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Reusing Patient Data to Train Artificial Intelligence for Medical Devices in the European Union

A Reutilização dos Dados dos Doentes para Treinar Inteligência Artificial para Dispositivos Médicos na União Europeia

Yuri LADEIA[1,2], Nuno SOUSA[2,3,4]
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Keywords: Artificial Intelligence; Confidentiality/legislation & jurisprudence; European Union; Health Records, Personal
Palavras-chave: Inteligência Artificial; Confidencialidade/legislação e jurisprudência; Registos de Saúde Pessoal; União Europeia

Health data have enabled significant breakthroughs in medicine. A recent endorsement is the Nobel Prize in Chemistry awarded to the AlphaFold project, the artificial intelligence (AI) tool developed by Google DeepMind to predict the structure of proteins, thus enhancing advances in deep learning and experimental approaches.[1]

Consequently, the diffusion of AI – "machine-based systems with different levels of autonomy and post-deployment adaptation" – in the life sciences has rendered the processing of training, validation and testing health data (hereafter collectively 'training data') increasingly vital, according to the definitions provided in article 3(1)(29), (30), (31), (32) and (37) of the European Union (EU) regulation 2024/1689, Artificial Intelligence Act (AIA),[2] which lays down harmonized rules on AI.

Provided IA is intended to be placed on the market, either as a safety component or itself as a product, it is a high-risk system. This is the case of AI as a medical device (AIaMD), which generally relies on the processing of high-quality and representative training data to safeguard performance and safety.[3] In this regard, the challenge is harmonizing AI and MD requirements with privacy rights, as per article 6(1) subparagraphs (a) and (b), and section A (11) of annex I to the AIA.[4]

Data protection is enshrined as a fundamental right in several international treaties in Europe and the EU, including in the European Convention on Human Rights, and enhanced mainly by Regulation (EU) 2016/679 – General Data Protection Regulation (GDPR)[5] – which safeguards the privacy of data subjects.[6] The GDPR provides agnostic and strict rules for personal data processing, regardless of sector, including healthcare. The safety of MD is affected by the requirements of Regulation (EU) 2017/745 — the Medical Devices Regulation (MDR)[7] — and Regulation (EU) 2017/746[8] — *in vitro* Diagnostic Medical Devices Regulation (IVDR). Member States' laws complement these EU Regulations.

To understand the impact in practice, for the sake of clarity, it is essential to bear in mind the following definitions: personal data (any directly or indirectly identifiable information relating to an individual person, including pseudonymized non-anonymous data – e.g., encrypted clinical episodes, user numbers, notes and more); data processing (series of processing activities, from collection, structuring, storage, interconnection and erasure, e.g.) and data controller (legal person who defines the means and purposes of the processing, e.g. manufactures, deployers, sponsors of a clinical study), under article 4 (1) (2) (7) and (8) of the GDPR.[9]

Once the key concepts have been established, the next step is to safeguard the interest in setting up datasets to train AIaMD overall. What is the most appropriate legal basis of the GDPR, and how does it make his interest legitimate, without jeopardizing biomedical innovation and patients' rights?

Putting the issue in perspective

The application of AIaMD has raised concerns about its reliability and safety. A 2019 study compared the performance of AI with that of human doctors in diagnosing diseases, revealing that although AI needs more data and refinement, it shows promising results, especially in fields like image recognition. However, challenges persist. In a study carried out in Uganda in 2023, an AI algorithm showed poor performance in identifying dermatological diseases in dark skin compared to light skin, e.g.[3] Diversifying training data throughout the device's lifecycle remains critical for continuous safety and performance monitoring across a wide

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spectrum of scenarios of AI application in healthcare.[10]

The digitalization of healthcare is generating a massive amount of data beyond human processing capacity. By increasing cognitive capacities, AI can support doctors in better-informed and precise decision-making. However, the success of AIaMD depends on the representativeness of the training data,[11] especially as the reliability of AI capabilities is fundamental to patient care, and for the trust and accountability of the doctor as the human operator and overseer of the AI system, as established in article 14(2), and recitals 66 and 73 of the AIA.

The World Health Organization 2021 guidelines report that "generating evidence for AI-Based MD" "emphasizes using high-quality and representative data". The recommendations underline the need for a robust database to ensure the safe performance of AIaMD in medical practice.[12]

From the data protection angle, processing training data for AIaMD requires a consistent legal basis. The GDPR provides several without hierarchy, including the subject's consent and the data controller's legitimate interest – manufacturer or deployer, for example.

The development and deployment data processing phases of artificial intelligence involve separate purposes (thus constituting separate processing activities). In life sciences, consent is often applied as a legal basis, as it provides data subjects with greater transparency and control. However, consent may not be the optimal data protection approach, particularly in large-scale cases where it is unfeasible to ensure individual consent and its conditions.[13]

Hence, if the conditions for consent are not met under GDPR article 7 at the data collection development phase, then in subsequent deployments, the lawfulness will be affected, thus contradicting the continuous monitoring and improvement requirements.[14] For instance, when data processing in the deployment phase is based on controller or third-party legitimate interest, in the event that the original data collection was unlawful (for example, consent conditions not appropriate due not informing data subjects about secondary data processing purposes), when assessing the legitimate interest adequacy as legal basis (data subjects may not expect such further processing, for example), it could be poisoned and compromised, according to "Opinion 28/2024" of the European Data Protection Board (EDPB) "on AI models for the processing of personal data".[15]

On the other hand, legitimate interest may provide a more appropriate legal basis in both phases, as long as it can be demonstrated that data processing is indispensable for safety and performance intended purposes of the AIaMDs. This quality and safety based legitimate interest must be carefully balanced so the rights of the data subjects are not jeopardized.

Strategic perspective

The GDPR may allow the processing of sensitive health-related personal data, as long as there are valid legal bases. The training data processing must ensure safety and performance, balancing the privacy of the data subjects. The decision between consent *versus* legitimate interest depends on the specific scenario, and a meticulous analysis is essential to determine the most appropriate legal basis on a case-by-case basis.

The data controller's legitimate interest relies on three cumulative conditions. As a balancing test, the interest should be lawful – not contrary to the law; clearly and precisely articulated – not general; real and present – not speculative, as per the "Guidelines 1/2024 on the processing of personal data based on Article 6(1) (f) GDPR" by EDPB.[15]

In the AIaMD development and deployment, under Quality Management Systems, those requirements are in place when the common purpose is related to ensuring high standards of quality, safety and privacy, as per article 10 AIA and the complementary legal basis under Article 9 (2) subparagraph (i) GDPR, allowing health data processing. It is also a condition for placing and maintaining the product on the EU market, under Article 5 MDR.

Therefore, it is suggested that collecting and (re)using health data (development and deployment) throughout the AIaMD lifecycle could be grounded in the legal basis of legitimate interest; provided this interest is not limited to the economic sense, and also provided there is recognition of this interest by the law, as is the case with security and quality purposes. Although controversies in case law that are not covered in this paper due to space constraints, in general, if the interest is purely material, this legal basis may have no effect.[10]

CONCLUSION

If the AI model is non-anonymous (the probabilistic chances of extracting personal data for development and from queries are not insignificant) as per EDPB "Opinion 28/2024", we suggest that legitimate interest based on quality and safety reasons could reveal a balanced legal basis for health data processing on development and deployment of AIaMDs, as the device's performance and patients' safety are commonly paramount to EU law, suppliers, deployers, doctors, and patients.

AUTHOR CONTRIBUTIONS

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Evaluation of Survival and Neurodevelopment in Neonates Born Very Preterm at a Tertiary Centre in Portugal

Avaliação da Sobrevivência e Neurodesenvolvimento de Recém-Nascidos Grandes Prematuros num Centro Terciário em Portugal

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ABSTRACT

Introduction: Advances in medical care have significantly improved survival rates for preterm infants globally, leading to an increase of population of newborns at neurological risk. Knowledge of gestational age-specific outcomes is essential to guide and provide the best medical care. This study aimed to evaluate the impact of gestational age in mortality and neurodevelopment of very preterm infants. As a secondary objective, we aimed to determine the influence of perinatal factors on the combined outcome of neurodevelopmental impairment or death.

Methods: We conducted a retrospective cohort study of all infants born before completing 32 weeks of gestational age, admitted to the Neonatal Intensive Care Unit in a tertiary maternity hospital in Portugal from 2013 to 2021. Neurodevelopment was assessed at 24 months of corrected age, using Griffiths Mental Developmental Scales II. Moderate to severe neurodevelopment impairment was considered in the presence of at least one of the following criteria: global development quotient < 70, cerebral palsy, severe visual impairment or profound sensorineural deafness.

Results: There were 311 very preterm infants assessed for eligibility, 10.9% neonatal deaths and 11.9% losses to follow-up. Neurodevelopment evaluation was performed on 274 infants, of whom 6.2% (17/274) had moderate to severe neurodevelopment impairment: 7.5% (5/67) born before 28 weeks of gestational age and 5.8% (12/207) between 28 - 31 weeks. Global development quotient < 70 was verified in 4.7% of cases. Cerebral palsy was diagnosed in 3.3%, severe visual impairment in 0.7% and profound sensorineural deafness in 0.7%. The survival rate without moderate to severe neurodevelopment impairment exceeded deaths at 25 weeks and was > 86% from 28 weeks onward. In multivariable logistic regression analysis, gestational age was identified as a protective factor for moderate to severe neurodevelopment impairment or death (aOR 0.81; CI 95% 0.68 - 0.98), whereas male sex (aOR 3.19; CI 95% 1.57 - 6.71) and resuscitation with tracheal intubation (aOR 8.17; CI 95% 3.16 - 20.96) were independent risk factors.

Conclusion: This study reaffirms gestational age as a key determinant of survival and neurodevelopmental outcomes in very preterm infants, with those born before 28 weeks facing higher risks of mortality and severe neurodevelopmental impairments. Understanding local survival rates and neurodevelopmental outcomes is paramount for guiding perinatal decision-making and providing accurate evidence-based counseling to parents of preterm infants.

Keywords: Child Development; Infant, Extremely Premature; Infant Mortality; Morbidity; Neurodevelopmental Disorders; Premature Birth

RESUMO

Introdução: A melhoria dos cuidados perinatais tem contribuído para maiores taxas de sobrevivência, condicionando um aumento da população de recém-nascidos com risco neurológico. O conhecimento sobre os *outcomes* por idade gestacional é fundamental para guiar a prática clínica e prestar os melhores cuidados médicos. O principal objetivo deste estudo foi avaliar o impacto da idade gestacional na mortalidade e no neurodesenvolvimento dos recém-nascidos grandes prematuros. Como objetivo secundário pretendeu-se analisar os fatores perinatais que podem influenciar o *outcome* combinado de sequelas moderadas a graves do neurodesenvolvimento ou morte.

Métodos: Estudo observacional retrospetivo de uma coorte de recém-nascidos com menos de 32 semanas de idade gestacional, nascidos entre 2013 e 2021 num hospital de apoio perinatal diferenciado em Portugal. O neurodesenvolvimento foi avaliado aos 24 meses de idade corrigida utilizando a Escala de Desenvolvimento Mental de Griffiths II. Considerou-se a existência de sequelas moderadas/graves na presença de pelo menos um dos seguintes critérios: quociente global de desenvolvimento < 70, paralisia cerebral, cegueira ou surdez neurossensorial profunda.

Resultados: Foram incluídos 311 recém-nascidos; ocorreram 10,9% mortes neonatais e 11,9% perdas de *follow-up*. A avaliação do neurodesenvolvimento foi realizada em 274, dos quais 6,2% (17/274) apresentavam sequelas moderadas/graves: 7,5% (5/67) com < 28 semanas e 5,8% (12/207) entre 28 e 31 semanas. Verificou-se quociente global de desenvolvimento < 70 em 4,7%, paralisia cerebral em 3,3%, cegueira em 0,7% e surdez neurossensorial profunda em 0,7%. A taxa de sobrevivência sem sequelas moderadas/graves superou a mortalidade a partir das 25 semanas e, a partir das 28 semanas, foi superior a 86%. Na regressão logística multivariada, verificou-se que a idade gestacional foi um fator protetor (aOR 0,81; IC 95% 0,68 -0,98) para o desenvolvimento de sequelas moderadas/graves do neurodesenvolvimento ou morte, o sexo masculino (aOR 3,19; IC 95% 1,51 - 6,71) e a necessidade de reanimação profunda ao nascimento (aOR 8,17; IC 95% 3,16 - 20,96) foram fatores de risco independentes.

Conclusão: Este estudo comprova que a idade gestacional é um fator determinante para a sobrevivência e desenvolvimento de sequelas do neurodesenvolvimento, com maior risco abaixo das 28 semanas. O conhecimento destes dados por idade gestacional é fundamental para uma tomada de decisão baseada em dados locais, bem como para esclarecer os pais de prematuros.

Palavras-chave: Desenvolvimento Infantil; Lactente Extremamente Prematuro; Morbilidade; Mortalidade Infantil; Nascimento Prematuro; Perturbações do Neurodesenvolvimento

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KEY MESSAGES

- This study provides valuable insights into the follow-up of a substantial cohort of very preterm infants (88.1%) and is considered representative of the outcomes at our center.
- The survival rate without moderate to severe neurodevelopment impairment surpassed the mortality rate at 25 weeks of gestational age and exceeded 86% from 28 weeks onward.
- Abnormal neurodevelopmental outcome and death were associated with lower gestational age, male sex, and resuscitation with tracheal intubation.
- Understanding survival rates and neurodevelopmental outcomes by gestational age is crucial for supporting perinatal decision-making and guiding parental counseling in cases of preterm delivery within our unit.

INTRODUCTION

Advances in medical care have significantly improved survival rates for preterm infants worldwide,[1-5] with the most notable gains occurring in infants born under 28 weeks of gestational age (GA) – extreme preterm (EPT) infants.[6] It is described that the increased survival of EPT infants is accompanied by a higher incidence of morbidity.[5,7] However, in the last decade, there has been an improvement in both survival and survival without severe or moderate disabilities rates, despite the higher risk of neurodevelopmental impairment (NDI) in this group.[3] Most studies analyzed exclusively infants born EPT, with a gap in the literature regarding survival and neurodevelopment outcomes in very preterm (VPT) infants, born under 32 weeks of GA. In fact, VPT infants are also considerably affected – it is estimated that 30% - 40% have some degree of NDI.[3,8-10]

The factors that influence neurological development are complex, with brain maturation after the neonatal period being affected not only by biological factors but also by environmental and socioeconomic influences.[9,11,12] It is important to assess not only the survival rate but also the sequela and quality of life of those children who survived. Rates of survival with and without morbidities vary significantly between countries.[2] Survival rate without NDI at 2 - 2.5 years was 20% in the United States of America (USA) for infants born at 22 - 24 weeks (w) of GA and 34% and 42% in England and Sweden, respectively, for those born between 22 - 26 weeks.[3] Besides GA and birthweight (BW), the factors most strongly correlated with neurodevelopmental sequela include major brain injuries, such as severe periintraventricular hemorrhage and cystic periventricular leukomalacia (PVL), bronchopulmonary dysplasia, retinopathy of prematurity and sepsis.[13-16] Additionally, the increase in multiple pregnancies over recent decades has inherently contributed to a corresponding rise in prematurity.[17,18] However, the association between multiple births and neurodevelopmental outcomes is still controversial.[19,20]

Identifying children born preterm who are at risk of later development delay could enable targeted interventions, potentially preventing future disabilities, as a timely intervention could have a positive impact on cognitive outcomes in infancy.[3,21]

Understanding local survival rates and neurodevelopmental outcomes is essential for guiding perinatal decision-making and providing informed parental counseling in cases of extreme preterm deliveries.[2]

We aimed to evaluate the impact of GA in mortality and neurodevelopment in VPT infants. As a secondary objective, we aimed to determine the influence of perinatal factors on the combined outcome of neurodevelopmental impairment or death.

METHODS

Study design and patient selection

We conducted a retrospective cohort study of all preterm infants born before 32 weeks of GA admitted to the Neonatal Intensive Care Unit (NICU) in a tertiary maternity hospital from June 2013 to June 2021.

Neonates with major congenital malformations and/or chromosomal abnormalities were excluded.

An *a priori* power analysis, using an alpha error of 0.05 and a power of 95%, calculated that the minimum sample size would be 246 (201 without moderate to severe NDI and 45 with moderate to severe NDI or death).

Data collection

Clinical data were collected through the review of the perinatal and neonatal medical records using the NICU's database.

Prenatal and postnatal data

Collected maternal data included parity and sociodemographic characteristics, such as age and educational level (dichotomized as 'high': university degree or equivalent; or 'low': high school graduation or lower).

The perinatal factors evaluated included multifetal gestation, antenatal corticosteroid therapy for pulmonary fetal maturation (complete when either two doses of betamethasone or four doses of dexamethasone were administered),

cesarean or vaginal delivery, outborn status (infants born in other facilities and transported to our unit after delivery), sex, GA, BW, and endotracheal intubation during neonatal resuscitation.

Neonatal characteristics and morbidity were also explored. Small for gestational age (SGA) was defined as BW below the 10th percentile for GA by Fenton growth charts.[22] Neonatal sepsis was defined as clinical sepsis and abnormal laboratory findings (leukocyte count above 30 000/μL or under 5000/μL and C-reactive protein above 2 mg/dL), irrespective of blood culture results. Early-onset sepsis was considered when it occurred in the first 72 hours of life and late-onset sepsis when it occurred after 72 hours.[23] Bronchopulmonary dysplasia was defined as the need for oxygen at 36 weeks postmenstrual age.[24] Periventricular leukomalacia was considered when it was equal to or higher than grade II, according to the classification by De Vries *et al*.[25] Severe peri-intraventricular hemorrhage was considered if grade III or whenever hemorrhagic infarction was present, according to Volpe's classification.[26] Mechanical ventilation, postnatal surfactant, and corticosteroid administration were also assessed.

Follow-up data

According to the institution's protocol, all survivors are included for longitudinal follow-up at 24 months of corrected age (CA). This follow-up program is conducted by a specialized multidisciplinary team that includes pediatricians, nurses and trained educators. In this study we analyzed all infant's evaluation at 24 months of CA that met the inclusion criteria.

Neurodevelopment was assessed at 24 months of CA using the validated Griffiths Mental Developmental Scales II (GMDS-II). A global development quotient (GDQ) and development quotients for each specific area (locomotor, personal-social, hearing and language, eye and hand coordination and performance) were calculated.[27] The diagnosis of cerebral palsy (CP) was established according to the definition of the European Cerebral Palsy Network and the Global Motor Function Classification System, by an experienced neuropaediatrician.[28,29] Vision and hearing impairments were systematically evaluated by a pediatric ophthalmologist and otolaryngologist.

Moderate to severe NDI was considered in the presence of at least one of the following criteria: a GDQ for GMDS-II evaluation less than 70, diagnosis of CP, severe visual impairment (blindness) or profound sensorineural deafness requiring a hearing device.

Given that infants with severe perinatal complications have higher mortality rates and face a higher risk of adverse neurodevelopmental outcomes, we analyzed the combined outcome: moderate to severe NDI or death.

