiformes, hiperreflexia, mioclonias, confusão mental, convulsões, coma.
Cardíacas	Alterações do ECG do tipo '*wandering atrial pacemaker*', bradicardia sinusal, supra- e infradesnivelamento do segmento ST, inversão da onda T, QT longo.
Gastrointestinais	Náuseas, vómitos, dor abdominal, distensão abdominal e diarreia.

Tabela 2 – Recomendações para hemodiálise na intoxicação a lítio[8]

Indicações
Hemodiálise é recomendada: - Se insuficiência renal e litémia > 4,0 mmol/L; - Se diminuição do nível de consciência, convulsão, ou arritmia grave (independentemente dos níveis séricos de lítio).
Hemodiálise é sugerida: - Se litémia > 5,0 mmol/L; - Se síndrome confusional; - Se tempo estimado para alcançar litémia < 1,0 mmol/L, em condições ótimas, for > 36 horas.
Interrupção
- Quando litémia < 1,0 mmol/L ou evidência de melhoria clínica; - Após um mínimo de 6 horas de hemodiálise, na ausência de resultado de doseamento sérico. Realizar doseamentos seriados durante 12 horas, após interrupção, para determinar continuidade de tratamento.

Tabela 3 – Recomendações para monitorização dos níveis de lítio[15]

Fase peri-operatória	Recomendações
Pré-operatória (durante período de dieta líquida)	Doseamento semanal
Pós-operatório (0 - 6 semanas)	Doseamento semanal
Pós-operatório (> 6 semanas)	Doseamento quinzenal até aos 6 meses Dosemento mensal após 6 meses Doseamento na regularidade habitual após um ano

Se os níveis séricos aumentarem mais de 25% ou se aproximarem de 1,2 mmol/L, considerar reduzir a dose.
Se sinais de toxicidade, rever dose.
Avaliar estado mental periodicamente, recorrendo a escalas formais se possível.
Incentivar reforço hídrico oral (2,5 - 3 L/dia) na fase pré-operatória.

conservadora, ainda que a hemodiálise fosse uma abordagem possível e frequentemente necessária. As recomendações para hemodiálise são apresentadas na Tabela 2.[8]

Ainda que a toxicidade seja a preocupação mais importante nestes doentes, níveis subterapêuticos podem também ter consequências significativas em doentes com perturbações do humor graves. Dada a imprevisibilidade da absorção e outras alterações farmacocinéticas, os níveis subterapêuticos são também teoricamente possíveis, uma vez que a absorção do lítio se encontra condicionada pela redução de intestino funcional.[15]

O caso clínico apresentado alerta-nos para as particularidades de uma população especial de doentes. Ainda são raros os casos descritos na literatura científica internacional de intoxicações iatrogénicas a psicofármacos após cirurgia bariátrica. Uma proporção significativa de doentes que são submetidos a este tipo de intervenção sofrem de doença psiquiátrica, podendo a etiologia da obesidade (inevitavelmente multifatorial) ser consequência da doença e/ou dos efeitos iatrogénicos do tratamento. Assim sendo, e perante algum grau de desconhecimento e imprevisibilidade ainda existente relativamente ao grau de absorção dos psicofármacos, é recomendável um acompanhamento regular e uma boa articulação entre as equipas de cirurgia bariátrica e psiquiatria na gestão destes casos.

Não existem, até à data, *guidelines* baseadas em evidência científica publicadas relativamente à abordagem de doentes sob lítio, sujeitos a cirurgia bariátrica. Porém, baseado nos dados da literatura e na opinião de peritos, algumas recomendações podem ser feitas, designadamente, uma monitorização pós-cirúrgica clínica e laboratorial dos níveis de lítio sérico mais regular, como se pode verificar na Tabela 3.[15] Mais investigação sobre as alterações farmacocinéticas após este tipo de intervenções, nomeadamente a longo prazo, são necessárias para um acompanhamento clínico sustentado em maior evidência.

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 publicada em 2013.

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

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

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Sturge-Weber Syndrome: An Extensive Cutaneous Presentation

Síndrome de Sturge-Weber: Uma Apresentação Cutânea Extensa

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Acta Med Port 2021 May;34(5):387-387 ▪ https://doi.org/10.20344/amp.12671

Keywords: Glaucoma; Neurocutaneous Syndromes; Port-Wine Stain; Sturge-Weber Syndrome
Palavras-chave: Glaucoma; Mancha Vinho do Porto; Síndrome de Sturge-Weber; Síndromes Neurocutâneas

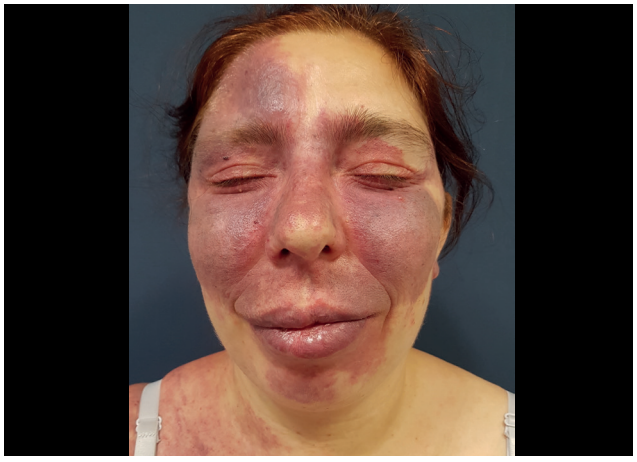

Figure 1 – Port-wine stain covering the right forehead, and the bilateral eyelids, maxillary region and chin

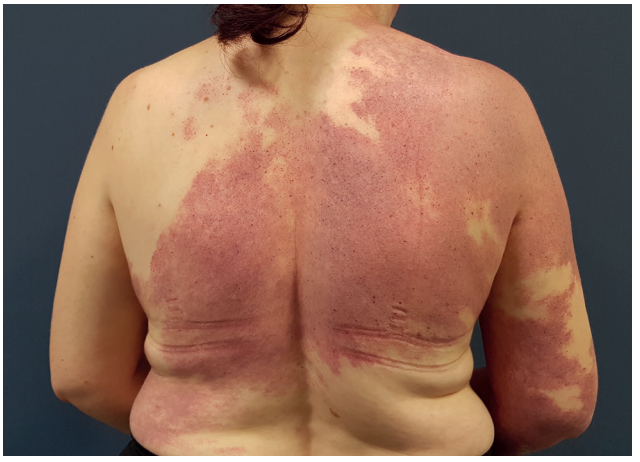

Figure 2 – Port-wine stain covering the posterior trunk and the right upper limb

A 40-year-old woman presented with a congenital and generalized port-wine stain. Her medical history was relevant for bilateral glaucoma and seizures of infancy. The physical examination revealed multiple purple to red patches, with irregular, well-defined borders, spreading bilaterally from the face (Fig. 1) to the trunk, right upper limb (Fig. 2) and thighs, without body asymmetries. The magnetic resonance imaging showed slight atrophy of the temporo-occipital right lobe, leptomeningeal enhancement and hypertrophy of the choroid plexus. The clinical and imaging findings supported the diagnosis of Sturge-Weber syndrome. The patient was referred for pulsed dye laser and maintained multidisciplinary follow-up.

Sturge-Weber syndrome is caused by a somatic mosaic mutation in the *GNAQ* gene, which induces malformations in the cephalic embryonic vasculature. It is characterized by a facial port-wine stain, often unilateral and rarely extra-facial, leptomeningeal angiomatosis and glaucoma.[1,2] Skin involvement significantly affects the quality of life of patients.[3] Nevertheless, neurological and ocular complications are the main prognostic determinants.[4]

PROTECTION OF HUMANS AND ANIMALS: The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013. **DATA CONFIDENTIALITY:** The authors declare having followed the protocols in use at their working center regarding patients' data publication. **INFORMED CONSENT:** Obtained. **CONFLICTS OF INTEREST:** All authors report no conflict of interest. **FUNDING SOURCES:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido: 09 de agosto de 2019 - **Aceite:** 26 de dezembro de 2019 - ***Online issue published*:** 03 de maio de 2021

Proposta de Protocolo para Redução dos Riscos e Otimização da Sensibilidade nos Exames de Imagem em Pessoas com Diabetes

Proposal for a Guideline of Risk Reduction and Sensitivity Optimization in Imaging Tests for People with Diabetes

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Acta Med Port 2021 May;34(5):388-394 ▪ https://doi.org/10.20344/amp.15486

RESUMO

A diabetes é uma doença crónica muito frequente na população portuguesa, sendo a sua prevalência estimada de 13,6% nos adultos. A melhor preparação e os riscos associados à realização de exames de imagem em pessoas com diabetes são frequentemente objeto de dúvidas. Neste artigo, pretendemos rever as principais precauções e sugerir um protocolo de atuação, de forma a reduzir os riscos e otimizar a sensibilidade destes exames nesta população. Revemos também a necessidade de suspensão de metformina após a administração de contraste iodado endovascular, pelo risco de acidose láctica, as precauções em pessoas com diabetes insulinotratadas ou sob fármacos que apresentam maior risco de hipoglicemia na realização de exames de imagem que obriguem a jejum, e a influência da hiperglicemia e da terapêutica anti-diabética na sensibilidade da PET-FDG. Com a revisão deste tema e apresentação de um protocolo de atuação pretendemos desmistificar a orientação dos indivíduos com diabetes que vão ser submetidos a exames de imagem, tornando mais simples a sua gestão.