Data analysis

Statistical analysis was performed with IBM SPSS Statistics® version 29. Nominal variables were expressed as numbers and percentages. Variables were tested for normality using the Kolmogorov-Smirnov test. Depending on their distributions, numeric variables were reported as mean and standard deviation or median and interquartile

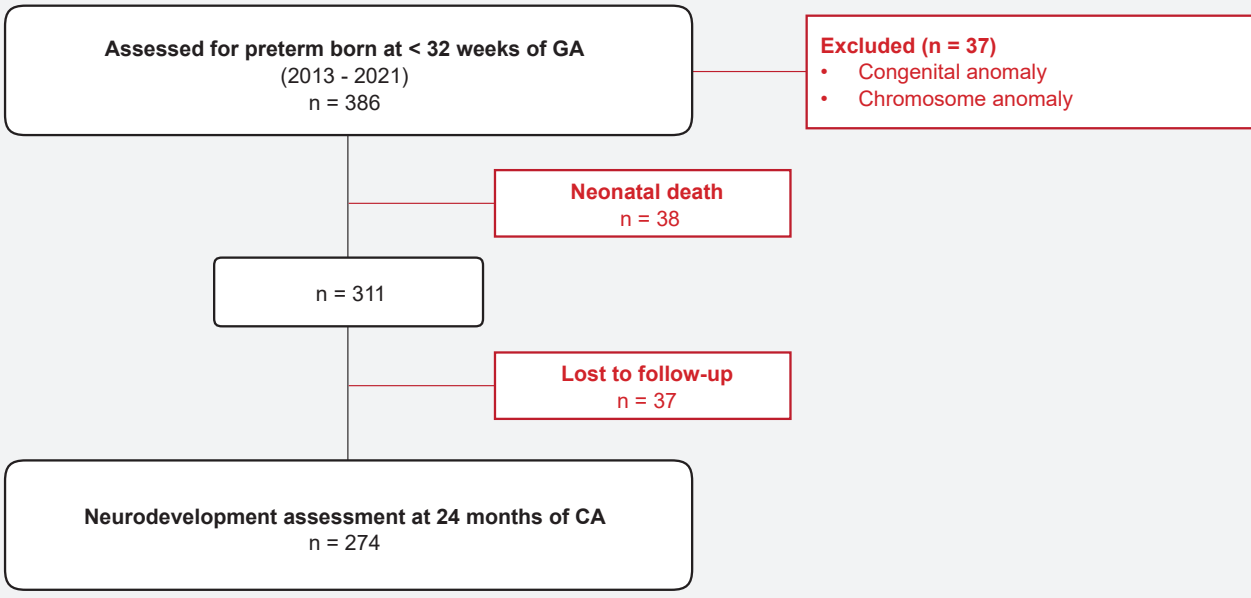


Figure 1 – Flowchart of patient selection
GA: gestational age; CA: corrected age

range (IQR). The χ^2 test or Fisher's exact test was used to compare nominal variables. Regarding quantitative variables, comparisons between groups were made using the non-parametric Mann-Whitney U test. The odds ratio (OR) and respective 95% confidence interval (95% CI) were presented as appropriate.

Adjustment by logistic regression was performed to identify the predictors for NDI. We constructed a model by adjusting for statistically significant and relevant maternal and perinatal factors, with the exclusion of variables with significant collinearity and with a very small number of cases. Quality of fit was verified by the Hosmer and Lemeshow test and the model was verified by the Omnibus test.

All reported *p* values are two-tailed with values inferior to 0.05 indicating statistical significance.

Approval was obtained from the local Ethics Committee (OBS_SF_192/2023).

RESULTS

During the study period, 311 VPT infants were assessed for eligibility. A flowchart illustrating the study's recruitment process is shown in Fig. 1. There were 38 (10.9%) neonatal deaths.

There were 37 (11.9%) losses to follow-up. When comparing the two groups (with and without follow-up) there were no statistically significant differences in GA ($p = 0.232$), BW ($p = 0.938$) and IMV ($p = 0.108$) – Table 1.

Global characterization

In this analysis, 274 children had neurodevelopmental assessments at 24 months of CA. The median GA was 29 weeks (IQR 2), with no sex predominance. The median BW was 1222 g (IQR 548) and 20% were SGA. Resuscitation with tracheal intubation was performed on 26%. During hospital stay, 42% needed invasive mechanical ventilation and the median of ventilation days was 1.5 (IQR 5.4).

Table 1 – Characteristics and comparison of infants with follow-up and lost to follow-up

Perinatal factors and morbidities	Infants with follow-up (n = 274)	Infants lost to follow-up (n = 37)	*p*-value	OR (CI 95%)
High educational level, n (%)	116 (44.8)	0 (0)		**0.55 (0.50 - 0.61)**[a]
Vaginal delivery, n (%)	110 (40.1)	14 (37.8)		1.10 (0.54 - 2.23)[b]
GA (weeks) (median | IQR)	29 | 2	30 | 2	0.232[c]	-
Twins, n (%)	82 (29.9)	6 (16.2)		0.57 (0.23 - 1.46)[b]
Monochorionic twins, n (%)	33 (40.7)	0		0.59 (0.50 - 0.71)[a]
TTTS, n (%)	5 (6.2)	0		0.94 (0.89 - 0.99)[a]
ACT, n (%)	232 (85.3)	35 (94.6)		3.02 (0.70 - 13.04)[b]
Outborn, n (%)	28 (10.2)	4 (12.5)		1.07 (0-35 - 3.23)[a]
Male, n (%)	140 (51.1)	19 (51.4)		1.01 (0.58 - 2.01)[b]
BW (gram) (median | IQR)	1222 | 548	1225 | 497	0.983[c]	-
SGA, n (%)	54 (19.7)	3 (8.1)		0.36 (0.11 - 1.21)[b]
Resuscitation with tracheal intubation, n (%)	72 (26.4)	6 (16.2)		0.54 (0.22 - 1.35)[b]
IMV, n (%)	114 (41.6)	10 (27.0)		0.52 (0.24 - 1.12)[b]
IMV duration (days, median | IQR)	1.5 | 5.4	3.0 | 0.5	**< 0.001**[c]	-
NIVM, n (%)	219 (79.9)	21 (56.8)		**0.33 (0.16 - 0.67)**[b]
Surfactant administration, n (%)	104 (38.0)	9 (24.3)		0.53 (0.24 - 1.16)[b]
Sepsis, n (%)	54 (20)	5 (14)		0.64 (0.24 - 1-71)[b]
BPD n (%)	21 (7.7)	1 (2.7)		0.34 (0.04 - 2.56)[a]
Severe PIVH, n (%)	21 (7.7)	1 (2.7)		0.33 (0.43 - 2.53)[a]
Cystic periventricular leukomalacia, n (%)	5 (1.5)	1 (2.7)		1.85 (0.20 - 17.05)[a]
Hydrocephalus needing derivation, n (%)	8 (2.9)	0		0.97 (0.95 - 0.99)[a]
Posnatal corticosteroids, n (%)	23 (8.4)	1 (2.7)		0.30 (0.04 - 2.31)[a]
Breastfeeding or mixed feeding at discharge, n (%)	224 (81.7)	19 (51.4)		**4.24 (2.08 - 8.67)**[b]

ACT: antenatal corticosteroid therapy; BPD: bronchopulmonary dysplasia; BW: birth weight; CI: confidence interval; GA: gestational age; IMV: invasive mechanical ventilation; IQR: interquartile range; PIVH: periventricular-intraventricular hemorrhage; NIMV: non-invasive mechanical ventilation; OR: odds ratio; SGA: small for gestation age.; TTTS: twin-twin transfusion syndrome. Bolded values are statistically significant ($p < 0.05$)
a: Fisher exact test; **b**: χ^2 test; **c**: Mann-Whitney U

Regarding comorbidities, sepsis was diagnosed in 20% (5% early-onset; 15% late-onset), bronchopulmonary dysplasia in 8% and severe peri-intraventricular hemorrhage in 8% of the infants. The remaining baseline characteristics are shown in Table 1.

Neurodevelopment assessment at 24 months CA

Neurodevelopment assessment revealed that 6.2% (17/274) of VPT infants had moderate to severe NDI: 7.5% (5/67) with GA < 28w and 5.8% (12/207) with GA 28 – 31 w. GMDS-II global development quotient < 70 was verified in 4.7% (12/274), with hearing and language being the most affected area. Profound sensorineural deafness was diagnosed in 0.7% (2/274) and severe visual impairment in 0.7% (2/274). Cerebral palsy was diagnosed in 3.3% (9/274): eight with spastic bilateral involvement and one spastic unilateral. The prevalence of CP was 4.5% (3/67) in GA < 28w and 2.9% (6/207) at GA 28 – 31w. Among the six patients born between 28 – 31w and diagnosed with CP, three had PVL and two had severe peri-intraventricular hemorrhage with hydrocephalus that needed derivation.

The overall survival rate and survival rate without NDI were inversely related to GA (Fig. 2). The survival rate without moderate to severe NDI exceeded mortality rate at 25 weeks of GA and was > 86% from 28 weeks onward (Fig. 2).

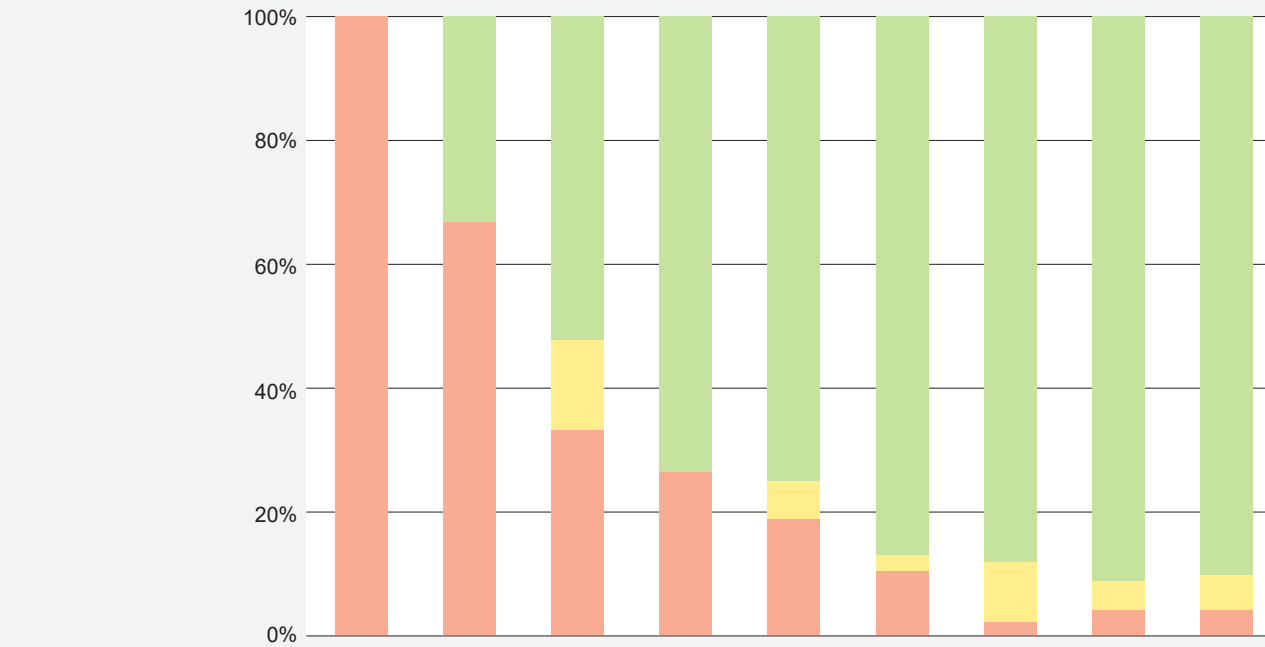
Impact of perinatal factors on the combined outcome of NDI or death

A comparison between the group with combined outcome of moderate to severe NDI or death with the group without NDI/death, showed statistically significant differences, as displayed in Table 2.

Multivariable logistic regression analysis was performed on the significant factors from the above analyzis and the model (p = 0.115) verified by the Hosmer and Lemeshow test was selected for further analysis, suggesting that the fitting condition of the model was good. After adjustment, (R^2 0.2), GA was a protective factor for moderate to severe NDI or death (aOR 0.81; CI 95% 0.68 - 0.98), whereas male sex (aOR 3.19; CI 95% 1.51 - 6.71) and resuscitation with tracheal intubation (aOR 8.17; CI 95% 3.16 - 20.96) were independent risk factors (Fig. 3).

DISCUSSION

Preterm infants are a vulnerable population at high risk of mortality, morbidity, and neurodevelopmental



GA (w)	23	24	25	26	27	28	29	30	31
Survival with no sequelae (n)	0	2	11	25	24	33	37	62	63
Survival with sequelae (n)	0	0	3	0	2	1	4	3	4
Deaths (n)	1	4	7	9	6	4	1	3	3

Figure 2 – Outcomes by gestational age (weeks)
GA: gestational age; w: weeks
Sequelae refers to moderate to severe neurodevelopment impairments

Table 2 – Characteristics and comparison between infants with combined outcome of moderate to severe NDI and death with the group without NDI/death

Perinatal factors and morbidities	Infants without moderate to severe NDI (n = 257)	Infants with moderate to severe NDI or death (n = 55)	*p*-value	OR (CI 95%)
Male, n (%)	127 (49.4)	40 (72.7)		**2.73 (1.44 - 5.19)**[a]
Maternal educational level – university degree, n (%)	131 (54.1)	12 (21.8)		**4.23 (2.12 - 8.42)**[a]
GA (weeks) (median | IQR)	29 | 2	27 | 2	**< 0.001**[b]	-
Twins, n (%)	78 (30.8)	15 (32.6)		1.01 (0.55 - 2.12)[a]
Monochorionic twins, n (%)	33 (42.9)	5 (35.7)		0.74 (0.23 - 2.42)[a]
Twin-to-twin transfusion syndrome, n (%)	5 (6.5)	3 (21.4)		3.93 (0.82 – 18.80)[c]
ACT, n (%)	218 (85.5)	42 (79.2)		0.648 (0.31 - 1.37)[a]
BW (grams) (median | IQR)	1230 | 540	925 | 550	**< 0.001**[b]	-
Vaginal delivery, n (%)	105 (40.9)	23 (41.8)		0.96 (0.53 - 1.74)[a]
Outborn, n (%)	28 (10.9)	5 (9.4)		0.85 (0.31 - 2.32)[a]
SGA, n (%)	50 (19.5)	5 (9.4)		0.43 (0 – 16 - 1.14)[a]
Resuscitation with tracheal intubation, n (%)	62 (24.2)	40 (75.5)		**9.63 (4.84 - 19.16)**[a]
IMV, n (%)	103 (40.1)	43 (81.1)		**6.43 (3.1 - 13.37)**[a]
NIMV, n (%)	203 (79.0)	30 (56.6)		**0.35 (0.19 - 0.65)**[a]
Surfactant administration, n (%)	93 (36.2)	33 (62.3)		**2.91 (1.58 - 5.36)**[a]
Sepsis, n (%)	49 (19.1)	10 (18.9)		0.99 (0.47 - 2.10)[a]
BPD, n (%)	10 (3.9)	2 (3.8)		0.99 (0.21 - 4.56)[c]
Posnatal corticosteroids, n (%)	21 (8.2)	2 (3.8)		0.44 (0.10 - 1.94)[c]
Severe PIVH, n (%)	18 (7.1)	20 (37.7)		**7.95 (3.82 - 16.55)**[a]
Cystic periventricular leukomalacia, n (%)	3 (1.2)	2 (3.8)		3.28 (0.54 – 20.14)[c]
Hydrocephalus needing derivation, n (%)	5 (1.9)	3 (5.7)		2.24 (0.2 - 15.4)[c]

ACT: antenatal corticosteroid therapy; BPD: bronchopulmonary dysplasia; BW: birth weight; CI: confidence interval; GA: gestational age; IMV: invasive mechanical ventilation; PIVH: periventricular-intraventricular hemorrhage; NDI: neurodevelopment impairment; NIMV: non-invasive mechanical ventilation; OR: odds ratio; SGA: small for gestational age.
Bolded values are statistically significant ($p < 0.05$).
a: χ^2 test; **b**: Mann-Whitney U test; **c**: Fisher exact test

impairments that carry lifelong consequences.[2,3,15,30,31] Some authors have shown an improvement in survival rates and sequelae-free survival in recent decades, however, these children are still at high risk of NDI.[3,32] Assessing neurodevelopment outcomes is important because of-its impact on the child's quality of life, especially in VPT. The gestational age-specific data and knowledge presented in our study is crucial for providing parents with accurate information regarding the risks of mortality and NDI in this group of newborns.

In our study, the mortality rate < 32 weeks GA was 10.9%. This is slightly higher than that reported in other studies and might be explained by the fact that we included deaths that occurred in the delivery room, which is not the case in other studies (eNewborn).[30] A previous Portuguese study analyzing the same age group reported a mortality rate of 15%.[33]

We observed a decline in mortality rates with increasing GA up to 28 weeks, after which mortality stabilized below 4% (Fig. 2). This trend is consistent with findings from the eNewborn European Network database study, which also includes Portuguese data.[30]

Our follow-up rate of 88.1% is higher than reported in other studies and close to the ideal value in this age group, as referred by the guidelines of the American Academy of Pediatrics (90%).[3,7,34] When comparing the two groups (with and without follow-up), there were no statistically significant differences in GA, BW and invasive mechanical ventilation. None of the infants lost to follow-up were born to a mother with higher education.

In our study, the survival rate without moderate to severe NDI exceeded the number of deaths at 25 weeks of GA. Similar data was reported in a 2006 study (EPICure).[32] Our survival rate without moderate to severe NDI improved with increasing gestational age, exceeding 86% from 28 weeks onward. The survival rate without NDI was higher

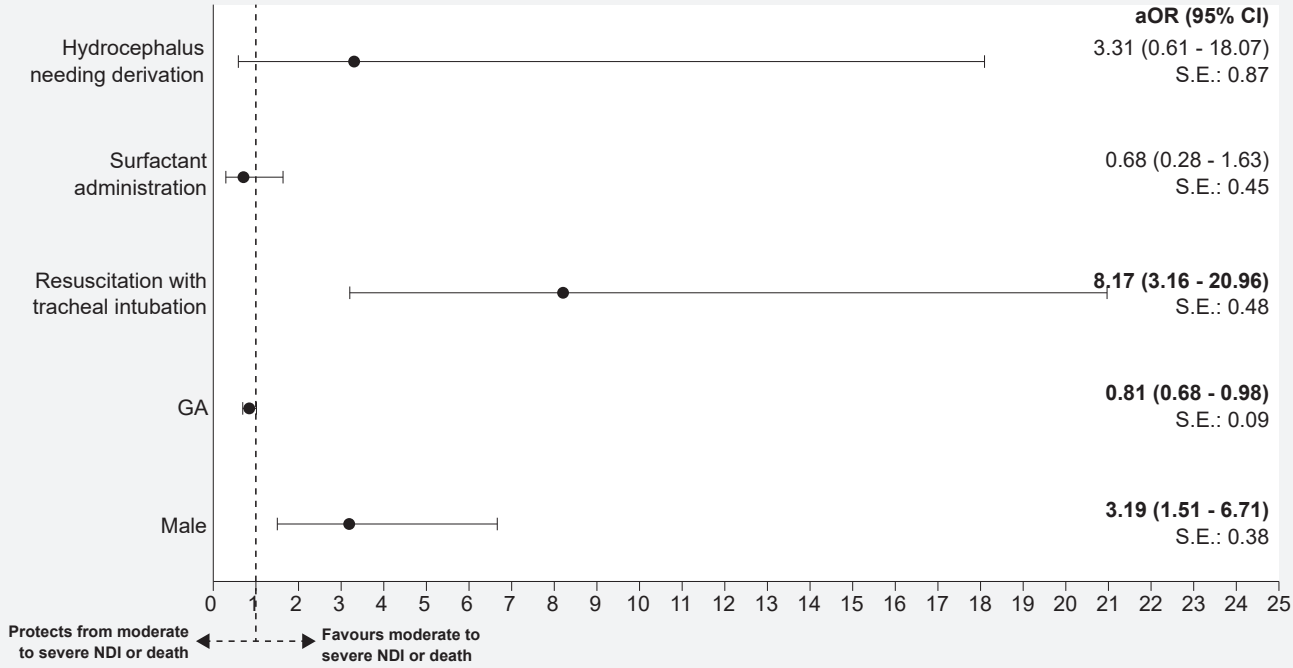


Figure 3 – Multivariate logistic regression including factors that may influence moderate to severe NDI or death
Variables included in multivariate logistic regression: male sex, gestational age, resuscitation with tracheal intubation, surfactant administration and hydrocephalus needing derivation.
aOR: adjusted odd ratio; CI: confidence interval; GA: gestational age; NDI: neurodevelopment impairment; SE: standard error.
Bolded values are statistically significant ($p < 0.05$).

in our study than what is reported in EPIPAGE for GA ≤ 26 weeks (67.8% *vs* 45.5%) but slightly lower at 27 – 31 weeks (87.6% *vs* 90%).[3]

Regarding NDI, in our study 6.2% of VPT had moderate to severe NDI at 24 months of CA, which is lower than the 10% reported in Resende *et al*, a Portuguese study conducted at the same hospital with similar methods but with inclusion of VPT and/or BW < 1500 g.[35] Comparison of GMDS-II GDQ < 70 and CP also revealed better results (GMDS-II GDQ < 70: 4.7% *vs* 6.8% and CP: 3.3% *vs* 6%), which can be justified by the continuous improvement of medical care.[35]

The EPICure study reported 13.4% of severe NDI in infants < 28 weeks of GA, while our group reports 7.5% for the same GA.[32] However, comparison with other studies regarding the presence of NDI must be done cautiously, since the methodology, scale applied and the population studied varied across different publications.

In our study, the incidence of CP (4.5% in GA < 28 w and 2.9% at 28 – 31 weeks) was lower than what is reported in the European CP surveillance program (14% at < 28 weeks of GA, 6% at 28 – 31 weeks and < 1% at 32 – 36 weeks).[6,28] However, it bears mentioning that the diagnosis of CP was performed in children with ≥ 5 years of age (*vs* 24 months CA in our study) which may lead to an underestimation of our results, as milder cases may not have been identified.

There are currently few studies in Portugal evaluating neurodevelopment in VPT. Furthermore, none of them are stratified by GA and neither analyzed the correlation with possible risk factors and serious mortality complications.

In our study, abnormal neurodevelopmental outcomes were associated with lower GA, male sex and resuscitation with tracheal intubation. Lower GA is well described to be associated with neurodevelopment impairment and mortality.[3,35-37] In our cohort, this was evident, with survival rates without serious sequela exceeding mortality rates at 25 weeks and being over 86% from 28 weeks of GA onwards. Since lower GA is related to a higher risk of morbidities, the literature is more centered in EPT, with limited studies regarding neurodevelopment outcomes in VPT.[1,5,7,38,39] Concerning sex, there are theories about males being more vulnerable to injury due to differences in brain organization and genetic or hormonal predisposing factors.[2,13,40,41] However, a systematic review that included studies conducted later in childhood, revealed that the influence of sex on general cognition was largely reduced at five years old.[41] Resuscitation with tracheal intubation at birth is related to a lower Apgar score, and in accordance to what is described in the literature, the need for advanced resuscitation at birth, in our study, was associated with moderate to severe NDI or

death.[37]

The aim of the evaluation of maternal education was to infer about the socioeconomic status, as it is described in the literature that a lower status is a risk factor for NDI.[3,4,7,41] In our study, the bivariate analysis showed that a higher level of maternal education was a protective factor for NDI. In a systematic review, unlike factors related to infant characteristics, the influence of parental education appeared to persist until middle childhood.[41]

A previous study in the same NICU found that fetal growth restriction was associated with a significantly increased risk of poor neurodevelopmental outcome at 24 months of CA, compared to infants with appropriate weight for GA.[42] However, in this study we only evaluated the weight percentile for GA and no differences were found. In the literature, there is often no clear definition of fetal growth restriction and sometimes SGA is used, which can confuse the results and make comparison difficult.

When comparing singletons to multiples, there were no differences in mortality and NDI, which is similar to the results reported in an Italian study and in a recent systematic review.[19,43] In contrast to Taborda *et al,* who reported that monochorionic twins had an increased risk of severe neurodevelopmental delay.[20] Current results can be related to better prenatal care with closer monitoring of twin pregnancies.

To our knowledge, this is one of the few and most recent Portuguese studies to show neurodevelopment at two years of age in this population, with stratification by GA. The low rate of children lost to follow-up and the fact that they were not significantly different from our cohort are this study's major strengths. Nevertheless, being a retrospective and single-centre study, our analysis carries some limitations, as the findings may not be representative of other NICUs. Memory and registration biases can be minimized in this study, since the data on this population is recorded in our NICUs database by some of the authors that report to a national level database (National Registry of Very Preterm Newborns) and is systematically recorded from birth to discharge.[30] Another limitation is that children's neurodevelopment is only monitored and assessed up to 24 months of CA, as some neurodevelopment disorders may appear later. Therefore, an evaluation at school age would be important.

CONCLUSION

This study reinforces GA as a key factor influencing survival and neurodevelopmental outcomes in VPT infants. Our findings reveal that preterm infants born before 28 weeks face significantly higher risks of mortality and severe NDI. Furthermore, from 25 weeks of GA onward, the survival rate without moderate to severe sequela surpasses the mortality rate. Even though these data demonstrate improvements in both survival and survival without disabilities, it remains essential to maintain systematic follow-up and conduct thorough neurodevelopmental assessments in preterm infants. Understanding local survival rates and neurodevelopmental outcomes is crucial for perinatal decision-making and parental counseling in cases of preterm delivery.

AUTHOR CONTRIBUTIONS

MCS, CC: Study conception and design, data collection, analysis and interpretation, drafting and critical review of the manuscript.

CLD: Study conception and design, data collection, analysis and interpretation, critical review of the manuscript.

AD, DF: Study conception and design, data interpretation, critical review of the manuscript.

AT: Study conception and design, data analysis and interpretation, drafting and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Attitudes and Perceptions of Portuguese Psychiatrists and Psychologists on the Clinical Use of Ketamine

Atitudes e Perceções dos Psiquiatras e Psicólogos Portugueses sobre o Uso Clínico de Cetamina

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ABSTRACT

Introduction: Ketamine has garnered attention for its rapid efficacy in alleviating depressive symptoms in treatment-resistant depression, offering a novel mechanism as a non-monoaminergic agent. Despite its potential, limited research has explored mental health professionals' perspectives on its use. This study assesses the attitudes, knowledge, and concerns of Portuguese psychiatrists and psychologists regarding the clinical application of ketamine in treatment-resistant depression.

Methods: A cross-sectional survey study was conducted from June 2022 to January 2024 among Portuguese psychiatrists and psychologists. The anonymous online questionnaire assessed perceptions of ketamine's therapeutic utility, risks, and knowledge sources. Statistical analyses examined subgroup differences by age, sex, profession, and prior psychedelic use.

Results: Among 156 participants (mean age = 37.2; 68.6% female), 53.8% were psychologists, and 46.2% were psychiatrists or trainees in Psychiatry. Only 35.9% reported substantial knowledge of ketamine's therapeutic potential, while 59% were open to integrating it clinically. The majority expressed interest in training, though 73% raised concerns about inadequate professional training. Significant differences emerged, with psychiatrists reporting higher knowledge levels and openness to ketamine compared to psychologists, while younger professionals showed greater interest in training and usage.

Conclusion: There was a favorable attitude toward ketamine use among Portuguese psychiatrists and psychologists, yet substantial educational gaps remain. Customized training addressing age, sex, and professional background is essential for safe and effective clinical integration of ketamine in treatment-resistant depression. Further studies should focus on longitudinal outcomes of ketamine treatment under standardized protocols to ensure efficacy and safety in clinical practice.

Keywords: Attitude of Health Personnel; Depressive Disorder, Treatment-Resistant/drug therapy; Ketamine/therapeutic use; Surveys and Questionnaires

RESUMO

Introdução: A cetamina é um fármaco que tem despertado um maior interesse devido à sua eficácia rápida na atenuação dos sintomas depressivos na depressão resistente ao tratamento, oferecendo um mecanismo inovador enquanto agente não monoaminérgico. Apesar do seu potencial, há uma escassez de investigação sobre as perspetivas dos profissionais de saúde mental relativamente à sua utilização. Este estudo avalia as atitudes, o conhecimento e as preocupações dos psiquiatras e psicólogos portugueses quanto à aplicação clínica da cetamina na depressão resistente ao tratamento.

Métodos: Foi realizado um estudo transversal através de um inquérito entre junho de 2022 e janeiro de 2024, abrangendo psiquiatras e psicólogos portugueses. O questionário, anónimo e online, avaliou perceções sobre a utilidade terapêutica, os riscos e as fontes de conhecimento sobre a cetamina. As análises estatísticas examinaram diferenças entre subgrupos segundo idade, sexo, profissão e experiência prévia com psicadélicos.

Resultados: Entre os 156 participantes (média de idade = 37,2 anos; 68,6% do sexo feminino), 53,8% eram psicólogos e 46,2% eram psiquiatras ou médicos internos de Psiquiatria. Apenas 35,9% relataram ter um conhecimento substancial sobre o potencial terapêutico da cetamina, enquanto 59% demonstraram abertura para a sua integração na prática clínica. A maioria mostrou interesse em obter formação específica, embora 73% tenham expressado preocupações quanto à insuficiência da formação profissional disponível. Observaram-se diferenças significativas: os psiquiatras reportaram níveis de conhecimento e abertura superiores aos dos psicólogos, enquanto os profissionais mais jovens mostraram maior interesse na formação e utilização da cetamina.

Conclusão: Pareceu existir uma atitude favorável à utilização da cetamina entre psiquiatras e psicólogos portugueses; no entanto, persistem lacunas educacionais significativas. A formação personalizada, considerando idade, sexo e contexto profissional, é essencial para uma integração clínica segura e eficaz da cetamina no tratamento da depressão resistente ao tratamento. Estudos futuros deverão focar resultados longitudinais do tratamento com cetamina sob protocolos padronizados, garantindo eficácia e segurança na prática clínica.

Palavras-chave: Atitude do Pessoal de Saúde; Cetamina/uso terapêutico; Inquéritos e Questionários; Perturbação Depressiva Resistente a Tratamento/tratamento farmacológico

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KEY MESSAGES

- Ketamine shows promise as a treatment for depression, with rapid antidepressant effects and potential benefits for treatment-resistant cases.
- Most participants expressed openness to using ketamine clinically, with 78.9% seeking further training and 79.4% advocating for more research.
- Significant knowledge gaps were evident, as only 35.9% of participants reported good understanding of ketamine's therapeutic potential.
- Concerns about safety included inadequate training, risk of psychosis, and potential for misuse, emphasizing the need for structured protocols.
- Strengths of the study include its diverse sample and comprehensive insights, while limitations include self-selection bias and reliance on self-reported data.

INTRODUCTION

Over the last decades, ketamine – a glutamatergic modulating drug with psychedelic properties, formally approved as an anesthetic – has stood out in the scientific literature and psychiatric clinical practice due to its rapid onset of action and effectiveness in relieving depressive symptoms.[1] Its mechanism of action is unique, being a non-monoaminergic agent with proven efficacy in major depression.[2] A single infusion of ketamine in sub-anesthetic doses demonstrates a rapid antidepressant effect, with a peak effect within 24 hours, and which remains superior to placebo for up to 10 - 12 days.[1] Meta-analytic evidence reveals that repeated administrations of ketamine sustain the antidepressant response, an effect observed up to four weeks after the last treatment applied.[1]

Scientific support for the off-label use of ketamine in psychiatric disorders – mainly in treatment-resistant depression (TRD) – relies on more than 20 years of research through placebo and active-treatment-controlled clinical trials, systematic reviews with meta-analysis, and real-world evidence.[3] Positive results from more than 40 randomized controlled trials led to the recent recognition of intravenous ketamine as level 1 evidence (higher quality of evidence), supporting its integration as a second-line treatment in the management of TRD in a recent update of the international treatment guidelines for depression from The Canadian Network for Mood and Anxiety Treatments (CANMAT), which are among the most widely used by psychiatrists around the world.[4] The intravenous administration of ketamine (0.5 - 1.0 mg/kg) is therefore no longer considered an "experimental treatment" according to the guidelines authors, but now appears as one of the options to be considered after failure of treatment with antidepressants, together with other equally established treatments with level 1 evidence such as lithium, quetiapine or intranasal esketamine (one of the enantiomers of ketamine, and therefore possessing similar effects).[4]

Furthermore, despite lingering questions about the therapeutic value of ketamine's subjective experience, several studies suggest that the presence of psychedelic experiences promotes greater benefits and may improve mental health and well-being.[5] This has generated a lot of debate about its subjective effects and also uncertainty about how its use can be optimized or which model of approach is safer and more effective to be used in patients with psychiatric disorders. Preliminary data also suggest ketamine holds potential for treating alcohol and other substance use disorders in combination with structured behavioral therapy.[6-8]

Over the past decade, some researchers have examined mental health professionals' attitudes and beliefs about integrating psychedelic substances into clinical practice. Studies in the United States provided important insights into these perspectives. Barnett *et al* found that psychiatrists generally viewed psychedelics as dangerous and supported keeping them illegal for recreational use.[9] However, a follow-up study published in 2024 showed a significant shift, with many psychiatrists now recognizing the therapeutic benefits of psychedelics and planning to use psychedelic-assisted therapy in their practice if approved, with younger psychiatrists being particularly optimistic.[10] Similarly, a survey with clinical psychologists found generally favorable attitudes toward psychedelic-assisted therapy, although they remained cautious about potential psychiatric and neurocognitive risks.[11] The survey also revealed a significant lack of education and training about psychedelics. Most of these studies, however, only integrated perspectives from mental health professionals concerning classic psychedelic substances [such as psilocybin and lysergic acid diethylamide (LSD)] and 3,4-methylenedioxymethamphetamine (MDMA), which still lack sustained scientific evidence that could result in their approval for clinical use. On the other hand, professional perspectives regarding the clinical use of ketamine have not been explored as much, despite being a more common and widespread practice worldwide. However, a study conducted by Levin *et al* included the

perspectives of psychiatrists on different psychedelic substances, including ketamine, with participants rating psilocybin and ketamine as safer and with greater therapeutic potential than substances like alprazolam.[12] Overall, these findings highlight the need for comprehensive educational programs to prepare healthcare professionals to safely and effectively use psychedelic-assisted therapies.

In Portugal, the antidepressant properties of ketamine sparked interest in Portuguese psychiatric services. Since 2021, ketamine treatments have been made available according to different protocols in both public and private institutions, most of them taking advantage of its psychedelic effects, and usually with psychological support before, during and after ketamine administration. Despite that, data regarding the efficacy and safety of this approach in any of these institutions have not yet been published. Taking these recent developments into account, it is timely to assess the knowledge, attitudes, and perceptions of Portuguese psychiatrists and psychologists regarding ketamine and its therapeutic potential for psychiatric disorders. This assessment is crucial to understand the readiness and receptivity of healthcare providers to integrate new treatments with psychedelic drugs into their clinical practice. It will also identify educational gaps and inform the development of specific training programs to ensure that healthcare professionals are well-equipped to use psychedelic therapies safely and effectively.

METHODS

The present study has been developed by the Interdisciplinary Centre for the Study of Human Performance's (CIPER) Behavioral Regulation research group at the University of Lisbon, in partnership with the Portuguese Society for Clinical Application of Entheogens (SPACE). It also results from a research partnership with the Johns Hopkins School of Medicine (JHSM) which is conducting a similar study in the United States of America. The study was approved by the Faculty of Human Kinetics Review Board. It represents a cross-sectional study that employed a descriptive online survey from an opportunistic volunteer sample. The target population was currently practicing Portuguese clinical psychologists, psychiatrists and Psychiatry trainees, and registered in their respective professional organizations.

Participants were asked to answer an anonymous and confidential online survey that encompassed professional characterization and their perceptions and attitudes towards the clinical use of ketamine in Psychiatry at a single time point. The survey was originally developed by psychedelic science specialists at JHSM. The measures included are a series of self-constructed items that assess knowledge, perceptions and attitudes on ketamine treatments for which no previous measures were found in the literature. Topics addressed were: attitudes and beliefs, perceived knowledge, acceptability, concerns, sources of knowledge, trusted sources for future training, secondary effects, and treatment indications. All items were subject to a backtranslation process and were reviewed by bilingual experts to ensure accuracy and cultural relevance.

Data was collected between June 1st, 2022 and January 31st, 2024, through a secure internet-based survey platform and stored in a password-protected *LimeSurvey* institutional account. The survey was disseminated in social media, institutional newsletters, and survey lists through collaboration with professionals' associations (Portuguese Psychologists Association; The Portuguese Society of Psychiatry and Mental Health and its online platform of the Mental Health Observatory). Preliminary results of this study were presented as part of the official program of the XVI National Congress of Psychiatry, held in November 2022, in order to also foster the engagement of participants.

All analyses were carried out using IBM-SPSS® 29.0 statistical software. Sample characteristics were reported as frequencies and percentages for categorical variables, and as means and standard deviations (SD) for continuous variables. Data were not normally distributed (they deviated from normality sufficiently to affect statistical inference). Differences between groups were assessed with non-parametric tests (Mann-Whitney U test or Kruskal-Wallis test, as appropriate) for continuous variables. Subgroup analyses were conducted according to sex, age groups, and profession. Data are expressed with significance threshold of $p < 0.05$.

RESULTS

A total of 156 Portuguese mental health professionals (68.6% women) completed the questionnaire [mean age = 37.2 (SD = 10.9)]. From this sample, 53.8% were psychologists and 46.2% were medical doctors (15.4% psychiatrists

Table 1 – Descriptive statistics for participant characteristics

Variable	Value
Age (Mean ± SD)	37.2 ± 10.9
Women (%)	68.6%
Education Level (%)	
- Bachelor	18.6%
- Masters	75.6%
- PhD	7.2%
Profession (%)	
- Medical doctor	46.2%
- Psychiatrist	15.4%
- Psychiatry trainee	30.8%
- Psychologist	53.8%

and 30.8% psychiatrists in training) (Table 1). A minority of the sample (43.6%) declared doing research in some way, and 39.7% of participants reported having had a previous personal experience with a psychedelic substance. Figure 1 and Fig. 2 demonstrates the attitudes of mental health professionals, as well as knowledge and concerns towards ketamine clinical use in Psychiatry.

Perceptions, attitudes and acceptability

Only 35.9% of participants reported good knowledge on the therapeutic potential of ketamine and only a third (32.7%) reported good knowledge of its risks and side effects. The majority of participants (59%) indicated that they did not have good knowledge of ketamine's pharmacology. A small percentage (13.5%) reported having patients who have used ketamine. Most participants (62.9%) agreed that ketamine is a promising treatment and expressed openness to using ketamine in treating their patients (59.6%). A significant majority (78.9%) desired training on the clinical use of ketamine for psychiatric disorders, and 79.4% believed more research on ketamine was warranted. Only 4.4% disagreed that ketamine can be safely administered in a clinical setting, while 31.4% were undecided. Lastly, 37.4% agreed that health professionals' prior personal experience with ketamine is important for effectively integrating treatment with their patients, with 28.4% remaining neutral.