Palavras-chave: Diabetes Mellitus Tipo 1; Diabetes Mellitus Tipo 2; Diagnóstico por Imagem; Meios de Contraste; Tomografia com Emissão de Positrões

ABSTRACT

Diabetes is a very common chronic disease in the Portuguese population, with an estimated prevalence of 13.6% in the adults. Doubts often arise regarding the best preparation and the risks associated with doing imaging tests in these patients. In this article we intend to review the main precautions in imaging tests in people with diabetes and to suggest a guideline to reduce the risks and optimize the sensitivity of these tests in this population. The main topics addressed in this article are the need to suspend metformin after the administration of endovascular iodinated contrast due to the risk of lactic acidosis, the precautions in insulin-treated patients or those taking medicines with a higher risk of hypoglycemia when performing imaging tests that require fasting, and the influence of hyperglycemia and of anti-diabetic therapy on the sensitivity of PET-FDG. With this review and the presentation of a guideline, we intend to demystify and simplify the management of individuals with diabetes who are undergoing imaging tests.

Keywords: Contrast Media; Diabetes Mellitus, Type 1; Diabetes Mellitus, Type 2; Diagnostic Imaging; Positron-Emission Tomography

INTRODUÇÃO

A diabetes é uma doença crónica cuja prevalência está a aumentar em todo o mundo.[1] Os últimos dados do Observatório Nacional da Diabetes apontam para uma prevalência na população portuguesa de 13,6% de indivíduos com diabetes e de 28,0% com pré-diabetes entre os 20 e os 79 anos.[2]

A utilização dos exames de imagem nestes doentes, à semelhança do que acontece na população geral, também tem sido crescente.[3,4] Frequentemente surgem dúvidas quanto à melhor preparação e quanto aos riscos associados à realização dos mesmos, em particular quando se administra contraste radiológico iodado endovascular.

Os exames de imagem que com maior frequência colocam problemas na pessoa com diabetes são: 1) os que envolvem a administração de contraste iodado endovascular (tomografia computorizada (TC) e angiografia), uma vez que podem provocar lesão renal aguda (LRA) associada ao contraste e propiciar acidose metabólica associada à utilização de metformina; 2) exames que obriguema jejum em indivíduos que estejam sob terapêuticas com risco de hipoglicemia, uma vez que podem aumentar o risco deste efeito secundário; 3) a tomografia com emissão de positrões (PET) com 18F-fluorodesoxiglicose (FDG), na qual tanto a hiperglicemia como algumas terapêuticas (metformina e insulina) podem diminuir a sensibilidade do exame.

Cerca de 90% das pessoas com diabetes têm diabetes tipo 2 (DM2), que se encontra associada ao excesso de peso/obesidade e envelhecimento.[5] Esta é provocada fundamentalmente por uma resistência periférica à ação da insulina associada a disfunção da célula β pancreática.[5,6] A prevalência estimada de diabetes tipo 1 (DM1) na Europa é de 2,12/10 000 habitantes e encontra-se também a

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Recebido: 10 de dezembro de 2020 - **Aceite:** 19 de fevereiro de 2021 - ***First published*:** 31 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

Tabela 1 – Gestão da metformina de acordo com os níveis de TFGe

TFGe	Dose máxima	Recomendações
> 60 mL/min/1,73m²	2550 mg/dia	
45 – 60 mL/min/1,73m²	2000 mg/dia	
30 – 45 mL/min/1,73m²	1000 mg/dia	Não deve ser iniciada
< 30 mL/min/1,73m²	-	Deve ser suspensa

aumentar. [7] Está relacionada com um défice de produção pancreática de insulina e o seu tratamento exige administração de insulina exógena.[7,8]

A metformina pertence à classe das biguanidas e é considerada de primeira linha na terapêutica farmacológica da DM2.[5,8] O seu mecanismo de ação não se encontra totalmente conhecido, mas leva a otimização da sensibilidade à insulina a nível hepático e a redução da insulinorresistência periférica.[5,8] Os efeitos secundários são mais comuns no início da terapêutica e podem ser minimizados pela introdução gradual do fármaco.[5,8] Os mais frequentes são náuseas, diarreia e dor abdominal.[8]

Esta terapêutica é frequentemente utilizada na prática clínica, não só na DM2, mas também na diabetes secundária a corticoterapia, diabetes pós-transplante, diabetes gestacional, pré-diabetes, síndrome do ovário poliquístico e até, por vezes, na DM1.[8-10] Em 2018 em Portugal, venderam-se cerca de 3 milhões de embalagens de metformina no ambulatório.[2] Devido à sua eficácia, baixo custo e à sua boa tolerância em geral é facilmente perceptível a razão pela qual isto acontece.[8]

A metformina não é metabolizada e a sua excreção é feita apenas por via renal, pelo que a dose máxima deve ser ajustada à taxa de filtração glomerular estimada (TFGe).[8,11,12] Na Tabela 1 apresentam-se as recomendações de gestão da metformina de acordo com o valor de TFGe.[5,8,11,12]

A doença renal diabética acomete 20% – 40% das pessoas diabéticas. Geralmente surge 10 anos após o início da doença na DM1 e pode já estar presente ao diagnóstico na DM2.[11]

A insulinoterapia é uma terapêutica muito utilizada para o tratamento de pessoas com diabetes, não só no tipo 1, mas também nas formas de diabetes secundárias, na DM2 de longa evolução onde já existe insulinopenia e na diabetes gestacional.[5,8,9]

Neste artigo pretendemos rever quais as principais precauções nos exames de imagem em pessoas com diabetes e sugerir um protocolo de atuação de forma a reduzir os riscos e otimizar a sensibilidade destes exames nesta população.

Lesão renal aguda associada ao contraste

A lesão renal aguda (LRA) associada ao contraste é a principal causa iatrogénica de LRA.[13,14] O seu risco prende-se sobretudo com a utilização de contraste iodado, uma vez que o gadolínio, nas doses aprovadas para utilização em ressonância magnética, não se parece associar.[13,14]

Embora não exista nenhum procedimento particular em pessoas com diabetes, a utilização de gadolínio em doentes com doença renal crónica avançada ou lesão renal aguda pode-se associar a eventual fibrose sistémica nefrogénica.[15]

A administração endovascular de contraste iodado é utilizada nos estudos por TC e angiografia.[13] Destes, os exames mais frequentemente realizados são as TC, tendo-se realizado no ano de 2018 em Portugal, 205 por cada 1000 habitantes em ambiente hospitalar.[16] Neste tipo de exames é usado contraste intra-venoso, enquanto nas angiografias pode ser usado contraste intra-venoso ou intra-arterial.[13]

A definição de LRA pós-contraste não é uniforme entre os estudos, o que torna difícil comparar a incidência de efeitos adversos.[13,14] No entanto, a definição mais consensual é um agravamento da creatinina maior ou igual a 0,3 mg/dL (26,5 µmol/L) ou maior ou igual a 1,5 vezes o valor basal, 48 a 72 horas após a administração de contraste intravascular.[13,14,17]

A fisiopatologia da LRA associada ao contraste não se encontra ainda totalmente conhecida. No entanto, parece haver contribuição simultânea de três mecanismos básicos: vasoconstrição renal e hipóxia medular, toxicidade celular tubular, e formação de espécies reativas de oxigénio. Estas alterações culminam em apoptose celular endotelial e epitelial e diminuição da TFG.[18]

Na Tabela 2 encontram-se os fatores de risco para ocorrência de LRA pós-contraste.[13,17]

É considerado contraste intra-arterial com primeira passagem renal aquele que chega às artérias renais relativamente não diluido (administração de contraste no coração esquerdo, aorta torácica e supra-renal ou artérias renais), e contraste intra-arterial com segunda passagem renal o contraste que chega às artérias renais após diluição na circulação periférica e pulmonar (administração contraste no coração direito, artérias pulmonares, carótidas, subclávias,

Tabela 2 – Fatores de risco associados a LRA pós-contraste[13]

Fatores de risco para LRA pós-contraste:
TFGe < 45 mL/min/1,73 m² se contraste intra-arterial com primeira passagem renal ou doente em UCI
TFGe < 30 mL/min/1,73 m² se contraste intra-venoso ou intra-arterial com segunda passagem renal
LRA conhecida ou suspeita
Dose alta de contraste intra-arterial com primeira passagem renal
Contraste com elevada osmolalidade
Múltiplas administrações de contraste nas úlitmas 48 – 72 horas

UCI: unidade de cuidados intensivos

coronárias, mesentéricas ou infra-renais).[13,17]

A LRA pós-contraste é potencialmente prevenível, e existem várias recomendações na literatura sobre como reduzir a sua incidência.[13,14,17] Em doentes com doença renal crónica, a utilização de fármacos potencialmente nefrotóxicos (ex: anti-inflamatórios não esteroides, inibidores seletivos da COX-2), fármacos anti-microbianos (ex: gentamicina), ou agentes de quimioterapia (ex: cisplatina), deve ser minimizada sempre que possível antes da realização do contraste iodado.[13] No entanto, esta interrupção pode levar a descompensação da doença de base e à sua suspensão permanente pelo doente.[13]

Baseados em vários ensaios randomizados e controlados a European Society of Urogenital Radiology recomenda que os doentes com fatores de risco para LRA pós-contraste façam profilaxia com hidratação endovenosa antes da administração de contraste iodado.[13] Esta profilaxia depende do tipo de contraste que vai ser administrado, e encontra-se descrita na Tabela 3.[13]

A evidência atual sugere que a eficácia dos protocolos com infusão salina e com bicarbonato seja semelhante na profilaxia de LRA pós-contraste.[13]

Atualmente não existe evidência suficiente para recomendar hidratação oral como a única forma de profilaxia.[13] Também não se encontra recomendada a administração de N-acetilcisteina, medicação transitória com estatina em alta dose, inibidores da enzima de conversão da angiotensina, antagonistas dos receptores da angiotensina ou vitamina C, com o intuito hipotético de evitar LRA pós-contraste.[13]

Para reduzir o risco de LRA pós-contraste, é recomendado administrar a dose mínima necessária para o propósito, preferir contrastes com baixa ou normo-osmolalidade e utilizar uma razão $\frac{\text{dose de contraste em gramas}}{\text{TFG absoluta}} < 1{,}1$ e uma $\frac{\text{volume de contraste em mL}}{\text{TFGe}}$ razão inferior a 3 no contraste intra-arterial com primeira passagem renal.[13]

A metformina tem sido associada à ocorrência de acidose láctica. No entanto, a evidência mais recente indica que este evento é muito raro (3 - 9/100 000 doentes/ano) e acontece quase exclusivamente em doentes que têm alto risco para acidose láctica independentemente da administração de metformina.[5,13] Apesar de ser um efeito secundário grave, potencialmente letal, precisa de um evento associado para acontecer, como por exemplo, falência respiratória, insuficiência renal, sépsis, hipoperfusão ou cirrose.[8,11-13]

O risco de utilização da metformina aquando da administração de contraste iodado prende-se com o facto de, caso haja LRA pós-contraste, o agravamento da função renal poder levar à diminuição da excreção renal de metformina, aumentando os seus níveis plasmáticos e podendo propiciar a ocorrência de acidose láctica.

Atualmente, não existe consenso em relação à melhor abordagem sobre a suspensão de metformina em pessoas com diabetes que vão ser submetidas à administração de contraste iodado.[11,13,17] As recomendações que nos parecem ter maior evidência são as feitas pelas European Society of Urogenital Radiology, American College of Radiology e Sociedade Holandesa de Radiologia, baseadas em vários estudos e metanálises.[13]

Devido à falta de evidência publicada sobre a utilização de metformina em doentes submetidos a contraste iodado, as recomendações prévias eram baseadas em consensos e muito limitativas.[13] À medida que se foi percebendo o baixo risco de acidose láctica, as recomendações têm sido cada vez menos restritivas.[13,17]

Na Tabela 4 apresentamos as recomendações sobre a suspensão de metformina em pessoas com diabetes sob esta terapêutica.

A TFGe deve ser avaliada nos sete dias antes da administração de contraste iodado em doentes com doença aguda, deterioração aguda de doença crónica ou em caso de internamento, e nos três meses antes em todos os outros doentes.[13] A TFGe deve ser também avaliada 48 horas após a administração de contraste iodado, em doentes com TFGe inferior a 30 mL/min/1,73 m^2 submetidos a contraste intravenoso ou contraste intra-arterial com segunda passagem real, e em todos os doentes submetidos a contraste iodado intra-arterial com primeira passagem renal independentemente da TFGe de base.[13,17]

Nos doentes que estejam sob terapêutica de substituição da função renal (ex: diálise) não é necessário adaptar o momento de administração de contraste intravascular ao esquema de diálise. No entanto, isto pode ser feito para reduzir a sobrecarga de volume.[13]

Importa ainda referir que TFGe deve ser calculada nos adultos através da fórmula CKD-EPI e nas crianças através da fórmula de Schwartz revista.[13]

Precauções em pessoas com diabetes submetidas a exames que necessitam de jejum

O risco da realização de exames de imagem que necessitem de jejum merece particular atenção nos indivíduos

Tabela 3 – Tipo de profilaxia recomendada de acordo com o tipo de administração de contraste[13]

Tipo de contraste	Esquema de profilaxia
Contraste intravenoso ou intra-arterial com segunda passagem renal	3 mL/kg/h de bicarbonato a 1,4% 1 hora antes administração contraste
	1 mL/kg/h de cloreto de sodio a 0,9% 3 – 4 horas antes da adminstração de contraste e 4 – 6 horas após a administração de contraste
Contraste intra-arterial com primeira passagem renal	3 mL/kg/h de bicarbonato a 1,4% 1 hora antes administração contraste e 1 mL/kg/h 4 – 6 horas após a administração de contraste
	1 mL/kg/h de cloreto de sodio a 0,9% 3 – 4 horas antes da adminstração de contraste e 4 – 6 horas após a administração de contraste

Tabela 4 – Recomendações sobre a suspensão de metformina das diferentes sociedades médicas[11,13,17]

TFGe	Tipo de contraste	Recomendações
ESUR, ACR, SHR		
> 30 mL/min/1,73 m² sem evidência de LRA	IV ou IA com 2ª passagem renal	Manter administração
< 30 mL/min/1,73 m²	IV ou IA com 2ª passagem renal	Parar metformina Reavaliar TFGe 48 horas após a administração de contraste iodado Reiniciar metformina se TFGe estável
-----	IA com 1ª passagem renal	
Com evidência de LRA	----------	
SSUR		
> 45 mL/min/1,73 m²	IV ou IA com 2ª passagem renal	Manter administração
< 45 mL/min/1,73 m²	IV ou IA com 2ª passagem renal	Parar metformina Reavaliar TFGe 48 horas Reiniciar metformina se TFGe estável
Razão dose contraste (g)/TFGe ≥ 1	IV ou IA com 2ª passagem renal	
LRA ou risco de LRA	-----	
-----	IA com 1ª passagem renal	
ADA		
30 – 60 mL/min/1,73 m³	----------	Deve ser temporariamente suspensa

ESUR: European Society of Urogenital Radiology; ACR: American College of Radiology; SHR: Sociedade Holandesa de Radiologia; IV: intravenoso; IA: intra-arterial; SSUR: Sociedade Sueca de Radiologia Urogenital; ADA: American Diabetes Association

sob insulinoterapia e anti-diabéticos orais com risco de hipoglicémia.[8,19] Durante o período de jejum num indivíduo sem diabetes, a ligeira redução inicial da glicemia leva à diminuição da produção pancreática de insulina, a um aumento da produção de glucagon e à resposta catecolaminérgica, o que permite a manutenção da glicemia.[20] Numa pessoa com diabetes insulinotratada, a insulina encontra-se já em circulação e, dependendo do caso, o pâncreas pode não ter capacidade para adaptar a secreção de glucagon. [20] Desta forma, a pessoa com diabetes está frequentemente dependente apenas da resposta catecolaminérgica que também pode estar limitada pela presença de neuropatia autonómica ou hipoglicemias recorrentes.[20]

As insulinas de ação curta ou rápida são as que se encontram associadas ao maior risco de hipoglicemia, já que ao mimetizar a secreção de insulina associada à refeição têm um rápido e marcado pico de ação.[8]

A pessoa com diabetes sob anti-diabéticos orais com risco de hipoglicemia – sulfonilureias (glibenclamida, gliclazida, glimepirida e glipizida) e glinidas (nateglinida) - tem também maior risco de hipoglicemia durante o jejum, sendo recomendado que estes doentes adiem a toma do fármaco até que haja ingestão de alimentos, após o exame.[8,19]

Assim, para minimizar o risco de hipoglicemia, os exames dos doentes insulinotratados que obriguem a jejum devem ser marcados para o início da manhã, de forma a reduzir as alterações necessárias ao esquema de insulina. Em geral, este procedimento evita a necessidade de alteração da insulina basal, sendo recomendável o adiamento da administração de insulina de ação curta ou rápida até à ingestão de alimentos após o término do exame.