Concerns

The most frequently reported concerns involving ketamine, rated as very or extremely worrying, included the lack of professionals with specialized training (73%), abuse or exploitation of patients (56%), and improper recreational use (58%). Moreover, 50% of the participants were very or extremely concerned about the administration of ketamine to patients with contraindications and 48% were concerned about the potential for psychotic outbreaks. A smaller percentage of participants (44%) expressed concerns related to the potential risk of ketamine addiction.

Sources of knowledge and training

Participants reported that they primarily obtained information from the scientific and academic literature (51.9%), other health professionals (42.4%), informal conversations (37.3%) and the media (34.8%). When asked about their trusted sources, health professionals favored research centers (84.2%), professional organizations (79.7%), and more experienced colleagues (74.7%) (Table 2).

Contexts of administration and therapeutic potential

Participants reported that the most suitable places for the clinical administration of ketamine were specialized clinics (67.1%), followed by hospital settings (59.8%) and rehabilitation clinics (43.7%). Some mental health professionals indicated that current evidence suggests ketamine can be

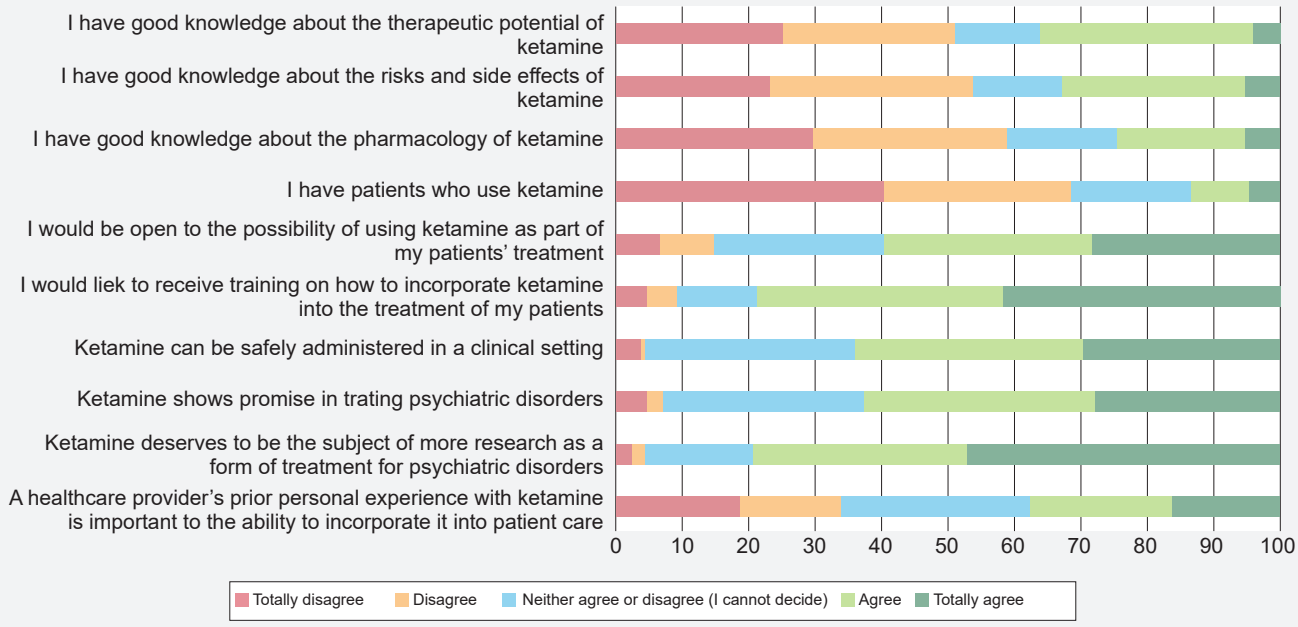

Figure 1 – Attitudes and knowledge towards ketamine

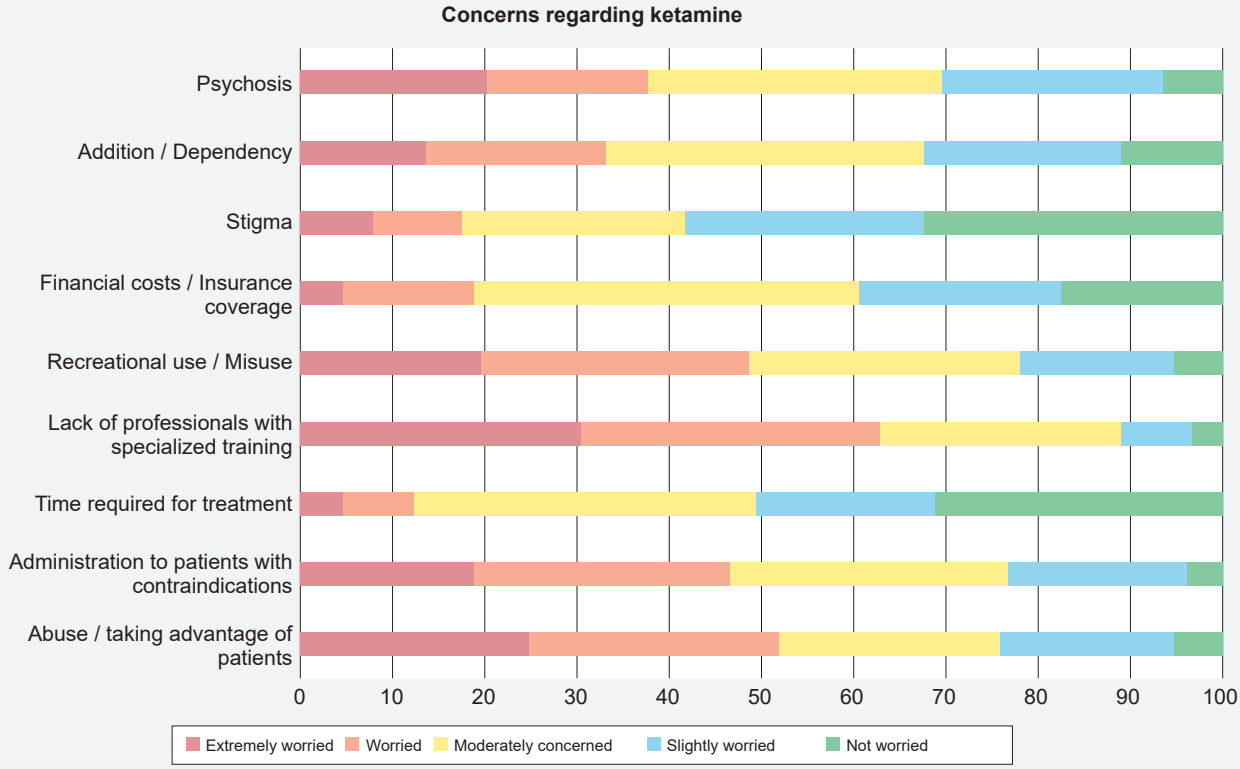

Figure 2 – Concerns regarding ketamine

useful in the treatment of depression (77.9%) and suicidal ideation (40.9%).

Influence of training/profession

Psychiatry doctors reported significantly higher perceptions of having good knowledge about ketamine's therapeutic potential ($p < 0.001$), its risks and side effects ($p < 0.001$), and also its pharmacology ($p < 0.001$). They also reported greater openness to integrating ketamine treatments into their clinical practice ($p < 0.001$), receiving specific training ($p < 0.001$), also recognizing that it can be used safely in clinical settings ($p < 0.001$), and that this is a promising intervention ($p < 0.001$) that should be the target of further future research ($p = 0.0038$). Regarding concerns, there were also significant differences between the two professional categories. Psychologists expressed greater concern about the risk of psychosis ($p = 0.005$), addiction ($p = 0.028$), and misuse of ketamine ($p = 0.028$). They were also more concerned about the lack of properly trained professionals ($p = 0.044$), administration of ketamine to patients with contraindications ($p < 0.001$), and potential for patients' abuse or exploitation ($p = 0.001$).

Table 2 – Sources of knowledge and training

Sources of knowledge and training	% (156)
Formal clinical training (e.g., university, private organization, or pre/postgraduate)	32
Colleagues	42
Scientific/academic literature	52
Presentations at conferences or workshops	34
Media (e.g., books, films, podcasts, social networks, online forums)	35
Informal conversations	37
Previous experiences with patients	10
Personal experiences	7
I have no knowledge	19

Influence of age

The Kruskal-Wallis test was conducted to determine if there were statistically significant differences in responses between different age groups. The age groups were defined as follows: ≤ 35 years, 36 - 49 years, and ≥ 50 years. The test results showed statistically significant differences between age groups in the self-assessment of knowledge about the therapeutic potential of ketamine (p = 0.001), about its risks and side effects (p = 0.0013), and also its pharmacology (p = 0.001). Post-hoc comparisons showed that self-perceived knowledge was significantly higher in those three parameters amongst the ≤ 35 years group compared to the 36 - 49 years group (p = 0.001, p = 0.004 and p = 0.001, respectively), while the same was true for the ≥ 50 years group compared to the 36 - 49 years group regarding knowledge about the therapeutic potential of ketamine (p = 0.050), and its pharmacology (p = 0.002). Additionally, there were statistically significant differences between group ages regarding willingness to use ketamine as part of treatment for their patients (p = 0.001), willingness to receive training (p = 0.005) and on the perception that ketamine can be safely administered in clinical settings (p = 0.045). Post-hoc comparisons indicated both attitudes were significantly higher for the ≤ 35-year-old group than the 36 - 49-year-old group (p = 0.001, p = 0.002, and p = 0.027, respectively). About the concerns on the clinical use of ketamine, the Kruskal-Wallis test indicated that there were significant differences between different age categories only regarding the risk of psychosis (p = 0.035). Post-hoc comparisons presented that this concern was higher amongst the 36 - 49 years group compared to the ≤ 35 years group (p = 0.012).

Influence of gender

The Mann-Whitney test indicated that there were significant differences between gender groups in their attitudes and perceptions. Specifically, men showed significantly more positive perceptions regarding knowledge about ketamine's therapeutic potential (p = 0.001), about its risks and side effects (p = 0.001), and also its pharmacology (p = 0.001). Additionally, men were more willing to use ketamine as part of treatment for their patients (p = 0.008) and favored the perceptions that it can be administered safely in clinical settings (p = 0.05) and that ketamine is promising for the treatment of psychiatric disorders (p = 0.019). Men agreed significantly more often with the perspective that a healthcare provider's prior personal experience with ketamine is important to their ability to incorporate it into patient care (p = 0.042). There were no significant differences between male and female participants in their levels of concern for any of the aspects regarding its clinical administration.

Influence of previous psychedelic use

Significant differences were observed in perceptions and attitudes about ketamine between participants who had previously used psychedelic substances compared to those who had not. The results indicated that previous users reported greater interest in considering using ketamine as part of their patients' treatment (p = 0.025), desire to receive information on incorporating ketamine into their clinical practices (p = 0.001) and agreement with the importance of personal experience with ketamine for health professionals (p = 0.003). Significant differences were also observed regarding several concerns, where previous psychedelic users showed that they were less concerned about addiction/dependence (p = 0.007), psychosis (p = 0.036), and time required for treatment (p = 0.002).

DISCUSSION

Especially during the past decade, there has been a global increase in clinical research on psychedelics. Concurrently, countries with specific regulatory frameworks, such as Switzerland, Australia, and Canada, have progressively integrated psychedelic substances like psilocybin and MDMA into their mental health services.[13-16]

Clinical use of ketamine for psychiatric disorders (mostly depression) has been more significant and widely available, driven by the accumulation of scientific evidence of its efficacy and safety, making it essential that mental health professionals become well informed about this therapeutic approach.[17,18] To our knowledge, this is the first published study that sought to describe attitudes and perspectives of Portuguese psychiatrists and clinical psychologists regarding the use of ketamine for psychiatric disorders. This is important given the availability of ketamine treatment in Portugal. Assessment of Portuguese professionals is also of interest given that Portugal has been an early innovator in drug policy reform. This research provides valuable insights into perceptions, acceptability, concerns, and the influence of demographic factors such as sex, age, and work experience on these attitudes.

According to our findings, there is a general openness among Portuguese mental health professionals towards the clinical use of ketamine for psychiatric disorders. Almost 80% desired further training in ketamine treatment models, as most participants considered ketamine to be a promising treatment and expressed openness to using ketamine in treating their patients. These findings align with previous studies on the clinical use of other psychedelic drugs, which also reported high levels of interest and perceived the need for further research and training among mental health professionals.[10,19,20]

Despite this, it is worth highlighting that the psychiatrists and psychologists who participated in this survey currently

lacked sufficient knowledge on the therapeutic potential of ketamine and its risks and side effects. However, most participants correctly recognized that ketamine has frequently been studied and used in the treatment of depression and suicidal ideation.[1,21] Considering this, it is relevant to highlight that only about half the sample reported acquiring their knowledge about ketamine primarily through the scientific and academic literature and about a third acquired knowledge or training through formal clinical training. This highlights the need for targeted education and training programs, something which has already been identified in the literature.[11,22] This is particularly relevant because the main concern expressed by the participants in this survey was precisely the administration of ketamine by professionals who are not properly trained, as explored below. Another relevant aspect is related to perceptions of trustworthiness regarding sources of information on the clinical use of ketamine. When asked about their trusted sources, mental health professionals predominantly chose research centers, professional organizations, and more experienced colleagues. It is important to notice that participants were much more reluctant regarding receiving information from private institutions and from pharmaceutical corporations. These findings indicate that professional, formal and peer-reviewed sources are crucial for mental health professionals to access trusted information about ketamine treatments for psychiatric disorders. Therefore, universities, research centers and professional societies should be informed of their important role in educating and training mental health professionals in this specific field.

The present study showed that the main concerns regarding ketamine's clinical use were the lack of trained professionals, the administration to patients with contraindications, and the potential for patient abuse/exploitation. Similar concerns have been highlighted in other studies regarding interventions with psychedelics, indicating a common apprehension about the current readiness of the professional community to manage psychedelic therapies safely.[22] These concerns thus emphasize the need for comprehensive training programs and stringent regulatory frameworks to ensure safe and ethical clinical practices, something that has been highlighted by the recent increase in articles published on this particular topic.[23-29] In this regard, although the offer of professional training in this area is increasing throughout the world, there is a large heterogeneity in training programs and in the skills and background of the trainers.

In Portugal, to date, there has been no training program specifically dedicated to the clinical use of ketamine, so Portuguese professionals currently involved in this practice underwent their training in different international centers. Despite this, SPACE currently provides an online introductory course on the clinical use of psychedelics and also published a scientific manual on this subject, initiatives that had the scientific support of The Portuguese Society of Psychiatry and Mental Health.[30] A practical guide regarding the clinical use of ketamine aimed at Portuguese mental health professionals was also published, derived from a national collaboration between clinicians with theoretical training and practical experience in administering ketamine for mental health disorders. Some of these experts were responsible for implementing the first ketamine-assisted therapy protocols in the Portuguese National Health Service.[31] Concomitantly, a multidisciplinary group was set up in Portugal, involving several professional societies and the national ethics authority, to anticipate challenges in the regulation of treatments with psychedelics.[32] One of the objectives of this group is to promote ethical and safe practices, having recently proposed practical recommendations in this area, for public discussion.

Participants reported that the most appropriate settings for the clinical administration of ketamine were specialized clinics, followed by hospital settings. The current regulation of ketamine in Portugal requires that it can only be administered in hospitals or similar settings. Over the last few years, ketamine treatment has been made available in Portugal in hospitals and specialized clinics, although each entity has specific protocols approved by the respective ethics and pharmacy committees. No data regarding the efficacy and safety of these interventions have been published yet by any of these clinical teams.

Regarding safety, only a minority of the participants disagreed with the statement that ketamine can be safely administered in a clinical setting, though 31.4% remained undecided. Overall, scientific evidence suggests that the use of ketamine in depression and suicidal ideation is considered a safe and effective treatment.[4,33-35] Recently, CANMAT established a task force to evaluate the evidence on both the efficacy and safety of ketamine in clinical settings.[4] Despite recognizing the effectiveness of this intervention, CANMAT determined that due to potential side effects and feasibility issues, intravenous ketamine (as well as intranasal esketamine) should be considered a second-line treatment for depression.[4] Reported adverse events from ketamine infusions include both psychological symptoms (such as dissociation or anxiety) and physiological effects (more commonly a transient increase in blood pressure). However, the current literature indicates that with basic medical screening, the incidence of serious medical adverse events is very low (~0.1%) when ketamine is used for psychiatric disorders.[4,36] Concerns about the potential for psychotic outbreaks were shared by almost half of our respondents. The development of psychotic symptoms has been described, but primarily in individuals who are

prolonged recreational users of ketamine.[37] Furthermore, most clinical trials have excluded patients with a personal history of psychotic episodes.[38] Despite the theoretical risk of ketamine aggravating psychotic symptoms, several case studies demonstrated that treatment with ketamine not only improved mood, but also improved psychotic symptoms in patients with treatment-resistant depression with psychotic features.[38-40] However, the safety of ketamine in these patients is controversial since ketamine is known to induce psychotomimetic and dissociative effects and further evidence is necessary to establish the efficacy and the safety of ketamine in this population.[38,39]

Another concern was related to the potential risk for ketamine addiction. Morgan *et al* found that chronic ketamine recreational users (compared to controls) showed more attentional bias (the preferential allocation of attention to cues associated with reward, influencing perception and behavior) to incentive stimuli, consistent with the designation of ketamine as a potentially addictive drug.[41] In this regard, and although a specific withdrawal syndrome has not yet been identified, tolerance to the drug in daily users may develop rapidly.[41] Notably, despite ketamine's potential for recreational use, no studies or reviews to date have reported a transition to illicit use stemming from therapeutic introduction to ketamine, although anecdotally such cases exist.[3] In fact, clinical trials tend to exclude potential patients who have previously abused this substance. Interestingly, it is important to recognize that ketamine has also been studied and used clinically in the treatment of substance use disorders, with therapeutic success reported in studies on different substances, most frequently alcohol.[7,42-45] Future research should continue to monitor this potential adverse effect of ketamine, especially in patients who need maintenance treatments.

Between group differences in attitudes and concerns

Professional background influenced perceptions and attitudes, with psychiatrists being more familiar with ketamine treatments and showing greater openness. Psychologists seem more concerned about ketamine's possible deleterious effects, which may also be due to lower self-perceived knowledge regarding this treatment. This divergence may reflect differences in training and clinical exposure between these professional groups, suggesting the need for interdisciplinary education and collaboration to harmonize understanding and practices. It may also reflect differences in the scope of professional activities, given that only psychiatrists prescribe medicines. These findings are also consistent with previous studies who also reported varying levels of knowledge and attitudes across different professional groups.[9,19]

Age-related differences also emerged, with younger professionals (≤ 35 years) showing higher levels of willingness to use ketamine in treatment and a stronger desire for more information compared to older groups. Barnet *et al* (2018) found similar results suggesting that today's trainees and young psychiatrists may encounter more favorable information about psychedelics in both the medical literature and the lay press.[9] In our sample, this trend was statistically significant when comparing the youngest group with the 36 – 49-year-old group, but was not verified when comparing the youngest with the oldest group (> 50 years). This older group also showed significantly greater knowledge of the therapeutic potential of ketamine and its pharmacology when compared to the intermediate age group. These results highlight important asymmetries to be explored in the future and may indicate the group of mental health professionals between 36 - 49 years old as a specific target for education/training.

Regarding differences between men and women, men perceived themselves as more knowledgeable of the therapeutic potential, risks, and pharmacology of ketamine and reported more positive attitudes towards its clinical use, findings that are aligned with those from Grover *et al* (2023).[46]

Significant differences in attitudes were observed based on clinicians' prior psychedelic use, with past users of psychedelics reporting more positive attitudes towards ketamine's clinical use. This suggests that personal experience with psychedelics may influence professional perspectives, a finding supported by different other studies who noted similar trends in the United States of America and Australia.[19,46,47] Currently, there is an open discussion in the scientific and therapeutic community about the role of personal experience in the quality of professional practices in this field.[48]

Strengths and limitations

This study encompassed different professional groups, having obtained a greater number of participants compared to similar studies in other countries.[46] Secondly, the study expands the existing literature by assessing clinicians' knowledge, current clinical practices, and comfort levels in discussing clinical use of ketamine in psychiatric disorders. This approach includes evaluating the associations between these variables, thereby identifying specific knowledge gaps and targets for future education efforts in Portugal. However, this study also has several limitations, such as the potential for selection bias due to the self-selected nature of this sample. Individuals who are more open to or have strong opinions about psychedelics may have been more motivated to participate, potentially skewing the results. This bias limits the external validity of the findings, as professionals with less openness or more neutral views might be underrepresented. Additionally, while the sample

included almost an equal distribution of psychologists and psychiatrists, this does not reflect the actual proportions in the Portuguese professional landscape, where there are far more psychologists than psychiatrists. Finally, the study relied solely on self-reported data that can be subject to biases such as social desirability or inaccurate recall. Future research should include other professionals (e.g., nurses) and an increased sample size.

CONCLUSION

This study reveals a generally positive but cautious view among Portuguese mental health professionals regarding the clinical use of ketamine. There is a clear need for more education, training and research to address knowledge gaps and safety concerns, as well as comprehensive training programs to prepare professionals for integrating psychedelic therapies into practice.[25,46] Accordingly, future studies should focus on examining the long-term effects of ketamine treatments for patients with psychiatric disorders under standardized protocols.

AUTHOR CONTRIBUTIONS

PM: Data collection, writing of the manuscript.

JE, LCC: Statistical analysis, critical review of the manuscript.

CC: Data collection, critical review of the manuscript.

AGR, MWJ, PJT: Survey questionnaire design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

PM received consulting fees from Teva Pharmaceuticals.

AGR received consulting fees from NeonMind Biosciences and Innerwell.

MWJ received grants or contracts from the National Institutes of Health (NIH) Heffter Research Institute Fifth Generation, Inc; received consulting fees from AJNA Labs, AWAKNLife Science, Beckley Psytech, Ltd., Clarion Clinics.

All other authors have declared that no competing interests exist.

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Custos e Consequências da Doença Renal Crónica em Pessoas com Diabetes em Portugal: Um Estudo de Modelação

Costs and Consequences of Chronic Kidney Disease in People with Diabetes in Portugal: A Modelling Study

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RESUMO

Introdução: A doença renal crónica é a doença crónica com maior crescimento de prevalência, e uma das maiores causas de mortalidade global de acordo com o *Global Burden of Disease Collaboration*. O presente estudo teve como objetivo projetar a evolução desta doença em pessoas com diabetes, de modo a quantificar os custos e consequências no contexto português. Tal foi conseguido através do desenvolvimento e parametrização de um modelo analítico refletindo a epidemiologia da doença renal crónica e integrando os vários estádios de progressão da doença.

Métodos: Foi utilizado um modelo populacional de coorte com uma mecânica de Markov, onde pessoas com diabetes e doença renal crónica foram seguidas ao longo de 50 anos, em ciclos anuais, sendo registada a sua progressão através das diferentes categorias de risco da doença renal crónica. O modelo considerou a progressão natural da doença renal crónica através de 18 categorias de risco baseados na matriz de estadiamento de KDIGO, bem como a probabilidade de os doentes receberem terapêutica de substituição renal, designadamente, diálise e transplantação renal e a probabilidade de morte. A cada estádio estão associados um custo anual e um ponderador de incapacidade, pelo que o modelo permitiu estimar a sobrevivência, os anos de vida perdidos por incapacidade (*years lived with disability*), e os custos incorridos ao longo da vida, para a totalidade da população e para doentes em diferentes categorias de risco.

Resultados: Durante o tempo total de evolução da coorte, o modelo estimou, para a população total com doença renal crónica e diabetes, uma sobrevivência média de 8,62 anos, com 0,59 anos perdidos por incapacidade, e um custo médio *lifetime* de €24 613. Estes valores correspondem a mais de 410 mil anos de vida perdidos por incapacidade e um custo total, ao longo da vida, de 17,0 mil milhões de euros. A análise por nível de risco demonstra que a progressão da doença renal crónica está associada a menor sobrevivência, mais anos perdidos por incapacidade e maiores custos.

Conclusão: Os resultados deste estudo caracterizam a progressão natural da doença renal crónica em pessoas com diabetes *mellitus* tipo 2 bem como os custos e consequências associados no contexto nacional. Sendo a diabetes *mellitus* tipo 2 um fator de risco da doença renal crónica, é expectável que nas próximas décadas o impacto real seja maior do que o estimado. A análise por nível de risco permite verificar que a progressão da doença está associada a piores resultados.

Palavras-chave: Anos de Vida Ajustados por Deficiência; Diabetes Mellitus Tipo 2; Doença Renal Crónica; Custos Médicos

ABSTRACT

Introduction: Chronic kidney disease is the fastest-growing chronic disease in terms of prevalence and one of the biggest causes of global mortality according to the Global Burden of Disease Collaboration. This study aimed to project the natural disease progression of this disease in people with diabetes, and to quantify the costs and consequences in the Portuguese context. This was achieved by developing an analytical model reflecting the epidemiology of chronic kidney disease and integrating the various stages of disease progression.

Methods: A population-based cohort Markov model was used, to follow an adult cohort of people with diabetes and chronic kidney disease as they progressed through different risk categories, in annual cycles, over a period of 50 years. The model considered the natural progression of chronic kidney disease through 18 risk categories based on the KDIGO classification system, as well as the probability of patients receiving renal replacement therapy, including dialysis and kidney transplantation, and the probability of death. Each stage is associated with an annual cost and a disability weight, so the model allowed survival, years lived with disability and lifetime costs to be estimated for the entire population with chronic kidney disease and for patients in different risk categories.

Results: Over the cohort´s lifetime, the model estimated, for the total population with chronic kidney disease and diabetes, an average survival of 8.62

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years, with 0.59 years lived with disability, and an average cost of €24 613. These figures correspond to a loss of more than 410 000 years lived with disability and a total lifetime cost of 17.0 billion euros. The progression of this disease was associated with lower survival, more years lived with disability and higher costs.
Conclusion: The results of this study characterize the natural progression of chronic kidney disease in people with diabetes *mellitus* type 2, as well as the associated costs and consequences in the national context. Since diabetes *mellitus* type 2 is a risk factor for chronic kidney disease, it is expected that the real impact will be greater than estimated in the coming decades. Analysis by risk level shows that progression of the disease is associated with worse outcomes.
Keywords: Diabetes Mellitus, Type 2; Disability-Adjusted Life Years; Health Care Costs; Kidney Failure, Chronic

KEY MESSAGES

- O presente estudo pretende colmatar a escassez dos dados existentes acerca dos custos e consequências da doença renal crónica (DRC) em pessoas com diabetes em Portugal. De acordo com a informação que temos disponível, este é o primeiro estudo deste género para o contexto português.
- Os custos e as consequências associadas à DRC em pessoas com diabetes, ao longo da vida, são substanciais.
- A progressão da DRC está associada a menor sobrevivência, mais anos perdidos por incapacidade e maiores custos para os sistemas de saúde
- O eventual atraso na progressão da DRC permitirá obter ganhos em saúde e diminuir custos de seguimento.
- O modelo foi parametrizado com a melhor evidência disponível para a realidade portuguesa.

INTRODUÇÃO

Em Portugal, a doença renal crónica (DRC) tem uma prevalência estimada em 20,9%[1] da população. É definida como a presença de alterações da estrutura ou função dos rins, presentes por um mínimo de três meses, com implicações para a saúde. Em caso de progressão, a doença pode evoluir para DRC estádio 5 com necessidade de terapêutica de substituição renal (TSR).[2]

A DRC é uma das complicações mais comuns da diabetes *mellitus* tipo 2 (DM2), sendo que ocorre em cerca de 20% a 40% das pessoas com DM2.[1,3–5] Deste modo, o crescimento da DRC deve-se em parte ao aumento da incidência de DM2 bem como a uma maior longevidade associada à DM2, resultante dos avanços terapêuticos disponíveis. A sua etiologia engloba, no entanto, um conjunto diverso de fatores de risco, que incluem a duração da DM2, o controlo adequado dos valores glicémicos, a hipertensão arterial, a dislipidemia e a história de doença renal.[6]

A DRC está associada a um risco aumentado de morbilidade cardiovascular, a mortalidade prematura e a redução da qualidade de vida.[7,8] De acordo com o estudo *Global Burden of Disease*, a DRC foi classificada em 29.º lugar na lista das causas de mortalidade global em 1990, tendo subido para o 18.º lugar em 2019.[9–11] Estima-se ainda que, em 2040, a DRC seja a 5.ª maior causa de anos de vida perdidos, globalmente.[12]

Um estudo efetuado em 31 países/regiões, estimou um custo associado à DRC e TSR em 344 mil milhões de euros anuais, sendo que uma grande parte dos custos totais decorreram de custos associados à TSR.[13]

A deteção precoce e o tratamento adequado da DRC são fundamentais para atrasar a sua progressão e obter melhoria de resultados clínicos através da redução de complicações, tais como eventos cardiovasculares e evolução para DRC estádio 5 com necessidade de TSR.[14]

Os dados referentes à epidemiologia nacional da DRC são escassos. O estudo mais recente de caracterização da prevalência de DRC em Portugal, o estudo RENA, publicado por Vinhas *et al* em 2020,[1] incluiu uma população adulta seguida em cuidados primários e estimou uma prevalência de 20,9%. Este valor compara com a média Europeia reportada numa revisão e meta-análise de estudos de prevalência da DRC (18,1%).[15]

Este estudo teve como objetivo projetar a evolução da DRC em pessoas com diabetes, de modo a quantificar custos e consequências na realidade portuguesa através do desenvolvimento e parametrização de um modelo de Markov integrando os vários estádios da doença. Neste trabalho foram consideradas estimativas para a totalidade da população e para doentes em diferentes categorias de risco. Neste contexto, pretende-se contribuir para o conhecimento acerca da DRC em pessoas com diabetes em Portugal, particularmente no que concerne ao impacto da doença em termos de sobrevida, anos de vida perdidos por incapacidade e custos.

MÉTODOS

Descrição do modelo

De modo a projetar a evolução da DRC em pessoas com diabetes e estimar custos e consequências na realidade portuguesa, foi desenvolvido um modelo de Markov. O modelo, com ciclos anuais, reflete a epidemiologia e progressão natural da DRC através de diferentes categorias de risco (baixo, moderado, alto ou muito alto). A caraterização da progressão da DRC em diferentes categorias de

Tabela 1 – Matriz KDIGO: prognóstico da doença renal crónica

				Albuminuria (mg/g)		
				A1 Normal ou com aumento mínimo < 30	A2 Moderada 30 – 300	A3 Grave > 300
Taxa de filtração glomerular (mL/min/1,73 m²)	G1	Normal	≥ 90	G1A1	G1A2	G1A3
	G2	Diminuição ligeira	60 - 89	G2A1	G2A2	G2A3
	G3a	Diminuição ligeira a moderada	45 - 59	G3aA1	G3aA2	G3aA3
	G3b	Diminuição moderada	30 - 44	G3bA1	G3bA2	G3bA3
	G4	Diminuição severa	15 - 29	G4A1	G4A2	G4A3
	G5	Uremia	< 15	G5A1	G5A2	G5A3

Fonte: KDIGO (2013)

risco foi baseada na matriz de estadiamento *Kidney Disease: Improving Global Outcomes* (KDIGO), que considera a taxa de filtração glomerular (TFG) e os valores da albuminúria.[14] De acordo com esta classificação, são possíveis 18 categorias resultantes das combinações de diferentes níveis de TFG e de albuminúria. A Tabela 1 ilustra a matriz KDIGO.

Adicionalmente, são incluídos no modelo dois estádios referentes a doentes em TSR, designadamente, 'diálise e transplantação renal' e o estádio 'morte'.

Assume-se que, em cada ciclo anual, as transições entre categorias KDIGO estão circunscritas a alterações de um nível na TFG e/ou na albuminúria. Assim, por exemplo, um doente que em determinado ano esteja na categoria G3aA2 apenas pode transitar para as categorias KDIGO representados na Fig. 1.

A Fig. 1 ilustra de modo simplificado o esquema do modelo de Markov exemplificando as transições possíveis para um dos estádios.

O modelo projeta a evolução da coorte durante 50 anos, sendo os resultados atualizados a uma taxa de 4% de acordo com as mais recentes orientações metodológicas para estudos de avaliação económica de tecnologias de saúde para o contexto português.[16] A cada estádio estão associados um custo anual e um ponderador de incapacidade, pelo que o modelo permite estimar a sobrevivência, os anos perdidos por incapacidade, e os custos incorridos ao longo da vida.

População em estudo

A estimativa dos custos e consequências da DRC implica a parametrização do modelo com a prevalência da diabetes e DRC na população portuguesa em 2021, de acordo com a sua distribuição por cada um dos estádios do modelo.

Identificação dos dados clínicos

O modelo de evolução natural da DRC é essencialmente baseado em dados nacionais. A informação provém das seguintes fontes: a) o estudo RENA;[1] b) uma análise realizada pelos autores usando dados do Sistema de Informação da Administração Regional de Saúde (SIARS) da Administração Regional de Saúde de Lisboa e Vale do Tejo, I.P. (ARS LVT); c) uma análise realizada pelos autores usando

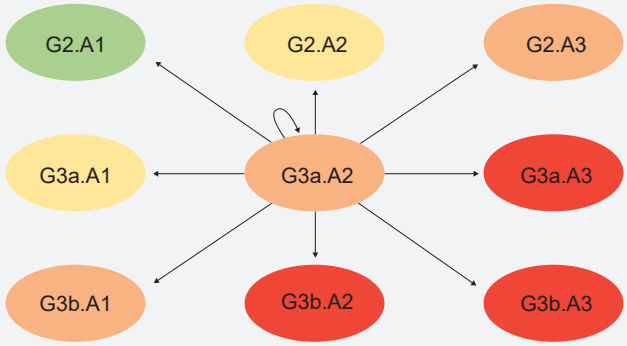

Figura 1 – Esquema do modelo de decisão analítico

dados do Hospital Beatriz Ângelo (HBA); d) informação divulgada pelo Gabinete de Registo de Doença Renal Crónica (GRDRC) da Sociedade Portuguesa de Nefrologia relativa a doentes em TSR;[17] e) um estudo internacional sobre mortalidade em portadores de doença renal crónica;[18] f) um painel de peritos sobre consumo de recursos de pessoas com DRC; g) a Base de Dados de Morbilidade Hospitalar; e h) fontes oficiais relativas a custos unitários.

Prevalência da DRC e distribuição por estádios

Para a estimativa da distribuição da prevalência de DRC pelos diferentes estádios do modelo, foram utilizados dados de diversas fontes.

Para a estimativa da distribuição da prevalência de DRC pelas categorias de risco KDIGO, foi utilizada uma abordagem mista e conjugados dados da distribuição por níveis de TFG reportados no estudo RENA[1] com dados da distribuição por níveis de albuminúria estimados através da base de dados do HBA.

O estudo RENA de Vinhas *et al*[1] estimou a prevalência global de DRC baseada na TFG numa amostra de 3135 utilizadores de cuidados primários em idade adulta (18 anos e mais). A prevalência de DRC foi estimada em 20,9% [intervalo de confiança a 95% (IC 95%): 6,5 - 35,3%] e a prevalência de diabetes em pessoas com DRC em 32,0% (IC 95%: 26,5 - 37,5%). A prevalência nas categorias KDIGO (G1A1 a G5A3) foi estimada em 20,72%.

A base de dados do HBA contém informação anual sobre o seguimento dos doentes com DRC referenciados ao Serviço de Nefrologia, entre fevereiro de 2012 e dezembro de 2017. Nesse período, foram incluídos na análise 1267 doentes (idade média de 72 anos, e 56% do sexo masculino), seguidos durante um período mediano de três anos. A análise dos dados, realizada pelos autores, permitiu estimar a distribuição desta população por estádios KDIGO, bem como realizar uma análise longitudinal para a estimativa das probabilidades de transição entre estádios KDIGO e das probabilidades de início de TSR.[19]

Foram utilizadas como fonte de prevalência em estádios de TSR estimativas do GRDRC da Sociedade Portuguesa de Nefrologia (2019) que estimaram uma prevalência de diálise de 1301,50 por milhão de habitantes e uma prevalência de transplantação renal de 706,94 por milhão de habitantes.[17]

A Tabela 2 ilustra a distribuição final da prevalência da DRC pelos diferentes estádios do modelo resultante da integração das diversas fontes de dados.

Probabilidades de transição entre estádios

Categorias KDIGO

As probabilidades de transição entre as categorias KDIGO foram estimadas a partir da base de dados do HBA. O cálculo baseia-se nas transições que efetivamente ocorreram entre ciclos anuais, sendo consideradas todas as transições de cada doente (ou seja, a cada doente corresponde um número de transições equivalente aos anos em seguimento e com informação disponível).

Tomando como exemplo o estádio G1A1 [ver Tabela S1 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/

Tabela 2 – Distribuição da prevalência de doença renal crónica

		Albuminuria			
		A1	A2	A3	Total
Taxa de filtração glomerular	G1	0,5%	0,6%	0,8%	1,9%
	G2	15,0%	14,8%	16,6%	46,4%
	G3a	10,7%	15,6%	11,9%	38,1%
	G3b	2,8%	4,2%	3,1%	10,1%
	G4	0,4%	0,9%	0,9%	2,2%
	G5	0,1%	0,1%	0,3%	0,4%
	Diálise				0,6%
	Transplantação				0,3%
	Total	29,4%	36,0%	33,6%	100,0%[a]

a: O total apresentado corresponde à soma da coluna, contabilizando os doentes em diálise e transplantação renal

view/22573/15648)], foram identificadas 25 transições anuais de doentes neste estádio: 19 doentes permaneceram no mesmo estádio, um transitou para G1A2, e cinco transitaram para G2A1, não tendo nenhum doente transitado para G2A2 (o que corresponderia a alteração simultânea de um nível na TFG e na albuminúria). A ausência desta transição nos dados deve-se provavelmente ao tamanho amostral e não implica que a sua probabilidade seja nula. Para mitigar este efeito e garantir que o modelo melhor reflete a progressão natural da doença, foi implementado um método de ajustamento que consiste na adição de '1' a todas as transições possíveis. Este procedimento, validado pelos peritos clínicos consultados, assegura que todas as trajetórias clinicamente plausíveis sejam representadas no modelo [conforme ilustrado na Tabela S1 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)]. As matrizes de probabilidade de transição entre categorias KDIGO, estimadas através deste ajustamento, estão apresentadas no Apêndice 1, nas tabelas S2 a S7 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648).