Na impossibilidade destes exames serem realizados no início da manhã, não deve ser administrada a insulina de ação curta ou rápida para as refeições omitidas. Se o doente estiver marcado para a tarde, em geral, poderá ingerir o pequeno-almoço e ser tratado com a insulina habitual dessa refeição. Relativamente à insulina basal, é importante que os indivíduos com diabetes tipo 1 mantenham a sua insulina basal, embora na maioria das situações um eventual atraso na administração deste tipo de insulina (de uma a três horas) não tenha consequências relevantes. De igual modo, atrasos superiores aos indicados na administração da insulina degludec são tolerados sem descontrolo glicémico relevante.[21,22]

Apesar da manutenção da insulina basal parecer ser segura, a dose de insulina basal glargina ou detemir da manhã poderá ser reduzida entre 20% a 25%, dependendo do nível de controlo glicémico de cada doente, do seu risco de hipoglicemia e do tempo de jejum requerido.[22,23] Relativamente à insulina NPH, poderão considerar-se necessárias reduções na ordem dos 50% nessa manhã, em função do seu perfil com pico de maior ação por volta das quatro horas.[23] Doentes com hiperglicemia recente não devem, na maioria dos casos, sofrer reduções na dose de insulina basal.

No caso de prolongamentos imprevistos do jejum, em que tenha sido administrada a dose habitual de insulina basal, recomenda-se intensificar a vigilância por glicemia capilar e, dependendo do nível de glicemia e tempo estimado para concluir o jejum, pode iniciar-se uma perfusão de dextrose a 5%.[24] Muitas instituições têm protocolos sobre controlo da diabetes durante procedimentos cirúrgicos e peri-operatório, sendo razoável aplicar aos exames de imagiologia uma conduta semelhante aos protocolos para cirurgia *minor*.[23,24]

A terapêutica com sulfonilureias deve em geral ser omitida na manhã em que o doente permanecerá em jejum dependendo de controlo glicémico e com vigilância glicémica reforçada nesse período.[23]

Durante o período de jejum, a pessoa com diabetes tratada com fármacos com risco de hipoglicemia deve vigiar a glicemia a cada quatro a seis horas, e sempre que clinicamente recomendado.[24]

PET-FDG

A PET-FDG é um exame realizado frequentemente na prática clínica, tanto para estadiamento ou vigilância de patologia oncológica, como para estudo de patologia neurológica, inflamatória ou infeciosa. [25]

A estrutura química da FDG é semelhante à da glicose natural pelo que, na presença de hiperglicemia, há competição direta entre a captação celular de glicose plasmática e da FDG.[25] Esta redução da captação da FDG pode levar a redução da sensibilidade do exame, que parece acontecer apenas para glicemias capilares superiores a 200 mg/dL.[25] Por isso, com o objetivo de não comprometer a sensibilidade do exame, recomenda-se que a glicemia capilar seja inferior a esse valor antes da administração de FDG.[25]

Caso o exame seja realizado para estudo de doença neurológica ou lesão no sistema nervoso central, a glicemia capilar deve ser inferior a 160 mg/dL, pois para valores superiores a estes o contraste entre a substância cinzenta e a substância branca pode ser perdido, para além de que o aumento do ruído pode reduzir a sensibilidade do exame.[25]

A metformina pode, também, alterar a sensibilidade da PET-FDG, uma vez que aumenta a acumulação da FDG a nível intestinal, particularmente no cólon.[25] Este aumento de captação provocado pelo fármaco pode levar a diminuição da sensibilidade do exame e a um aumento de falsos negativos no estudo de neoplasias abdominais e pélvicas.[25] Não existem recomendações sobre como atuar em doentes sob terapêutica com metformina que vão realizar PET-FDG, nem quando esta deva ser suspensa caso o objetivo do exame seja avaliar lesões abdominais.[25] O risco de diminuição da sensibilidade do exame tem de ser considerado caso a caso e equilibrado com o risco de hiperglicemia associado à suspensão da terapêutica.[25] Caso se opte pela suspensão, há alguma evidência de que deverá ter uma duração mínima de 72 horas.[25]

Ao alterar a biodistribuição da FDG, a terapêutica com insulina também influencia a sensibilidade deste exame.[25] A insulina de ação curta ou rápida não deve ser administrada nas quatro a seis horas antes, e a insulina basal deverá ser administrada apenas após a administração da FDG e a realização da PET.[25] Não existem atualmente recomendações sobre o período de tempo entre a administração das novas insulinas de ação ultra-rápida (insulinas aspártica ultra-rápida e lispro-aabc). No entanto, de acordo com a sua farmacocinética e até que existam recomendações específicas, recomendamos um procedimento semelhante ao conselhado para as insulinas clássicas de ação curta ou rápida.[26,27] Em indivíduos sob terapêutica com perfusão subcutânea contínua de insulina recomenda-se suspensão da infusão pelo menos quatro horas antes da administração da FDG.[25]

Não se encontra ainda bem determinada a influência dos inibidores de SGLT2 na avaliação renal por PET-18FDG.[28] Sabe-se que estes medicamentos podem acelerar o trânsito de glicose renal, parâmetro que é importante na avaliação da função renal por PET-FDG.[28]

Atualmente, não existe evidência sobre a influência de outros fármacos anti-diabéticos na sensibilidade da PET-18FDG, à excepção da pioglitazona, que parece aumentar a captação de FDG pelas lesões malignas.[29]

Proposta de protocolo

Após revisão da literatura, criámos uma proposta de protocolo de atuação para as pessoas com diabetes que vão realizar exames de imagem.

Na Tabela 5 apresentam-se as medidas gerais de prevenção de LRA associada à administração de contraste.

Tabela 5 – Medidas gerais recomendadas na prevenção de LRA associada ao contraste

Medidas gerais na prevenção de LRA associada ao contraste:
Suspender, sempre que possível, os fármacos potencialmente nefrotóxicos
Fazer profilaxia com hidratação endovenosa se fatores de risco para LRA pós-contraste
Administrar a dose mínima de contraste iodado necessária para o propósito
Preferir contrastes de baixa ou normo-osmolalidade
Se utilização de contraste intra-arterial com primeira passagem renal: $\text{Razão} \frac{\text{dose de contraste em gramas}}{\text{TFG absoluta}} < 1{,}1$ e $\text{Razão} \frac{\text{volume de contraste em mL}}{\text{TFGe}} < 3$

Tabela 6 – Protocolo sobre administração de contraste iodado em pessoas medicadas com metformina

TFGe	Tipo de contraste	Recomendações
> 30 mL/min/1,73 m^2 sem evidência de LRA	IV ou IA com 2ª passagem renal	Manter administração
< 30 mL/min/1,73 m^2	IV ou IA com 2ª passagem renal	Parar metformina Reavaliar TFGe 48 horas Reiniciar metformina se TFGe estável e > 30 mL/min/1,73 m^2
-----	IA com 1ª passagem renal	
Com evidência de LRA	----------	

Tabela 7 – Protocolo de atuação em pessoas com diabetes insulinotratadas para exames que impliquem jejum

Recomendações para exames que impliquem jejum em doentes insulinotratados:
Marcar o exame para o inicio da manhã
Não administrar insulina de ação curta ou rápida da refeição que se omite
Na refeição após o exame administrar insulina de ação curta ou rápida de acordo com o esquema para aquela refeição
Glicemia deve ser avaliada ocasionalmente e sempre que clinicamente justificável
Contactar o médico assistente para avaliar a eventual necessidade de ajuste da insulina basal

Tabela 8 – Recomendações na pessoa com diabetes que vai ser submetida a PET-FDG

Objetivo glicémico	Geral < 200 mg/dL Estudo de doença neurológica ou lesão do SNC < 160 mg/dL
Metformina	Avaliação da necessidade de suspensão pelo médico assistente tendo em consideração: - Diminuição da sensibilidade para estudo de lesões abdominais e pélvicas - Risco de hiperglicemia associada à suspensão da terapêutica Caso se opte por suspender fazê-lo no mínimo 72 horas antes do exame
Insulina	Não administrar insulina de ação curta ou rápida nas 4 – 6 horas antes da administração de FDG Administrar Insulina basal após a realização do exame Se PSCI deve-se suspender a infusão 4 horas antes da administração de FDG

PSCI: perfusão subcutânea contínua de insulina

Há várias situações sem consenso na literatura sobre a melhor abordagem. Nestas tentámos identificar as que apresentam maior evidência científica.

Na Tabela 6 apresentamos o protocolo de atuação nos doentes submetidos a contraste iodado e que estejam sob terapêutica com metformina.

Optámos por favorecer as recomendações das European Society of Urogenital Radiology, American College of Radiology e Sociedade Holandesa de Radiologia, baseadas em vários estudos e metanálises, uma vez que são aquelas que apresentam melhor qualidade de informação.[13]

Em relação à realização de exames que impliquem jejum em indivíduos tratados com insulinoterapia, as nossas recomendações encontram-se na Tabela 7.

Para os indivíduos que vão ser submetidos a PET-FDG, as recomendações encontram-se na Tabela 8.

CONCLUSÃO

A gestão do indivíduo com diabetes é complexa. O risco de acidose láctica no indivíduo com diabetes sob terapêutica com metformina submetido a contraste iodado não parece ser tão elevado como se pensava inicialmente. Desta forma, as indicações para suspensão temporária de metformina são atualmente menos restritivas. Os exames que obriguem a jejum nos indivíduos sob insulinoterapia devem ser marcados para o início da manhã, de forma a serem necessárias menos alterações terapêuticas. Na maior parte dos casos poderá apenas ser recomendado adiar a administração de insulina de ação curta ou rápida para o momento da ingestão de alimentos, após o exame. Na PET-FDG, tanto a terapêutica (com metformina ou insulina) como a hiperglicemia podem diminuir a sensibilidade do exame. Em relação à terapêutica com metformina, a suspensão deve ser ponderada caso a caso, pelo risco de hiperglicemia associado. Em relação à terapêutica com insulina, as recomendações dependem do tipo de insulina, estando recomendado não administrar insulina de ação curta ou rápida nas quatro horas antes da administração de FDG, e administrar insulina basal após a realização do exame.

Com esta proposta de protocolo pretendemos resumir e simplificar a orientação dos indivíduos com diabetes que vão ser submetidos a exames de imagem.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos de confidencialidade de dados na realização da presente investigação.

CONFLITOS DE INTERESSE

Os autores declaram não haver conflito de interesses na realização da presente investigação.

FONTES DE FINANCIAMENTO

Não existiram fontes externas de financiamento para a presente investigação.

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Flu Vaccination Coverage in 2020 in the Baixo Vouga Health Centre Group in Portugal

A Taxa de Cobertura Vacinal Contra a Gripe em 2020 no Agrupamento de Centros de Saúde do Baixo Vouga em Portugal

Keywords: Influenza Vaccines; Portugal; Vaccination Coverage
Palavras-chave: Cobertura Vacinal; Portugal; Vacinas Contra a Gripe

Dear Editor,

According to the Centers for Disease Control and Prevention (CDC), the success of the 2020/2021 flu vaccination campaign was crucial not only to reduce the burden of flu in the national healthcare system but also to preserve healthcare resources that may be needed for the care of COVID-19 patients.[1]

This cross-sectional study describes the variation of flu vaccine coverage of patients with diabetes, chronic respiratory disease, or chronic heart disease, or age over 65 years between 2018 and 2020. Flu vaccine coverage was assessed through the prescribing of influenza vaccine or its administration in the previous 12 months. Data was collected on the 3rd January 2021 from the public database *'Bilhete de Identidade dos Cuidados de Saúde Primários'* concerning the 25 family health units (FHU) of the Baixo Vouga Health Centre Group, in Portugal (three FHU excluded due to missing data). The current study did not require ethical approval because it involved only aggregated data that is freely available in the public domain. No individual-level data was accessed by the authors.

In terms of the rate of influenza vaccination coverage on the 22 FHU studied, 17 FHU had an increase in coverage during the previous year (Table 1). Compared to the coverage in 2019, the percentage increase in 2020 ranged from 1.7% to 35.8%. In half of the FHU, this increase was much higher in 2019 - 2020 compared to 2018 - 2019. Five FHU had a decrease in the rate of vaccination coverage. The mean vaccination coverage has constantly been increasing in the last three years, although it is still below national coverage.[2]

An interesting observation was that in 64.7% of the FHU which saw an increase in their flu vaccination coverage in 2020, the percentage increase was even higher from 2019 to 2020 compared to the previous influenza season, despite the known shortage of vaccines in 2020. The observed in-

Table 1 – Flu vaccination coverage of patients with diabetes, chronic respiratory disease, chronic heart disease or age over 65 years, with the influenza vaccine prescribed or administered in the last 12 months in the FHUs (n = 22)

Family Health Unit	No. patients 65+ years	Flu vaccination coverage (year-month)			% increase or decrease	
		2018-11	2019-11	2020-11	2018 to 2019	2019 to 2020
1	2319	46.7	49.6	52.4	6.0	5.8
2	2403	35.0	41.7	51.6	18.9	23.8
3	1971	42.6	54.0	52.8	26.8	-2.3
4	1569	49.8	47.6	44.3	-4.5	-6.9
5	2891	42.1	43.4	56.5	3.0	30.1
6	4018	43.3	45.8	54.9	5.6	19.9
7	1510	39.6	53.3	44.2	34.7	-17.0
8	2089	36.5	35.2	47.8	-3.6	35.8
9	2663	35.4	38.2	48.3	7.9	26.5
10	3082	41.6	48.0	50.0	15.5	4.2
11	2568	36.9	40.7	49.3	10.4	21.1
12	2719	32.9	39.1	50.2	18.9	28.1
13	2419	42.0	48.0	50.9	14.2	6.1
14	2163	40.0	43.6	46.6	8.8	7.0
15	2219	43.7	48.1	49.2	10.0	2.3
16	2034	44.0	41.2	48.8	-6.4	18.4
17	2334	39.0	43.4	42.4	11.3	-2.3
18	1300	38.0	39.7	45.4	4.6	14.3
19	2254	41.1	46.3	56.0	12.6	21.1
20	2217	38.0	37.8	47.2	-0.3	24.7
21	1630	49.2	49.4	46.1	0.4	-6.6
22	2482	43.0	45.1	45.8	4.8	1.7
Mean		40.9	44.5	49.1	-	-

crease could be attributed to: i) the COVID-19 pandemic, with both patients and physicians perhaps giving more importance to contagious respiratory diseases that were previously believed to be somewhat trivial (including the flu),[3] and decided to be vaccinated or advise flu vaccination; ii) the awareness of the general public regarding the importance of the development a COVID-19 vaccine, promoted by the media and information campaigns, may have shattered some myths related to the adverse effects of vaccination and consequently increased confidence in vaccine safety. Both stated reasons were previously known factors for the non-uptake of the influenza vaccine.[3,4] Future studies should analyze the factors associated with the apparent increased uptake of the influenza vaccine during the COVID-19 pandemic to understand if those factors can be explored in future vaccination campaigns, including the one against SARS-CoV-2.

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Recebido: 03 de janeiro de 2021 - **Aceite:** 23 de fevereiro de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.15649

Knowledge and Attitudes Towards COVID-19: A Cross-sectional Study in Portugal

Conhecimentos e Atitudes em Relação à COVID-19: Um Estudo Transversal em Portugal

Keywords: Communication; COVID-19; Health Knowledge, Attitudes, Practice; Knowledge; Portugal
Palavras-chave: Comunicação; Conhecimento; Conhecimentos, Atitudes e Prática em Saúde; COVID-19; Portugal

Dear editor,

Disease-related literacy is critical in shaping practices and controlling the spread of an outbreak of an infectious disease.[1] Unfortunately, the dissemination of inaccurate information undermines those efforts.[1] An endless amount of misinformation about COVID-19 was published in scientific journals and broadcasted in the media. Furthermore, there were interventions from accredited institutions that spread confusion and misbeliefs. Understanding these misbeliefs is essential since they can be debunked using internet resources, like 'COVID-19 advice for the public: Mythbusters' launched by the WHO.[2]

We investigated the knowledge and attitudes towards COVID-19 through a cross-sectional study applying an online survey using 'google forms', and that included 22 questions about socio-demographics, knowledge, and attitudes (Table 1). The questions were applied following initial informed consent. Due to the non-interventional nature of the work and the impossibility of tracking the responses given to the survey, it was considered that there was no need for approval by an Ethics Committee. A total of 1004 responses were collected, 922 of them from residents in Portugal, which we analysed in detail. The median age was 40 years-old, and female respondents were predominant (71.9%). From the overall respondents, 47.4% had a graduate degree and 34.9% were healthcare professionals.