Probabilidade de transição para terapêutica de substituição renal

A probabilidade de iniciar TSR é também baseada nos dados do HBA. Durante o período de seguimento houve um total de 83 doentes a iniciar diálise e dois a realizar transplantação renal (sem diálise prévia). Assumindo que a transição para TSR apenas ocorre em doentes de muito alto risco, e que a probabilidade de transitar para TSR não pode ser inferior em estádios de maior risco, estimaram-se as matrizes de probabilidades de transição apresentada no Apêndice 1, na Tabela S8 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648).

Probabilidade de transplantação renal em doentes em diálise

A probabilidade de realizar transplantação renal em doentes em diálise foi estimada com base nos dados disponibilizados pelo GRDRC (2020). A proporção de doentes que realiza transplantação renal entre doentes em diálise variou entre 3,70% e 3,97%. No modelo, considerou-se a média dos valores apresentados, ou seja, 3,85% [Tabela S9 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

Mortalidade

Para a estimativa de mortalidade por todas as causas por estádio KDIGO, recorreu-se ao estudo de Nichols *et al.*[18] Este foi um estudo com dados de vida real, realizado nos Estados Unidos da América (mais especificamente em Oregon), que comparou pessoas com e sem DM2, emparelhados por sexo/idade, ao longo do tempo (*follow-up* mediano de 7,6 anos). Este estudo reportou um acréscimo de mortalidade com o aumento do risco definido em função da TFG e de albuminúria, a três anos. Os valores foram ajustados para a realidade portuguesa tendo em consideração as diferenças relativas de mortalidade entre a população portuguesa e a população de Oregon. Na Tabela S10 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648) estão reportadas as probabilidades anuais de morte por estádio KDIGO.

A mortalidade de doentes em TSR foi estimada com base nos dados disponibilizados pelo GRDRC (2020)[17] e pelo GRSPT (2022).[20] Para a estimativa da probabilidade de morte de doentes em diálise foi considerada a média dos valores reportados pelo GRDRC (2020) entre 2015 (12,0%) e 2019 (13,3%), que correspondeu a uma média de 12,7% [Tabela S11 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)]. Para a estimativa da probabilidade de morte de doentes pós-transplantação renal, foram considerados dados de sobrevida a cinco anos reportados pelo GRSPT (2022)[20] entre as décadas de 1980 e 2020, que permitiram calcular uma probabilidade anual de morte de 1,3% [Tabela S12 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

Ponderadores de incapacidade

Os anos de vida perdidos por incapacidade (*years lived with disability* – YLD) foram estimados aplicando, a cada estádio do modelo, os ponderadores de incapacidade baseados no *Global Burden of Disease* (GBD) 2019.[11] Deste modo, os YLD corresponderam ao produto entre o número de pessoas em cada estádio do modelo e os ponderadores de incapacidade associados a cada estádio da DRC. O GBD reporta ponderadores por nível de gravidade ou por estádio da doença. Em relação à DRC, os ponderadores dependem da gravidade da anemia (excetuando para TR). De acordo com o GBD, os estádios G1 e G2 não estão associados a incapacidade. Para os estádios G3 a G5, o ponderador médio foi calculado através de uma média ponderada dependente da distribuição por gravidade de anemia na base de dados do HBA. Para a diálise, foi calculada a média aritmética. Na Tabela S13 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648) estão representados os ponderadores de incapacidade utilizados.

Identificação e medição dos custos

Os custos associados à DRC foram estimados com base na perspetiva do Serviço Nacional de Saúde (SNS), tendo sido incluídos todos os custos médicos diretos relacionados com internamento, episódios de urgência e consultas em ambulatório, meios complementares de diagnóstico e terapêutica (MCDT) e tratamento farmacológico. A quantificação dos recursos consumidos nos vários estádios, nomeadamente os estádios KDIGO G3a.A1 a G5.A3 e os estádios de TSR, foi realizada com recurso a duas fontes principais: a base de dados do SIARS e um painel de peritos.

Custos das categorias KDIGO

Para estimar os custos associados a doentes em categorias KDIGO de risco inferior (estádios com TFG normal ou com diminuição ligeira com TFG ≥ 60 mL/min/1,73 m^2), cujo seguimento se realiza em unidades de cuidados de saúde primários, foram utilizadas estimativas de uma análise realizada pelos autores, usando a base de dados do SIARS (*trabalho não publicado*). Esta análise permitiu identificar e quantificar a utilização de consultas, MCDT e medicamentos associados.

Os dados provenientes do SIARS incluíram 20 652 adultos inscritos na Administração Regional de Saúde de Lisboa e Vale do Tejo, com registo de pelo menos uma consulta, durante o período compreendido entre 1 de janeiro de 2018 e 31 de dezembro de 2018, e com registo de diagnóstico de DM2. Destes, 12 270 doentes tinham informação suficiente para a sua distribuição por categorias KDIGO[14] permitindo assim a definição de um padrão de consumo de recursos para cada estádio. Entre estes, 9102 doentes enquadraram-se nas categorias G1A1 e G2A1, não apresentando critérios clínicos de DRC. Os restantes 3168 doentes enquadraram-se nas categorias KDIGO de risco moderado ou superior.

No SIARS não foram identificados doentes nos estádios A3; por conseguinte, consideraram-se os valores obtidos para os estádios A2. Os dados do SIARS foram também utilizados para quantificar o consumo de medicamentos nos doentes com TFG correspondente aos estádios G3a e G3b.

O custo estimado para cada estádio encontra-se detalhado na Tabela S14 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648).

Para estimar os custos anuais associados ao seguimento de doentes em categorias KDIGO de risco superior (estádios KDIGO G3a.A1 a G5.A3 com TFG < 60 mL/min/1,73 m^2), recorreu-se a um painel de peritos, com representatividade nacional. Os elementos do painel responderam de forma independente a questões específicas sobre o padrão de consumo de cuidados médicos, através do envio de um questionário por correio eletrónico. O questionário incluiu questões sobre a utilização de consultas, episódios de urgência, internamentos, MCDT e medicamentos. O resultado foi apurado por média simples.

Com base no painel de peritos, foram identificados recursos consumidos aquando da transição para níveis inferiores de TFG. Deste modo, o custo de seguimento no primeiro ano em cada estádio é diferente do custo de seguimento em anos subsequentes [Apêndice 1, Tabela S15 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

Custos da terapêutica de substituição renal

Para estimar os custos dos recursos consumidos por doentes em diálise foi utilizado o Despacho n.º 12-A/2020,[21] que define o preço da diálise por semana e por sessão, sendo estes distintos para doentes com e sem acessos vasculares. De modo a obter um preço único, foi calculado um preço ponderado com base nos valores estabelecidos no Despacho n.º 12-A/2020 e ponderados pelas percentagens de casos prevalentes de cada um (GRDRC, 2020). Adicionalmente recorreu-se a informação complementar proveniente do painel de peritos, que permitiu estimar os recursos associados ao início desta TSR, incluindo a criação do primeiro acesso vascular para hemodiálise e a colocação de cateter para diálise peritoneal.

A estimativa dos encargos com a transplantação renal baseou-se num estudo de dados de vida real[22] que considera o consumo de recursos e os incentivos previstos para a realização de transplante. O valor reportado pelos autores, referente a 2010, foi atualizado considerando a taxa de inflação. Os custos anuais por estádio de TSR estão disponíveis na Tabela S16 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648).

Valorização dos recursos

Os custos dos recursos identificados pelo painel de peritos foram estimados com base em fontes oficiais. Para estimar o custo dos internamentos foi utilizada a Base de Dados de Morbilidade Hospitalar do ano de 2017, tendo sido analisados apenas os episódios de internamento em doentes adultos codificados de acordo com a Classificação Internacional das Doenças – 10.ª revisão (ICD-10-CM/PCS).[23] Informação detalhada sobre os cálculos dos custos de internamento encontra-se disponível no Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648). Os custos dos fármacos de dispensa hospitalar foram obtidos através do Catálogo de Aprovisionamento Público da Saúde.[24] Dada a presença de diferentes alternativas na mesma clas-

se terapêutica, foi escolhida a intervenção com o menor custo. Os custos de fármacos de venda em ambulatório foram estimados com base em dados da IQVIA para o ano de 2021. Destes dados, foram excluídas as embalagens de dimensões e dosagens reduzidas, por não se julgarem representativas do tratamento de doenças crónicas. Para cada classe terapêutica foi calculado o custo médio ponderado com base no volume de vendas e preço por embalagem (preço sem imposto sobre o valor acrescentado), assumindo uma adesão terapêutica de 90%. Os custos unitários dos restantes recursos de saúde (consultas, urgências sem internamento e MCDT) baseiam-se nos preços definidos pela Portaria n.º 254/2018, de 7 de setembro.[25]

RESULTADOS

A Tabela 3 apresenta os resultados de sobrevivência (anos de vida), de YLD, e de custos acumulados durante todo o período do modelo, por grupo de risco. Verifica-se que, em pessoas com maior risco, a esperança de vida é menor e os YLD e os custos são superiores. Comparando os resultados de doentes de muito alto risco com o de doentes de baixo risco, em termos médios, a esperança de vida é diminuída em 34%, os anos perdidos por incapacidade duplicam e os custos aumentam cerca de 81%.

A Tabela 4 resume as estimativas para a população global. O modelo estima uma sobrevivência média de 8,62 anos, com 0,59 YLD, e um custo médio, durante o tempo total de vida da população modelizada, de €24 613. Considerando toda a coorte, prevê-se uma perda superior a 410 mil YLD e um custo total, ao longo da vida, de aproximadamente 17,0 mil milhões de euros.

A população de baixo risco corresponde a 15,6% da população com DRC. Nesta população estima-se uma maior sobrevida (10,54 anos por pessoa), menores YLD (0,42 por pessoa), e menores custos (18,1 mil euros por pessoa). Em termos agregados, estima-se que a DRC conduz a uma perda de 44,8 mil YLD e a um custo de 1,9 mil milhões de euros [Tabela S17 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

No que diz respeito à população de risco moderado (26,0% da população) estima-se que a sobrevivência média seja de 9,21 anos, com 0,49 YLD, e um custo médio de 20,0 mil euros por pessoa. Estima-se uma perda total de 87,8 mil YLD e custos de 3,6 mil milhões de euros, para esta população [Apêndice 1, Tabela S18 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

Para a população de risco alto estima-se uma sobrevivência média de 8,30 anos, 0,56 YLD e um custo médio de 22,7 mil euros por pessoa. A população de risco alto é a com maior proporção (35,7%), pelo que em termos agregados, é a que está associada a piores resultados: 138,2 mil anos de vida vividos com incapacidade e custos totais de 5,6 mil milhões de euros [Tabela S19 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

A população de risco muito alto é a que está associada a piores resultados médios, com uma sobrevivência média de 6,95 anos, uma perda de 0,84 YLD, e um custo médio de 32,7 mil euros por pessoa. Representando 21,8% da população com DRC, este subgrupo incorre numa perda de 126,5 mil YLD e custos totais de 4,9 mil milhões de euros [Tabela S20 do Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22573/15648)].

DISCUSSÃO

O presente estudo teve como objetivo projetar a evolução da DRC em pessoas com diabetes, de modo a quantificar os custos e consequências no contexto português. Tal foi conseguido através do desenvolvimento de um modelo de Markov que permite integrar os vários estádios de progressão da doença. O modelo foi parametrizado com dados que refletem a realidade portuguesa, utilizando a melhor evidência disponível.

As estimativas referentes à progressão natural da DRC bem como à sobrevivência, anos perdidos por incapacidade e custos associados são os mais atuais à presente data, apresentando-se, igualmente, valores não agregados para as diferentes categorias de risco baseados na matriz internacional de KDIGO. Durante o tempo total de evolução da coorte, o modelo estimou, para a população total com DRC e DM2, uma sobrevivência média de 8,62 anos, com

Tabela 3 – Resultados por nível de risco

Grupo de risco	Peso na população com DRC	Anos de vida, *per capita*	YLD, *per capita*	Custos *lifetime*, *per capita*	Custos, total do grupo de risco
População global	100%	8,62	0,59	€24 613	€17 045 827 148
População de baixo risco	15,6%	10,54	0,42	€18 058	€1 946 152 022
População de risco moderado	26,0%	9,21	0,49	€19 964	€3 592 737 068
População de risco alto	35,7%	8,30	0,56	€22 721	€5 617 401 877
População de risco muito alto	21,8%	6,95	0,84	€32 691	€4 934 120 620

YLD: *years lived with disability*

Tabela 4 – Resultados para a população global

a) Anos de vida, por pessoa

	A1	A2	A3
G1	0,21	0,17	0,10
G2	0,57	0,46	0,41
G3a	0,61	0,84	0,49
G3b	0,74	0,82	0,60
G4	0,37	0,56	0,53
G5	0,02	0,04	0,10
Diálise			0,53
Transplantação			0,46
Anos de vida			8,62

b) YLD, por pessoa

	A1	A2	A3
G1	0,00	0,00	0,00
G2	0,00	0,00	0,00
G3a	0,00	0,00	0,00
G3b	0,00	0,00	0,00
G4	0,04	0,06	0,06
G5	0,01	0,02	0,06
Diálise			0,31
Transplantação			0,01
YLD			0,59

c) Custos (€), por pessoa

	A1	A2	A3
G1	107	89	50
G2	320	262	232
G3a	348	572	540
G3b	376	505	597
G4	424	693	879
G5	23	59	209
Diálise			13 498
Transplantação			4830
Custos (€)			24 613

d) Resultados, por coorte

Anos de vida	5 967 968
YLD	410 203
Custos (€)	17 045 827 148

YLD: *years lived with disability*

0,59 anos perdidos por incapacidade, e um custo médio de €24 613. Estes valores correspondem a uma perda superior a 410 mil YLD e um custo total, ao longo da vida, de aproximadamente 17,0 mil milhões de euros. A análise por nível de risco permite verificar que a progressão da doença está associada a menor sobrevivência, mais anos perdidos por incapacidade e maiores custos para o SNS. Os resultados do modelo permitem constatar que um eventual atraso na progressão da DRC permitirá obter ganhos em saúde e diminuir custos de seguimento.

O presente estudo pretende colmatar a escassez de dados acerca dos custos e consequências em pessoas com DRC e diabetes em Portugal, sendo esta uma análise inovadora no contexto nacional. Contudo, apresenta algumas limitações. Uma das limitações prende-se com a ausência de uma base de dados única que permita distribuir a prevalência da DRC por categorias KDIGO; tal conduziu à necessidade de usar uma abordagem mista e conjugar dados de diversas fontes, conjugando informação de pessoas seguidas em cuidados de saúde primários (distribuição baseada na TFG de Vinhas *et al*, 2020) e em cuidados de saúde secundários (distribuição baseada nos valores de albuminúria da base de dados do HBA). Os valores estimados com base nas fontes disponíveis são naturalmente influenciados pelo contexto em que são realizados. No caso do estudo RENA,[1] verificam-se algumas limitações, nomeadamente no que diz respeito à representatividade geográfica e às características sociodemográficas da amostra. De facto, a predominância de indivíduos caucasianos, com idade relativamente mais avançada, e a ausência de participantes do Norte e do Algarve podem condicionar a generalização dos resultados para a totalidade da população portuguesa.

A distribuição por nível de albuminúria parece ser mais bem capturada num estudo de base hospitalar em que, por um lado, estão incluídos doentes nas categorias KDIGO de baixo risco, e por outro lado, serão seguidos mais doentes nos estádios com TFG inferiores. Acresce que a disponibilidade de dados longitudinais no HBA permitiu estimar a distribuição de albuminúria por cada nível de TFG ao longo do tempo, informando estes dados as probabilidades de transição do modelo. Estes dados apresentavam limitações como consequência do tamanho amostral, pelo que foi necessário aplicar um método de ajustamento validado pelos peritos clínicos consultados.

Outra limitação diz respeito à falta de informação sobre a mortalidade em pessoas com DRC na população portuguesa. Todavia, o modelo baseou-se na melhor evidência disponível na literatura internacional.

Apesar das limitações inerentes à metodologia utilizada, o presente trabalho apresenta informação relevante e necessária para a realidade portuguesa, contribuindo para o conhecimento sobre a DRC em pessoas com diabetes em Portugal, particularmente no que concerne ao impacto da doença em termos de sobrevivência, anos perdidos por incapacidade e custos.

CONCLUSÃO

Os resultados deste estudo caracterizam a progressão natural da DRC em pessoas com DM2 bem como os custos e consequências associados no contexto nacional. Sendo a DM2 um fator de risco da DRC, é expectável que nas próximas décadas o impacto real seja maior do que o estimado. A análise por nível de risco permite verificar que a progressão da doença está associada a piores resultados. Deste modo, torna-se imperativo direcionar investimentos públicos para a redução do impacto da DM2 e da DRC que incluam o diagnóstico precoce da DRC e das suas complicações em pessoas com DM2, bem como estratégias que possam reduzir a progressão natural da DRC e tratar comorbilidades associadas.

PRÉMIOS E APRESENTAÇÕES PRÉVIAS

Apresentação oral: Edgar Almeida *et al*. Estadiamento e predição da progressão da DRC. Apresentação oral no evento "Nefrologia em Diálogo: Para Um Diagnóstico e Intervenção Precoce Na Doença Renal Crónica" da Sociedade Portuguesa de Nefrologia realizado em Coimbra, a 9 de março de 2023 (Dia Mundial do Rim).

Apresentação de póster: L. Silva Miguel *et al* "SA45 Natural Evolution of Chronic Kidney Disease in Diabetic Patients: Costs and Consequences in Portuguese Reality" no evento ISPOR Europe 2023 realizado em Copenhaga, de 12 a 15 de novembro de 2023.

CONTRIBUTO DOS AUTORES

MB, JC, LSM: Desenho do estudo, desenvolvimento do modelo analítico, colheita e análise dos dados, escrita e revisão crítica do manuscrito.

EA, RA, GSD: Desenho do estudo, colheita e análise dos dados, revisão crítica do manuscrito.

RA, MBV, LF, MP, JR, JS, APS: Colheita e análise dos dados, revisão crítica do manuscrito.

CB, FS: Colheita e análise dos dados, escrita e revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

EA recebeu apoio da Vifor Pharma, AstraZeneca, BIAL e Bayer para participar em reuniões ou viagens; é o presidente da Sociedade Portuguesa de Nefrologia.

JC recebeu honorários de consultadoria da IQVIA, recebeu apoio de EAN, IQVIA e ERASMUS PLUS para participar em reuniões ou viagens; possui um papel de liderança ou fiduciário remunerado ou não remunerado em EAN.

MBV recebeu pagamentos ou honorários da Astrazeneca, Bayer, Boehringer Ingelheim, Bial e Lilly para palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educativos; recebeu apoio da Bayer, Boehringer Ingelheim, Bial e Lilly para participar em reuniões ou viagens.