Participants mostly considered having access to quality information – level four in five - and to have good knowledge about the disease – level four in five. Most of them identified fever, cough and shortness of breath correctly as COVID-19 symptoms.

Regarding routes of transmission, many of the participants adequately identified respiratory droplets and fomites; however, a significant proportion exhibited misconceptions, admitting transmission through consuming contaminated food or water, sexual contact, and insect bites. These incorrect ideas were particularly presented by highly educated participants (graduate degree to doctorate) which put them with a classification of level four or five in terms of access to information.

Almost all participants recalled the importance of using masks in closed public spaces, but only 23% considered it was enough to use a surgical mask when contacting with an infected person.

When caring for someone infected, only 1.2% admitted that wearing a mask, gloves and gown would be enough, with most participants considering that the ideal set of protective equipment consists of a mask, eye protection, head and neck cover, gloves, gown, and shoe protection (44.8%). This is probably due to the widespread idea that the more covered you are, the lower the risk of contracting the disease; nevertheless, it should be emphasized that wearing more equipment does not mean we are more protected, we also should use it properly.

Almost all participants took measures to reduce the spread of the disease at home and avoided visits to family members.

Our findings suggest that Portuguese participants have good knowledge and mostly correct attitudes towards the disease; nevertheless, important misconceptions that could perhaps be explained by the spread of misinformation were also identified. The results of our study advocate that education campaigns towards reduction of misbeliefs are urgently needed in order to properly educate the population and reduce the incidence of outbreaks in the most effective way.

Table 1 – Questions and answers about COVID-19 knowledge and attitudes (section 1 of 3)

Questions	Answers	Total No. (%)
Q1. I have access to enough information about COVID-19:	Level 1: No, I don't have access to information or it's of low quality.	2 (0.2%)
	Level 2	7 (0.8%)
	Level 3	140 (15.2%)
	Level 4	438 (47.5%)
	Level 5: Yes, I have access to high-quality information.	329 (35.7%)
Q2. I consider that my knowledge about COVID-19 is:	Level 1: None	2 (0.2%)
	Level 2	10 (1.1%)
	Level 3	189 (20.5%)
	Level 4	556 (60.3%)
	Level 5: Complete and updated	165 (17.9%)

Table 1 – Questions and answers about COVID-19 knowledge and attitudes (section 2 of 3)

Questions	Answers	Total No. (%)
Q3. What are the three symptoms you consider most distinctive of COVID-19?	Fever	810 (87.9%)
	Cough	629 (68.2%)
	Shortness of breath	615 (66.7%)
	Loss of smell	261 (28.3%)
	Sore muscles	130 (14.1%)
	Fatigue	119 (12.9%)
	Headache	114 (12.4%)
	Sore throat	64 (6.9%)
	Diarrhoea	14 (1.5%)
	Nausea and vomiting	6 (0.7%)
	Double vision	2 (0.2%)
Q4. The novel coronavirus can be transmitted:	Talking closely to someone infected (respiratory droplets)	916 (99.3%)
	By contact with contaminated surfaces	799 (86.7%)
	By providing hygiene care to infected people	556 (60.3%)
	Aerosol generating medical procedures (eg. intubation)	495 (53.7%)
	Through the air	302 (32.8%)
	By consuming contaminated food or water	162 (17.6%)
	By sexual contact	147 (15.9%)
	By insect bites	11 (1.2%)
	I don't know	0
Q5. On average, the novel coronavirus survives on surfaces:	Between 6 and 24 hours	321 (34.8%)
	Between 1 and 3 days	289 (31.3%)
	Less than 6 hours	147 (15.9%)
	I don't know	91 (9.9%)
	More than 3 days	74 (8.0%)
Q6. Do you consider that someone infected with COVID-19 but showing no symptoms can transmit the disease?	Yes	907 (98.4%)
	No	15 (1.6%)
Q7. What protective measures would you consider enough to avoid transmission of COVID-19 between two people talking? (multiple answers allowed)	Social distancing	901 (98.1%)
	Face Mask	887 (96.6%)
	Eye protection	176 (19.2%)
	Gloves	61 (6.6%)
Q8. If I am infected with COVID-19:	I must stay at home, isolated from the other inhabitants, staying in at any time	901 (97.7%)
	I must stay at home, staying in at any time, but I can contact the other inhabitants	9 (1.0%)
	I don't have to avoid close contacts or wear a mask	5 (0.5%)
	I must stay at home, but I can contact the other inhabitants and leave the house wearing a mask	1 (0.1%)
	I can contact the other inhabitants of the house and go to work wearing a mask	1 (0.1%)
Q9. When contacting closely with people infected with COVID-19, what mask would you use?	FFP2/N95 Mask	487 (52.8%)
	Surgical mask	212 (23.0%)
	Full face respiratory mask	194 (21.0%)
	Cloth mask	25 (2.7%)
	I don't know	4 (0.4%)
	No mask is required	0

Table 1 – Questions and answers about COVID-19 knowledge and attitudes (section 3 of 3)

Questions	Answers	Total No. (%)
Q10. When caring for people infected with COVID-19, what personal protective equipment would you use?	Mask, eye protection, head and neck cover, gloves, gown, and shoe protection	413 (44.8%)
	Full face mask and full body suit	359 (38.9%)
	Mask, gloves, eye protection and gown	120 (13.0%)
	Mask, gloves, and gown	11 (1.2%)
	I don't know	8 (0.9%)
	Mask only	7 (0.8%)
	Mask and gloves	4 (0.4%)
Q11. Would you know how to wear personal protective equipment?	Yes	649 (70.4%)
	No	272 (29.5%)
Q12. Out of home, everyone should wear a mask.	Yes, in closed public spaces only	575 (62.4%)
	Yes, always	341 (37%)
	No	5 (0.5%)
Q13. Out of home, everyone should wear gloves.	No	775 (84.1%)
	Yes, in closed public spaces only	125 (13.6%)
	Yes, always	20 (2.2%)
Q14. Out of home, everyone should wear eye goggles or face shield.	No	713 (77.3%)
	Yes, in closed public spaces only	187 (20.3%)
	Yes, always	22 (2.4%)
Q15. When in a family dinner between family members not living together:	Everyone should wear a mask except during the meal, always keep social distancing and wash frequently their hands	844 (91.5%)
	Only the elder and sick people need protective measures	39 (4.2%)
	Everyone should wear mask and gloves and is therefore not necessary to maintain social distancing	18 (2.0%)
	No protective measures are required	14 (1.5%)
Q16. To avoid infection at home, I adopted as attitudes:	I wash my hands as soon as I arrive home	870 (94.4%)
	I sanitize my personal objects (eg. cell phone)	724 (78.5%)
	I leave my footwear outside the house	648 (70.3%)
	I sanitize my groceries and mail	465 (50.4%)
	I created a division at home between "dirty area" and "clean area"	418 (45.3%)
	I didn't change my behaviour at home	6 (0.7%)
Q17. During the COVID-19 pandemic:	I avoided and continue to avoid visiting elderly or sick family members	349 (37.9%)
	I avoided and continue to avoid visiting all family members	335 (36.3%)
	I avoided visiting family members, but I now resumed visiting all family members	228 (24.7%)
	I never stopped visiting family members	9 (1.0%)

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Recebido: 04 de fevereiro de 2021 - **Aceite:** 26 de fevereiro de 2020 - ***First published*:** 07 de abril de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.15887

Prevalence of Fear of Death among Young Breast Cancer Patients during Adjuvant Endocrine Therapy: Results from a Portuguese Cohort

Prevalência do Medo de Morrer em Doentes Jovens com Cancro de Mama Durante a Hormonoterapia Adjuvante: Resultados de uma Coorte Portuguesa

Keywords: Antineoplastic Agents, Hormonal; Anxiety; Breast Neoplasms; Quality of Life
Palavras-chave: Ansiedade; Antineoplásicos Hormonais; Neoplasias da Mama; Qualidade de Vida

A breast cancer diagnosis can greatly impact many young women and trigger a series of psychological and social challenges, particularly a fear of death or recurrence. This type of fear can cause physical and mental disorders affecting quality of life (QOL) in those with breast cancer.[1] Endocrine therapy (ET) has also been associated with the worsening of anxiety symptoms.[2,3] The precipitating factors must be recognized and identified in order to develop appropriate strategies for these patients. Both QOL and the impact of ET can be measured through questionnaires. The Functional Assessment of Cancer Treatment (FACT) and its endocrine subscale, FACT-ES v4, are validated QOL questionnaires specific to women with both breast cancer and endocrine symptoms.[4]

We aimed to use the FACT (version 4) to investigate the prevalence of fear of death in young breast cancer patients during adjuvant ET.