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

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Clinical Outcomes of Chemo-Immunotherapy for Extensive Stage Small Cell Lung Cancer: A Real-World Single Centre Study in Portugal

Resultados do Tratamento com Quimio-Imunoterapia do Cancro do Pulmão de Pequenas Células em Estádio Avançado: Um Estudo Unicêntrico de Vida Real em Portugal

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ABSTRACT

Small cell lung cancer (SCLC) is an aggressive type of lung cancer. Recent studies have provided a new hope by adding atezolizumab to the standard treatment of extensive disease SCLC (E-SCLC). The aim of our study was to evaluate the real-life performance of atezolizumab plus chemotherapy in extensive stage SCLC in a Portuguese setting. Data was collected on twenty patients (70% were male with a mean age of 66.9 years) in treatment at a tertiary hospital in Portugal with E-SCLC treated with chemotherapy and atezolizumab between July 2022 and February 2024. All patients received a carboplatin plus etoposide regimen in combination with atezolizumab. The overall response rate was 55% (95% CI: 31.5 – 76.9) and the disease control rate was 70% (95% CI: 45.7 – 88.1). The median overall survival (OS) and progression-free survival (PFS) was 9.7 (95% CI:5.08 – 14.32) and 7.17 (95% CI:3.28 – 11.05) months, respectively. In total, 13 (65%) patients experienced disease progression and 10 (50%) died during follow-up from events related to the disease. Patients with a performance status score ≥ 2 had lower PFS (p = 0.003) and OS (p = 0.001). To the best of our knowledge, this is the first real-world clinical study in Portugal to evaluate real life outcomes for this combination therapy.

Keywords: Antibodies, Monoclonal, Humanized; Immune Checkpoint Inhibitors; Immunotherapy; Small Cell Lung Carcinoma/drug therapy

RESUMO

O carcinoma pulmonar de pequenas células (CPPC) é um cancro agressivo. Estudos recentes demonstraram benefícios ao adicionar atezolizumab ao tratamento padrão para CPPC em estágio extensivo (CPPC-E). Este estudo avalia o desempenho da combinação de atezolizumab com quimioterapia em contexto de vida real em Portugal. Foram recolhidos dados de vinte doentes (70% homens, com uma idade média de 66,9 anos) com CPPC-E tratados com quimioterapia e atezolizumab num hospital terciário em Portugal, entre julho de 2022 e fevereiro de 2024. Todos receberam carboplatina e etoposido com atezolizumab. A taxa de resposta global foi de 55% (IC 95%: 31,5 – 76,9) e a taxa de controlo da doença foi de 70% (IC 95%: 45,7 – 88,1). A mediana de sobrevivência global (OS) e sobrevivência livre de progressão (PFS) foi de 9,7 meses (IC 95%: 5,08 – 14,32) e 7,17 meses (IC 95%: 3,28 – 11,05), respetivamente. No total, 65% dos doentes apresentaram progressão da doença e 50% faleceram. Doentes com índice de performance (PS) ≥ 2 apresentaram menor PFS (p = 0,003) e OS (p = 0,001). Tanto quanto sabemos, este é o primeiro estudo clínico de vida real em Portugal a avaliar os resultados desta combinação terapêutica.

Palavras-chave: Anticorpos Monoclonais Humanizados; Carcinoma do Pulmão de Pequenas Células/tratamento farmacológico; Imunoterapia; Inibidores de Checkpoint Imunológico

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide and small cell lung cancer (SCLC) is responsible for 15% of cases.[1] Approximately 50% of all SCLC are diagnosed in a metastatic stage with a five-year survival rate below 7%.[1] Despite initial responses to chemotherapy, most patients experience rapid disease progression.[2] The IMpower133 trial has provided new hope by incorporating atezolizumab into the standard treatment of extensive disease SCLC (E-SCLC) alongside chemotherapy.[3]

While clinical trials provide vital data, real-world evidence is essential to assess treatment effectiveness in practical settings. This study evaluated the real-life impact of atezolizumab plus chemotherapy for E-SCLC in a Portuguese setting.

Data was collected on patients with histologically confirmed E-SCLC in follow-up at an oncological pulmonology department in a Portuguese tertiary hospital. The inclusion criteria were age 18 or older, diagnosed with stage III/IV (TNM Classification, 8th edition), had received at least one cycle of chemoimmunotherapy between July 2022 and February 2024, patients could have undergone prior treatments and had measurable disease per the response evaluation criteria in solid tumors (RECIST) version 1.1. Patients with synchronous neoplasia were excluded.

Initial assessments included a thoracic-abdominal-pelvic computed tomography scan (CT), with response evaluations every three cycles. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), and treatment toxicities were assessed according to the common terminology criteria for adverse events (CTCAE) version 5.0.

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Statistical analysis

Progression free survival (PFS) was calculated from the first day of treatment until PD or death from any reason. Overall survival (OS) was calculated from the initiation of treatment until death or was censored on the day of the last visit. The cut-off date was March 31st, 2024. Kaplan-Meier methodology was used to estimate the OS and PFS and the log-rank test was used for survival comparisons. Cox regression was applied to estimate hazard ratios (HRs). All statistical analyses were performed using the IBM® SPSS, version 27.0.

Patients

Characteristics

A total of 20 patients were included. Table 1 shows the patients' characteristics.

Treatment

All patients received a carboplatin/etoposide regimen in combination with atezolizumab. The median number of cycles of chemotherapy plus atezolizumab was 4 (range: 1 – 6) and of maintenance cycles was 2.5 (range: 0 – 19). At data cutoff, 13 (65%) patients had discontinued atezolizumab, due to PD in six (46.2%), death in five (38.5%) and grade ≥ 3 adverse events (AE) in two (15.4%). Second line treatment was initiated in three patients (15%).

Table 1 – Patient characteristics

Characteristics		Patients	PFS		OS	
			Median (95% CI)	***p*-value**	**Median** (95% CI)	***p*-value**
Total patients, n		20				
Age (mean, years)		66,9 ± 7,7				
< 70 years old		15 (75%)	7.2 (4.2 – 11.2)	0.562	6.5 (0.1 – 12.8)	0.463
Elderly (≥ 70 years old)		5 (25%)	5.9 (2.8 – 8.9)		9.7 (6.9 – 12.5)	
Sex						
Female		6 (30%)	7.2 (5.2 – 9.1)	0.828	9.7 (6.9 – 12.5)	0.782
Male		14 (70%)	4.6 (0.196 – 9.1)		6.5 (0.1 – 12.8)	
Smoking status						
Pack-years (mean)		55,5 ± 32,9				
Nonsmokers		1 (5%)	7.2 (3.5 – 10.9)	0.838	7.9 (1.2 – 14.7)	0.640
Ex-smokers/smokers		19 (95%)	7.3 (4.2 – 10.5)		9.7 (3.0 – 16.4)	
ECOG PS						
0 – 1		15 (75%)	7.3 (5.3 – 9.3)	**0.003**	11.3 (7.1 – 15.6)	**0.001**
≥ 2		5 (25%)	2.63 (0 – 6.6)		2.6 (0 – 6.6)	
Comorbidities						
COPD	No	4 (20%)	4.0 (0.2 – 7.8)	0.545	4.0 (0 – 8.3)	0.327
	Yes	16 (80%)	7.2 (5.4 – 8.9)		9.7 (5.8 – 13.6)	
Cardiovascular disease	No	11 (55%)	5.9 (3.6 – 8.2)	0.849	9.7 (3.2 – 16.2)	0.717
	Yes	9 (45%)	7.2 (0.2 – 14.2)		7.9 (0.3 – 15.6)	
Metastasis previous to treatment						
Hepatic metastasis	No	5 (25%)	5.9 (3.2 – 8.6)	0.425	9.7 (2.3 – 17.1)	0.572
	Yes	15 (75%)	7.3 (3.2 – 11.5)		7.9 (3.9 – 12.1)	
Brain metastasis	No	7 (35%)	5.9 (1 – 10.8)	0.365	7.9 (5.0 – 10.9)	0.585
	Yes	13 (65%)	7.2 (2.6 – 11.8)		9.7 (0 – 21.4)	
M1c – Multiple extrathoracic metastasis	No	15 (75%)	5.9 (3.1 – 8.8)	0.655	9.7 (4.1 – 12.1)	0.987
	Yes	5 (25%)	7.3 (4.1 – 10.5)		7.9 (1.6 – 14.3)	
Previous treatment						
Chemo-radiotherapy		11 (55%)	8.6 (3.7 – 13.5)	0.227	7.9 (2.2 – 13.8)	0.203
No		9 (45%)	7.2 (2.9 – 11.5)		11.3 (5.2 – 14.3)	

Treatment related AE were reported in 14 (70%) patients. Grade ≥ 3 events were reported in eight (40%). The most common AE was myelosuppression. Immune-related events were identified in three patients (15%), namely grade 3 colitis, grade 3 uveitis and grade 2 thyroiditis. No patient died of treatment-related AE.

Treatment and survival outcomes

The overall response rate (ORR) was 55% (95% CI:31.5 – 76.9) and the disease control rate (DCR) was 70% (95% CI:45.7 – 88.1). No patient achieved a CR, 11 (55%), three (15%) and six (30%) achieved PR, SD, and PD, respectively.

The median follow-up time was 5.3 months (range: 0.3 – 20.3). The median OS and PFS were 9.7 (95% CI: 5.1 – 14.3) and 7.17 (95% CI: 3.3 – 11.1) months, respectively. In total, 13 (65%) patients experienced PD and 10 (50%) died during follow-up from events related to the disease. Patients with a PS score ≥ 2 had lower PFS and OS than those with a PS score 0 – 1 {p = 0.014 [HR CI 95%: 6.7 (1.6 – 28.2)] and p = 0.006 [HR CI 95%: 10.7 (1.9 – 60.7)], respectively}. Analysis of PFS and OS is shown in Fig. 1 and Table 1.

Atezolizumab plus chemotherapy is the standard of care for extensive stage SCLC since the results of the IMpower133 trial. To our knowledge, this is the first real world clinical study in Portugal to evaluate real life outcomes for this combination therapy. Real-world data differs from clinical trials by including patients with conditions (e.g., higher PS and comorbidities) that often exclude them from trial participation.

This study shows the data of one of the largest pulmonary oncology dedicated departments in Portugal. Comparing data with IMpower133, we found a lower OS (9.7 *vs* 13.2 months) but an improved PFS (7.2 months *vs* 5.2 months).[4] While most real-world studies report PFS

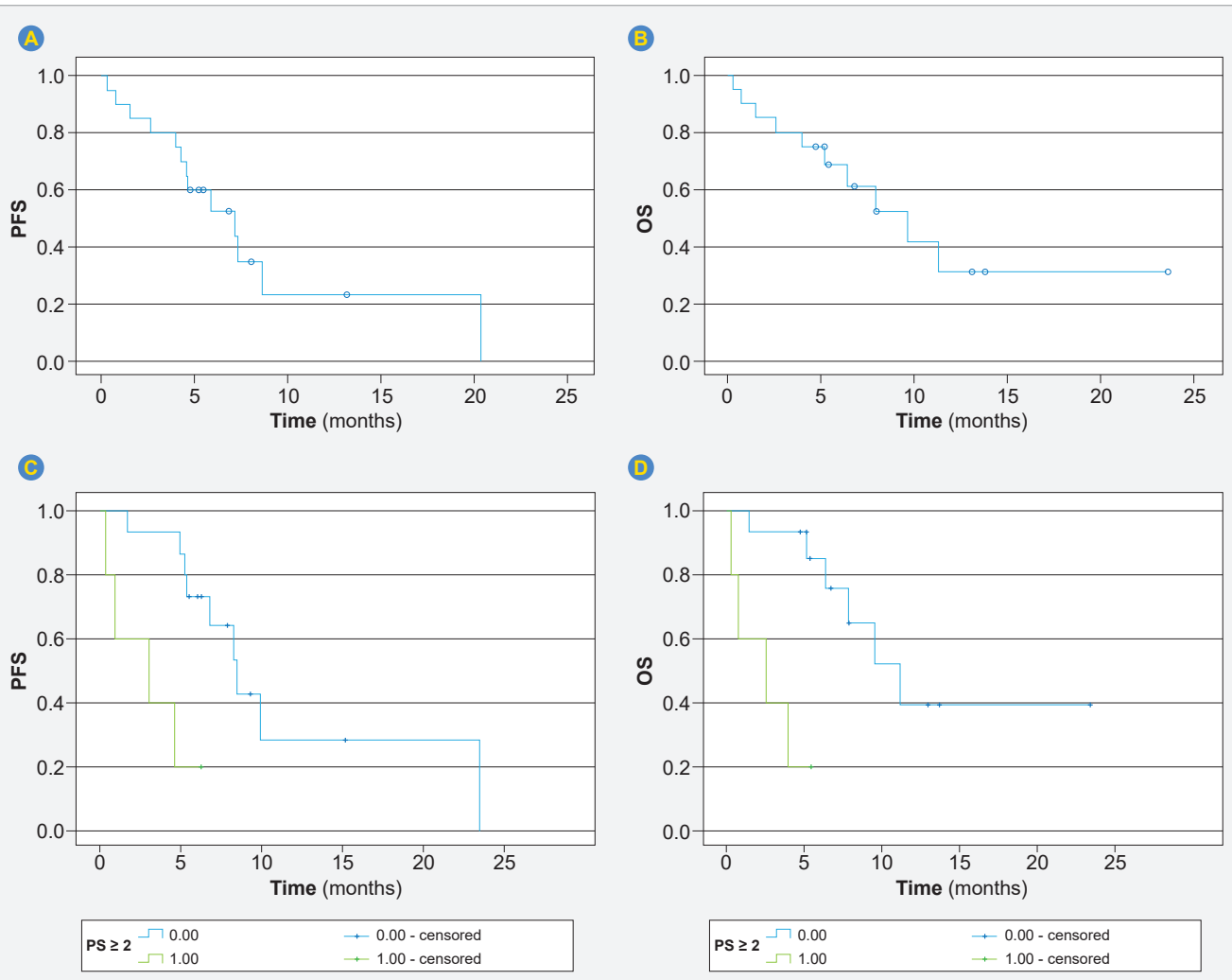

Figure 1 – Kaplan-Meyer analysis of PFS and OS (A and B). Kaplan-Meyer analysis of PFS and OS in patients with PS ≥ 2 (C and D).

comparable to the trial, OS is often higher, contrasting with our findings.[1,5,6] This discrepancy may stem from our inclusion of 25% of patients with PS ≥ 2, compared to fewer than 10% in most studies, thus significantly impacting OS. The higher PFS observed may reflect less strict timing for re-evaluation tests than in the trial. The ORR and DCR were 55% and 70%, respectively, which was similar to the original study as well as most of the real-world studies worldwide.[4-6]

Our study included patients with PS ≥ 2 and elderly patients. We found that patients with PS ≥ 2 had significantly lower OS and PFS, consistent with other studies suggesting immunotherapy benefits patients with lower PS scores.[1,5,7] Contradictory results can be found in the literature regarding older age.[1,4,5,8] In our study, older age was not associated with a difference in response rate or survival.

Comorbidities may influence SCLC outcomes significantly. Cardiovascular disease was associated with lower survival in a recent study.[7,9] We found no difference in OS or PFS in patients with cardiovascular disease.

In line with the original study, chemoimmunotherapy was safe and well tolerated. The most common AE were related to chemotherapy.[4] Immune-related toxicity occurred in 15% of patients, which was lower than the 39.9% observed in IMpower133 (39.9%).[4]

Considering the findings in this small, but relevant study, it is safe to say that chemoimmunotherapy combination is a safe option for patients with E-SCLC and its effect estimates are comparable to those in the IMpower133 trial in the Portuguese population. It is of extreme importance to identify which patients benefit more from this therapy.

Study limitations include its retrospective design, potential patient evaluation bias, and small sample size. Future multicenter studies are needed to further evaluate real-life outcomes.

AUTHOR CONTRIBUTIONS

DN: Data collection, writing of the manuscript.

MB, ASV, FF, ALM, DH, PV: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Update on Generalized Pustular Psoriasis

Atualização sobre Psoríase Pustulosa Generalizada

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ABSTRACT

Generalized pustular psoriasis (GPP) is a rare but severe inflammatory skin disease characterized by the eruption of widespread sterile pustules, often accompanied by systemic inflammation. Although GPP can coexist with plaque psoriasis, it is increasingly recognized as a distinct entity with unique clinicopathological, immunologic, and genetic features. The dysregulated IL-36 pathway, including mutations in the *IL36RN* gene, is implicated in GPP pathogenesis, providing a molecular basis for targeted therapies. Diagnosing GPP requires a comprehensive evaluation, including clinical presentation, potential triggers, patient history, histopathologic findings, and laboratory results. Disease severity must be assessed through both cutaneous symptoms and systemic involvement, as GPP flares can lead to life-threatening complications such as sepsis and multi-organ failure. Historically, GPP treatment primarily relied on therapies approved for plaque psoriasis, despite their limited specificity for this condition. Recent advances in understanding the molecular mechanisms of GPP, particularly the central role of interleukin-36 pathway, have led to the development of targeted therapies for this rare condition. Currently, spesolimab is the only therapy specifically approved for treating GPP flares in adolescents and adults, in both Europe and the United States of America. However, the management of GPP remains complex and challenging. This narrative review provides an overview of the epidemiology, pathophysiology, clinical features, comorbidities, and evolving therapeutic strategies for GPP.
Keywords: Antibodies, Monoclonal, Humanized/therapeutic use; Interleukin /therapeutic use; Psoriasis/drug therapy

RESUMO

A psoríase pustulosa generalizada (PPG) é uma doença inflamatória da pele, rara embora potencialmente grave, caracterizada pelo aparecimento de pústulas estéreis generalizadas, frequentemente acompanhadas por inflamação sistémica. Embora possa coexistir com psoríase em placas, a PPG é cada vez mais reconhecida como uma entidade distinta, com características clinicopatológicas, imunológicas e genéticas únicas. A desregulação da via da interleucina-36, incluindo mutações no gene *IL36RN*, está implicada na patogénese da PPG, proporcionando uma base molecular para terapêutica dirigidas. O diagnóstico de PPG requer uma avaliação abrangente, incluindo as características clínicas, possíveis fatores desencadeantes, antecedentes do doente, achados histopatológicos e resultados laboratoriais. A gravidade da doença deve ser avaliada através do atingimento cutâneo e do envolvimento sistémico, uma vez que as exacerbações da PPG podem levar a complicações com potencial risco de vida, incluindo sépsis e falência multiorgânica. Historicamente, o tratamento da PPG era baseado em terapêuticas aprovadas para a psoríase em placas, apesar da sua limitada especificidade para esta condição. Os avanços recentes na compreensão dos mecanismos moleculares da PPG, particularmente o papel central da via de interleucina-36, levaram ao desenvolvimento de moléculas direcionadas para esta doença rara. Atualmente, o spesolimab é a única terapêutica especificamente aprovada para o tratamento de exacerbações da PPG em adolescentes e adultos, tanto na Europa como nos Estados Unidos da América. No entanto, a gestão da PPG continua a ser complexa e desafiante. Esta revisão narrativa oferece uma visão geral da epidemiologia, fisiopatologia, características clínicas, comorbilidades e estratégias terapêuticas em evolução para a PPG.
Palavras-chave: Anticorpos Monoclonais Humanizados/uso terapêutico; Interleucinas/ Psoríase/tratamento farmacológico

INTRODUCTION

Pustular psoriasis is an uncommon variant of psoriasis distinguished by the presence of sterile neutrophilic pustules, with a variety of distribution patterns and a broad severity spectrum.[1,2] It can be categorized into three main phenotypes: palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH), both of which are localized acral forms; and generalized pustular psoriasis (GPP).[2–4]

Generalized pustular psoriasis is the rarest yet most severe form, characterized by the eruption of widespread sterile pustules, often accompanied by systemic inflammation.[2] It is an immune-mediated disease with a heterogeneous clinical course that can manifest as an acute flare, known as the von Zumbusch type, but can also be a chronic or relapsing disease in which flares of greater severity may

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overlap. The most commonly reported case is the development of GPP in patients with plaque psoriasis treated with corticosteroids, but it can more rarely occur after corticosteroid withdrawal for other conditions. Infections, particularly bacterial and viral, have been reported as triggers for GPP flares. Commonly implicated infections include upper respiratory tract infections but any infection can potentially be associated with a GPP flare. The exact incidence of infection-triggered GPP flares is not well established due to limited epidemiological data. Several medicines have been associated with GPP exacerbations, including tumor necrosis factor (TNF)-alpha inhibitors, hydroxychloroquine, lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), and certain systemic antifungals. The incidence of medication-induced GPP remains difficult to quantify due to limited data.[2,5] The differential diagnosis of GPP requires careful interpretation of the clinical picture, medical history, laboratory tests and histopathologic features to exclude other inflammatory skin conditions.[6]

Generalized pustular psoriasis flares have the potential to develop into life-threatening complications, such as sepsis and multisystem organ failure.[3,7] Therefore, GPP requires prompt accurate diagnosis and effective treatment, with most of the cases requiring inpatient management.[4] Established international guidelines are currently lacking and management guidance of GPP often follows that for plaque psoriasis. However, while about half of patients diagnosed with GPP have a prior diagnosis of plaque psoriasis, there is currently a consensus on GPP being phenotypically, genetically and immunologically distinct from plaque psoriasis.[1,8] Over the past decade, advances in the knowledge of the molecular basis behind GPP immunopathogenesis, namely the central role of the interleukin(IL)-36 pathway, have led to the development of targeted therapies for this rare disease.[9] Optimal treatment for GPP should ensure a rapid onset of therapeutic action, including skin clearance and prevention of systemic involvement, as well as the capacity to prevent the recurrence of flares, while providing a favorable safety profile both in the short- and long-term.[10] Spesolimab is currently the only therapy approved in both Europe and the United States of America (USA) for the treatment of GPP flares in adults, also with the indication of flare prevention in the USA.[11]

A literature review (up until October 2024) was performed to provide a comprehensive overview of the epidemiology, pathophysiology, clinical features, associated complications, and management of GPP.