This cross-sectional study included young breast cancer patients prescribed adjuvant ET (tamoxifen, aromatase inhibitors, or luteinizing-hormone-releasing hormone analogues) in three Portuguese hospitals. Patient demographics and both clinical and histopathological data were recorded in a Microsoft Excel 2018 spreadsheet. We excluded patients on ET for less than 12 months, those who discontinued ET for more than three months, and those aged over 45 years old. Using the Portuguese versions of the FACT and FACT-ES (version 4) questionnaires, fear of death and associated factors were assessed. The chi-squared test was used to study the association between each variable and fear of death.

This study was approved by the Human Research Ethics Committee of each institution.

Our sample included 70 young female breast cancer patients. The mean age was 41.6 years. Each patient received adjuvant chemotherapy, and mean ET duration was 3.5 years. We tallied the answers to the question, "I worry about dying" for each of the specified responses: "not at all," "a little bit," "somewhat," "quite a bit," or "very much" (Fig. 1). Only 20 patients (28.6%) denied being worried about fear of dying.

Death anxiety was not associated with age, marital status, employment status, ET, or sexual activity (all $p > 0.05$). However, we found a significant association with accepting the disease ($p < 0.05$). Therefore, the fear of death was lower when the patient accepted the disease ($p < 0.05$) and also when the patient had good social and family support ($p < 0.05$).

Most patients showed some degree of fear of death. A psychological approach facilitating acceptance of the disease could improve the quality of life of these patients. Health care providers should also evaluate the social and family support given to these patients.

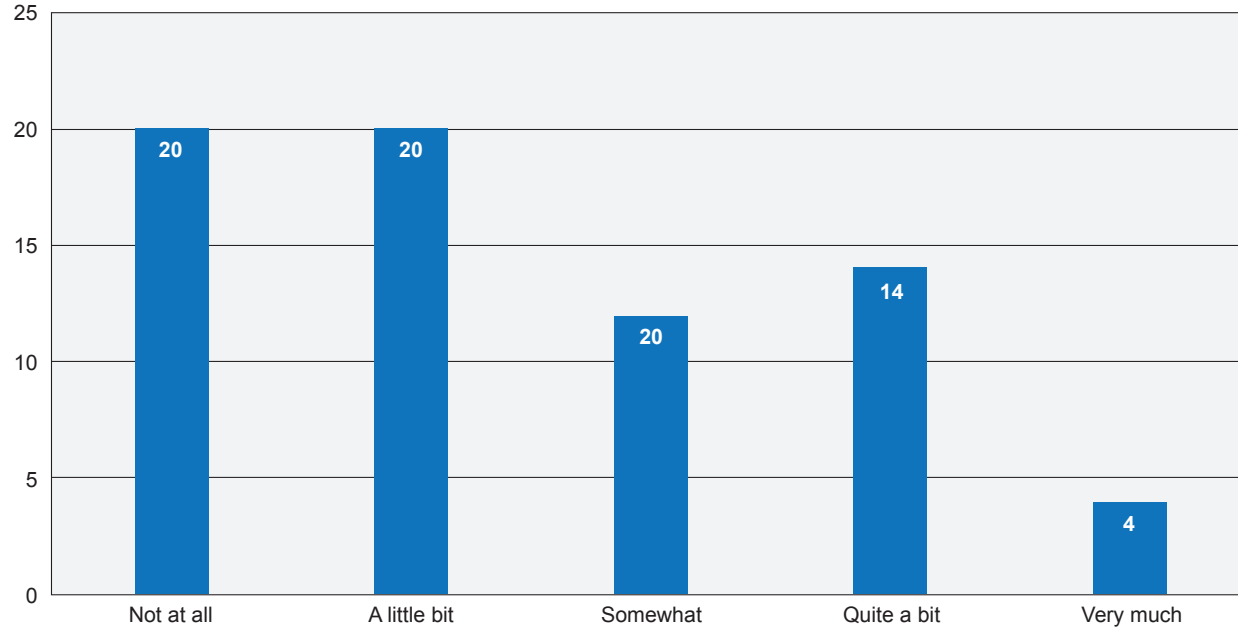

Figure 1 – Patient responses to "I worry about dying"

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 2013 Helsinki Declaration of the World Medical Association.

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.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido: 31 de outubro de 2020 - **Aceite:** 05 de março de 2021 - ***First published*:** 30 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.15201

Utilização Problemática de Internet Durante a Pandemia COVID-19: Um Novo Paradigma?

Internet Addiction During the Pandemic COVID-19: A New Paradigm?

Palavras-chave: Comportamento Aditivo; COVID-19; Pandemia; Perturbação de Dependência à Internet
Keywords: Behavior, Addictive; COVID-19; Internet Addiction Disorder; Pandemics

A pandemia COVID-19 tem precipitado uma mudança transformadora na sociedade atual.

A necessidade de implementar estratégias de mitigação por meio do confinamento, determinando o distanciamento social e o isolamento físico, impulsionou a importância das tecnologias de informação e comunicação (TIC) como fundamentais na resolução das dificuldades impreteríveis.[1]

As TIC adquiriram um papel central, a nível económico e laboral, facultando o *home offic*e e a continuação das atividades educativas (aulas *online)*, colmatando o isolamento, fomentando os laços sociais/familiares e proporcionando momentos de entretenimento/lazer.

Ainda que a utilização das TIC, na sua generalidade, seja adaptável às necessidades vigentes, existem subgrupos de pessoas mais vulneráveis que poderão desenvolver padrões de utilização problemática das tecnologias.[1] À maior angústia vivida pela incerteza quanto ao futuro, acresce ainda o medo de contágio e as eventuais repercussões estimadas ao nível da saúde mental, que tendem a condicionar ou agravar comportamentos de risco, como abuso de substâncias e de dependências comportamentais, nomeadamente, a utilização problemática de internet.[2,4]

O impacto que se tem vindo a sentir na esfera social, económica e na saúde tem precipitado um agravamento da sintomatologia ansiosa e depressiva, desencadeando maior sofrimento em resultado de eventos de *stress* e diminuição do bem-estar psicológico.[3]

Por outro lado, a necessidade do confinamento no domicílio promove um período substancial de tempo em que são utilizados aparelhos eletrónicos (utilização de Internet, videojogos, pornografia, entre outros), que poderão agravar ou propiciar dependências comportamentais pela sua utilização como modulador dos afetos negativos.[1,2]

Num inquérito *online* realizado na China, com uma amostra de 6416 indivíduos, verificou-se um aumento de 46,8% no número de indivíduos com dependência da utilização da Internet (UI) e 16,6% destes relatavam maior número de horas de UI.[3] Salienta-se, ainda, o aumento de 23% da prevalência (4,3%) de dependência de Internet grave comparativamente com o período prévio à pandemia (3,5%). Da mesma forma, verificou-se um aumento de comportamentos de uso abusivo de álcool e tabaco.[3]

Pela crescente inquietação em torno de toda a problemática que advém das dependências comportamentais numa sociedade por si tecnológica, a tónica merece ser direcionada em recomendações práticas para a utilização das TIC. Entre estas, destaca-se a automonitorização, regulando o tempo de ecrã, bem como a manutenção de contacto com amigos e familiares, favorecendo a regulação dos afetos e minorando os sentimentos de solidão. Por último, é necessário facultar informação clara e fidedigna, viabilizando a procura de ajuda, assegurando linhas de apoio especificas e assistência de profissionais de saúde mental.[1]

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Recebido: 04 de fevereiro de 2021 - **Aceite:** 10 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.15888

Os Diuréticos Tiazídicos e o Idoso Frágil: Para Lá das Normas de Orientação Clínica

Thiazide Diuretics and the Frail Elderly Patient: Beyond Guidelines

Palavras-chave: Diuréticos; Hipertensão; Idoso Frágil; Tiazídas
Keywords: Diuretics; Frail Elderly; Hypertension; Thiazides

Caro Editor

Recentemente foi avaliada em consulta domiciliaria de medicina geral e familiar uma doente hipertensa de 94 anos, com diversas comorbilidades e polifarmácia, que apresentou análises com hiponatrémia (127 mmol/L), tendo já sido internada há um mês por prostração (sódio de 110 mmol/L). A desprescrição do diurético tiazídico (hidroclorotiazida 25 mg) corrigiu progressivamente a natremia, mantendo-se a pressão arterial controlada.

De acordo com a última norma da Direção Geral da Saúde, os diuréticos constituem a terapêutica preferencial para a hipertensão arterial no doente idoso.[1] Por outro lado, para monitorizar a adesão clínica a esta norma nos cuidados de saúde primários, existe o indicador 021 que avalia a proporção de doentes com hipertensão que teve, pelo menos, um diurético tiazídico prescrito nos últimos 12 meses.[2] Os tiazídicos e análogos encontravam-se em 2019 no top 10 dos medicamentos mais prescritos por classe farmacoterapêutica em Portugal.[2]

Os diuréticos tiazídicos destacam-se entre os principais fármacos indutores de hiponatremia.[3] Estes fármacos inibem a reabsorção de sódio nos túbulos distais e aumentam a secreção inapropriada de hormona antidiurética, gerando uma excreção excessiva de eletrólitos face à eliminação de água, e, portanto, uma menor capacidade de diluição da urina (perdas hipertónicas). Pelo contrário, os diuréticos da ansa causam perdas hipotónicas sendo, inclusive, utilizados no tratamento da hiponatrémia (euvolémica e hipervolémica). [3]

Os fatores de risco para o desenvolvimento de hiponatrémia no idoso medicado com um tiazídico são: sexo feminino, dieta sem sal, elevada ingestão de água e utilização de doses elevadas.[3]

Um estudo sobre as idas dos idosos ao serviço de urgência por queixas inespecíficas, tais como fraqueza generalizada, identificou os diuréticos tiazídicos entre os fármacos mais fortemente associados a iatrogenia medicamentosa.[4]

Numa recente revisão sistemática da literatura (34 artigos) concluiu-se que é justificável o uso de uma baixa dose de diuréticos tiazídicos no tratamento da hipertensão em adultos com idade igual ou superior a 65 anos, exceto nos doentes com história de gota. A qualidade da evidência foi baixa e os estudos raramente descreveram as características dos participantes, como a polifarmácia e a fragilidade do idoso.[5]

Na prevenção quaternária, é inquestionável que o doente idoso exige uma atenção redobrada. No melhor interesse da pessoa humana, o médico deve evitar a aplicação cega e obstinada das normas clínicas existentes. O idoso vulnerável exige uma medicina de proximidade, alicerçada numa excelente relação médico-doente, em que a qualidade do ato clínico é, frequentemente, consubstancializada no princípio da não-maleficência.

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 publicada em 2013.

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

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

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Recebido: 03 de setembro de 2020 - **Aceite:** 22 de março de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.14856

Resposta à: Deteção Precoce de COVID-19 em Portugal: Uso de Registos Clínicos

Reply to: Early Detection of COVID-19 in Portugal: Use of Clinical Records

Palavras-chave: Brasil; COVID-19; Diagnóstico Precoce; Pandemia; Registos Médicos
Keywords: Brazil; COVID-19; Early Diagnosis; Medical Records; Pandemics

Caro Editor,

O artigo "Deteção Precoce de COVID-19 em Portugal: Uso de Registos Clínicos", publicado em março de 2021 na Revista Acta Médica Portuguesa, avalia a utilidade de indicadores relativos nos cuidados de saúde primários e hospitalares para melhora a vigilância da COVID-19 nos sistemas de saúde. Como conclusão, o artigo sugere que estes indicadores têm uma correlação forte com a taxa de incidência do coronavírus, tornando-se úteis para a detecção precoce de possíveis surtos da doença e facilitando as decisões em saúde pública, como a alocação de recursos.[1]

No Brasil, conforme a Portaria de Consolidação nº 01/GM/MS de 28/07/2017, é de competência da União Federativa a gestão dos *stocks*, abastecimento e provimento de *kits* de testagem aos Estados e ao Distrito Federal para dar suporte às ações laboratoriais e garantir a investigação, bloqueio e controle de casos e surtos de doenças.[2] Porém, a realidade brasileira de muitos centros de saúde está longe de ser a ideal. Essa disparidade estimulou-nos a escrever esta reflexão, pois a falta de recursos para testagem e diagnóstico do coronavírus acarretam o aumento da subnotificação de casos e, consequentemente, o início de novos surtos.

De acordo com estudos recentes, as taxas de notificação de casos confirmados divulgados oficialmente representam apenas 9,2% dos números reais.[3] Além disso, estima-se uma subnotificação média em capitais brasileiras de 40,7% para os óbitos relacionados com o COVID-19, com valores variando entre 25,9% a 62,7%.[4] Estes dados refletem a limitação da estratégia única de testagem em massa no combate e vigilância à COVID-19 adotada no Brasil, e expõem a necessidade de novas opções.

Nesse contexto, o uso dos indicadores citados no artigo, como o de pneumonias virais, poderiam antecipar o aumento do número de novos casos na população e permitir um melhor planeamento para testagem direcionada, identificando e isolando tais casos, impedindo a ocorrência de surtos[1]. Esta metodologia permitiria manter um maior controle sobre o desenrolar da pandemia e prevenir o colapso do sistema de saúde.

A presente situação exige outras estratégias no combate a essa grave pandemia. Não podemos depender apenas de meios sabidamente limitados por uma série de fatores, como a disponibilidade de financiamento e infraestrutura, como é o caso dos testes para a COVID-19. Portanto, a alternativa Portuguesa seria extremamente relevante no cenário brasileiro, podendo ser implementada em qualquer centro de saúde, sem restrições financeiras ou logísticas, promovendo uma maior eficácia no controle e erradicação dessa doença no país.

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Recebido: 11 de janeiro de 2021 - **Aceite:** 12 de janeiro de 2021 - ***Online issue published*:** 03 de maio de 2021

https://doi.org/10.20344/amp.16241

Correction to the article "Abnormal Uterine Bleeding in Adolescents: A Multidisciplinary Approach", Published on Acta Med Port 2021 Apr;34(4):291-297.

Errata ao artigo "Hemorragia Uterina Anormal em Adolescentes: Uma Abordagem Multidisciplinar", Publicado em Acta Med Port 2021 Apr;34(4):291-297.

On page 293, last paragraph on the left side column, **where it reads**:
"We will discuss in detail the approved pharmacologic agents to treat acute AUB in adolescents, followed by a pharmacological management algorithm, taking in consideration the hemodynamic stability and the haemoglobin level.[8,9,15]"

It should read:
"We will discuss in detail the approved pharmacologic agents to treat acute AUB in adolescents, followed by a pharmacological management algorithm, taking in consideration the hemodynamic stability and the haemoglobin level [Appendix 1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/12829/Appendix_01.pdf)].[8,9,15]"

Article published with errors: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/12829

Na página 293, último parágrafo da coluna do lado esquerdo, **onde se lê:**
"We will discuss in detail the approved pharmacologic agents to treat acute AUB in adolescents, followed by a pharmacological management algorithm, taking in consideration the hemodynamic stability and the haemoglobin level.[8,9,15]"

Deverá ler-se:
"We will discuss in detail the approved pharmacologic agents to treat acute AUB in adolescents, followed by a pharmacological management algorithm, taking in consideration the hemodynamic stability and the haemoglobin level [Appendix 1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/12829/Appendix_01.pdf)].[8,9,15]"

Artigo publicado com erros: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/12829

https://doi.org/10.20344/amp.16382

ERRATA

Errata ao artigo "Impacto do Confinamento em Crianças e Adolescentes", Publicado em Acta Med Port 2021 Apr;34(4):245-246.

Correction to the article "The Impact of Confinement on Children and Adolescents", Published on Acta Med Port 2021 Apr;34(4):245-246.

Na página 245, cabeçalho do artigo, **onde se lê** (assinalado a vermelho):
"Acta Med Port 2021 Apr;34(**3**):245-246"
Deverá ler-se:
"Acta Med Port 2021 Apr;34(**4**):245-246"

Artigo publicado com erros: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15854

On page 245, header of the article, **where it reads** (marked in red):
"Acta Med Port 2021 Apr;34(**3**):245-246"
It should read:
"Acta Med Port 2021 Apr;34(**4**):245-246"

Article published with errors: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15854

https://doi.org/10.20344/amp.16383