Epidemiology

Generalized pustular psoriasis is a rare disease with a paucity of epidemiological data available. Its exact prevalence is unknown, but it was estimated to range between 1.8 and 124 per million people in the general population, with significant ethnic and geographical variability. It is predominantly reported in East Asia, while its prevalence in European individuals seems to be considerably lower.[5,12,13] Estimates of GPP prevalence among patients with psoriasis range between 0.6% and 2.4%.[5]

It primarily affects adults, with a median reported age at diagnosis of around 50 years.[7,12] However, it can also occur in children, where it is more likely to be associated with an *IL36RN* mutation.[1,14] There does not seem to be a strong sex predilection, although some studies suggest a slight predominance among women.[7,12] In a recent Portuguese multicentric study, it was found that two-thirds of patients with GPP were women, with a mean age at presentation of 55 (± 21) years.[15]

Etiology and pathophysiology

Generalized pustular psoriasis may arise with pre-existing plaque psoriasis in about half of the patients, thus suggesting an overlap and interconnection between the immunologic pathways of both conditions. However, GPP has also been shown to present independently of plaque psoriasis and research conducted from the past two decades recognized it as distinct clinical entity, with its own genetic and immunologic determinants, and response to treatment. While plaque psoriasis is primarily driven by an adaptive immune response involving the IL-23/IL-17 axis, histopathological, molecular, and genetic data indicate that GPP is mainly driven by the hyperactivation of innate immunity, with a central role of the IL-36 pathway.[1,5,16,17] This has led some authors to classify GPP within the spectrum of autoinflammatory keratinization diseases.[18]

IL-36 cytokines belong to the IL-1 superfamily, and include the proinflammatory agonists IL-36α, IL-36β and IL-36γ, and the IL-36 receptor antagonist (IL-36Ra).[19] The role of the IL-36 pathway was first identified through the discovery of loss-of-function mutations in the IL-36 receptor antagonist (*IL-36Ra*), encoded by the *IL36RN* gene, that was found to be associated with GPP.[20] Mutations in *IL36RN* leading to unrestrained IL-36 activity are associated with a severe form of GPP characterized by early onset, more systemic inflammation and the absence of plaque psoriasis.[21,22] More recently, mutations and allelic variations in other genes functionally connected with the IL-36 pathway led to an enhanced inflammatory cascade and the recruitment of neutrophils and macrophages (e.g., loss-of-function of AP1S3, SERPINA3 and MPO; gain-of-function of CARD14) have also been found to be associated with GPP.[8,14]

IL-36 cytokines are produced by and target various skin cell types, including keratinocytes and immune cells, when stimulated by TNF, IL-17A, IL-22, and IL-1β. After proteolytic activation, IL-36 agonists bind to heterodimeric receptor

complexes [IL-36R and IL-1 receptor accessory protein (IL-1RAcP)], triggering downstream pathways involving protein myeloid differentiated protein 88 (MyD88), mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-κB). This leads to the release of proinflammatory mediators such as neutrophil-attracting chemokines (CXCL1, CXCL2, and CXCL8), additional IL-36 precursors, TNF, IL-1β and IL-17 cytokines, which recruit and activate neutrophils, T cells, and dendritic cells (Fig. 1). This creates a self-amplifying cycle of unchecked signaling and overproduction of chemokines, which promote epidermal neutrophil infiltration, clinically manifesting as pustules and associated systemic symptoms.[1,8,16,17,23,24] IL-36Ra regulates this process by competing with IL-36 agonists for IL-36R binding, balancing the inflammatory response.[19] The imbalance seen in GPP arises from either an overproduction of IL-36 agonists or a loss-of-function in the IL-36Ra antagonist.[9]

IL-36 cytokines contribute to link innate and adaptive immunity, including the T-helper (Th) 1 and Th17 pathways.[22] Thus, while GPP pathogenesis shares some mediators with plaque psoriasis, it is now known to be primarily driven by a distinct pathway centered on IL-36 signaling.[13] Additional evidence comes from gene expression studies of lesional skin biopsies, which show an overexpression of IL-36 agonists (IL-36α, β, and γ) in keratinocytes surrounding neutrophilic pustules compared to healthy controls. The involvement of TNF, IL-17A, IL-23, IL-1, and interferons (IFNs) in the pathogenesis of GPP was also documented, although GPP lesions exhibited higher levels of IL-1 and IL-36 and lower levels of IL-17A and IFN-ɣ compared to plaque psoriasis. Additionally, a significantly stronger expression of neutrophil chemokines (CXCL1, CXCL2, and CXCL8), as well as IL-1- and IL-36-related transcripts, was observed in GPP lesions, exceeding that seen in plaque psoriasis.[9,21]

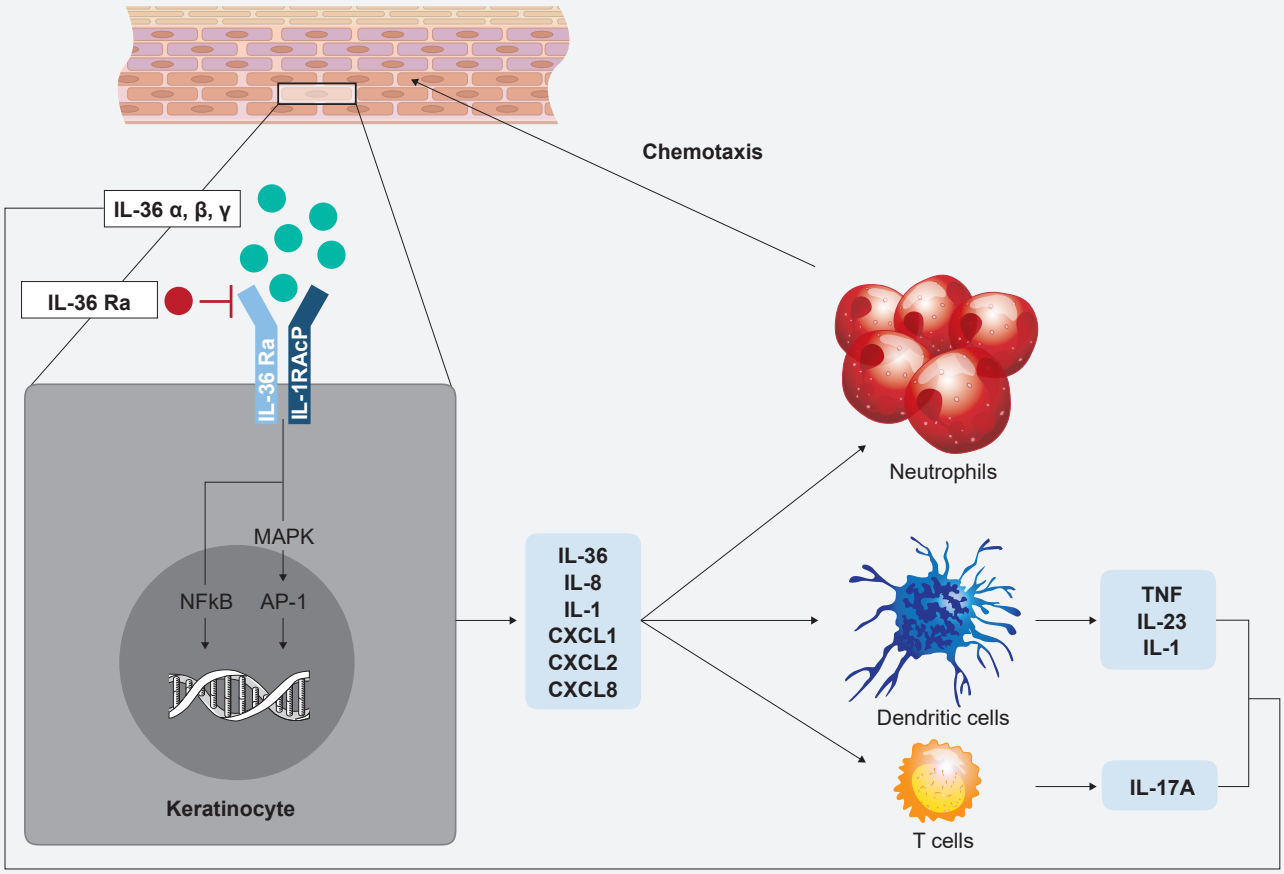

Figure 1 – Overview of IL-36 signaling. After processing by neutrophil-derived proteases, mature IL-36 agonists (α, β and γ) bind to IL-36R on the surface of keratinocytes, inducing an inflammatory cascade that promotes expression of more IL-36 precursors, neutrophilic chemokines (CXCL1, CXCL2, CXCL8) and various cytokines (IL-1β, IL-17A, IL-23, TNF), thus promoting recruitment and activation of neutrophils, T cells and dendritic cells through a self-amplifying loop. Hyperactivation of IL-36 pathways plays a key role in the pathogenesis of GPP. Adapted from Marrakchi *et al.*[1]

AP-1: activating protein-1; CXCL: chemokine (C–X–C motif) ligand; IL: interleukin; MAPK: mitogen-activated protein kinase; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; R: receptor; Ra: receptor antagonist; RAcP: receptor accessory protein; TNF: tumor necrosis factor.

Clinical features and diagnosis

Psoriasis includes both erythrosquamous and pustular lesions, which are distinct in their clinical and histological features but can occur together. In some cases, pustules may develop within psoriasis plaques as a pronounced inflammatory manifestation, as these plaques always contain some granulocytes detectable histologically. Intense inflammation in plaque psoriasis can lead to collections of neutrophils, like Munro's microabscesses and Kogoj's pustules. However, primary visible pustules do not usually form part of the spectrum of plaque psoriasis, except when occasionally arise exclusively within or at the edge of psoriasis plaques, often only detectable with dermoscopy. In these cases, the term to be used is 'psoriasis with pustules' and should not be considered a form of pustular psoriasis.[2]

Distinct phenotypes of pustular psoriasis have been described, universally characterized by persistent or recurrent primary, sterile, macroscopically visible pustules. Palmoplantar pustulosis and ACH are both localized acral forms, with PPP involving the palms and/or soles, while ACH primarily affects, though is not limited to, the nail apparatus.[2] In turn, GPP is characterized by widespread pustules on non-acral skin that are not confined to psoriasis plaques. Mixed forms, other terminologies and variants exist, including pustular psoriasis of pregnancy (previously referred to as 'impetigo herpetiformis'), annular pustular psoriasis and infantile/juvenile pustular psoriasis.[2,6]

Generalized pustular psoriasis is usually relapsing and remitting in nature, with a highly heterogeneous clinical course. The frequency, severity, and duration of the flares can vary both between different patients and between episodes in the same patient, but they have the potential of being life-threatening.[7] Generalized pustular psoriasis of the von Zumbusch type, the most severe form, is marked by the sudden appearance of numerous small, 2 to 3 mm sterile pustules that can merge to form large areas ('lakes') of pus. The underlying skin is red and swollen, and is typically accompanied by pain, pruritus, and burning sensation.

Table 1 – Characteristics of generalized pustular psoriasis

Characteristics of generalized pustular psoriasis	
Clinical presentation	• Sterile pustules on an erythematous background; often coalesce to form 'lakes of pus' • Widespread erythema typically affecting large areas of the body, often involving flexural areas • Extensive peeling of the skin follows, resulting in marked desquamation • Lesions are often painful and can be associated with burning or pruritus • Fever, chills, malaise, fatigue and arthralgias are common • Can present as recurrent flares with intervals of partial or complete remission, punctuated by acute episodes of pustulation • Erythroderma may occur
Triggers	• Withdrawal of systemic corticosteroids • Infections • Medications (e.g., lithium, antimalarials, vaccination) • Pregnancy • Hypocalcemia • Stress
Laboratory findings	• Leukocytosis • Elevated C-reactive protein and erythrocyte sedimentation rate • Hypoalbuminemia • Anemia • Hypocalcemia
Histopathology	• Overall epidermal architecture similar to plaque psoriasis: parakeratosis, elongated rete ridges, thinning of the suprapapillary epidermis. • Superficial dermal infiltrate composed of mononuclear cells, with neutrophils migrating from the papillary capillaries into the epidermis and forming subcorneal macropustules • Spongiform pustules of Kogoj (the Hallmark feature of GPP)
Main complications	• Secondary infections and sepsis • Electrolyte imbalances • Acute kidney injury • Liver dysfunction • Cardiovascular failure • Malnutrition • Neutrophilic cholangitis • Acute respiratory distress syndrome • Arthritis

Erythroderma may occur. Over the next few days days to weeks, the pustules dry out and leave behind residual redness and peeling skin. GPP is often associated with systemic involvement, as denoted by fever, fatigue, malaise and high systemic inflammatory markers. Other extracutaneous manifestations may include arthralgia, peripheral edema and mucosal involvement (e.g. conjunctivitis, uveitis, cheilitis, glossitis).[2–4,6,8]

The diagnosis of GPP is mainly clinical (Table 1).[4] A thorough medical history should be taken for all patients, inquiring about the clinical picture, pre-existing psoriasis history, previous infections and medication history. Although spontaneous in many cases, GPP flares may be caused by internal and external triggers. Systemic corticosteroid withdrawal, infections, medications, stress, pregnancy, vaccination and hypocalcemia have been reported as the main precipitating factors.[3,4,6] Laboratory blood tests are helpful for the assessment of the level of systemic inflammation (leukocytosis with neutrophilia, elevated C-reactive protein levels, increase of the erythrocyte sedimentation rate) and possible complications, such as kidney failure, abnormal liver function tests, and hypoalbuminemia. An arterial blood gas analysis should be carried out to investigate hypocalcemia and other hydroelectrolyte imbalances, and respiratory dysfunction. Blood cultures are mandatory in the presence of systemic inflammation.[3,4,6]

A skin biopsy should be performed to complement the differential diagnosis with other pustular dermatoses (Table 2). However, since histologic features may be nonspecific and often indistinguishable from acute generalized exanthematous pustulosis (AGEP), treatments should not be delayed while waiting for histology if the clinical suspicion is high and AGEP seems unlikely considering the clinical context of the patient. A key distinct histopathologic feature of GPP is the presence of spongiform pustules of Kogoj's, which form due to the subcorneal accumulation of neutrophils. Generalized pustular psoriasis pustules feature more apoptotic keratinocytes, usually do not have eosinophils, and are located at a higher level in the epidermis compared to those in AGEP. Also, the overall epidermal structure in GPP has matches with plaque psoriasis, exhibiting parakeratosis, acanthosis, hyperkeratosis, elongated rete ridges, diminished stratum granulosum, and capillary dilation of the papillary dermis. Munro's microabscesses and superficial perivascular mononuclear cell infiltrations can also be observed.[3,4,7,8,25]

Nonetheless, the classification and definitive diagnosis of GPP can be challenging owing to the lack of standardized global guidelines. The European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus diagnostic criteria (2017) define GPP as primary, macroscopic, sterile pustules not limited to the palms, soles or psoriatic plaques, with or without systemic inflammation, and manifesting with a relapsing or persistent (more than three months) pattern.[2] Japanese diagnostic criteria (2018) state that the definitive diagnosis of GPP can be made if the following four criteria are met: (1) presence of systemic symptoms; (2) widespread erythematous skin with numerous sterile pustules; (3) histopathological evidence of neutrophilic subcorneal pustules (Kogoj's spongiform pustules); and (4) recurrence of these clinical and histological criteria. Generalized pustular psoriasis should also be considered if only criteria 2 and 3 are present.[25]

There is a need to develop standardized international guidelines to improve the diagnosis and treatment of patients with GPP and rapidly exclude other skin conditions that require different treatment strategies. While genetic tests are not currently standard practice for confirming a GPP diagnosis, the future use of genetic strategies could eventually provide new opportunities to improve diagnosis.[6]

Table 2 – Differential diagnoses for generalized pustular psoriasis

Differential diagnoses for generalized pustular psoriasis
Acute generalized exanthematous pustulosis
Other drug-induced pustular eruptions
Subcorneal pustular dermatosis
Widespread suppurative folliculitis
Cutaneous candidiasis
Bullous Impetigo
Staphylococcal scalded skin syndrome
Disseminated gonococcal infection
Autoimune blistering disorders (e.g., dermatitis herpetiformis, IgA pemphigus, pemphigus foliaceus)
Miliaria pustulosa
Erythroderma withsecondary pustulization

Complications

Generalized pustular psoriasis flares can be life-threatening if not diagnosed accurately and treated promptly (Table 1).[6] It can cause a hypermetabolic state with cardiorespiratory dysfunction, extensive catabolism and malnutrition, acute kidney and liver injury, as well as serious electrolyte imbalances. Secondary infections and sepsis are among the most common complications. Rare complications include uveitis and neutrophilic cholangitis. In extreme cases, GPP can escalate to critical multiorgan failure.[3,5,7,13,26,27] Also, most flares typically last between two to five weeks and often require hospitalization, placing a heavy burden on both patients and healthcare providers, and increasing the risk of complications related with the inpatient setting.[15] Mortality data of patients experiencing an acute GPP episode are limited, but rates of 2% to 16% have been reported.[3]

More recently, GPP was recognized as a notable risk factor for various systemic diseases. Generalized pustular psoriasis was associated with an increased incidence of cardiovascular events, such as ischemic heart disease and stroke. It was also linked to a higher occurrence of kidney dysfunction, liver disturbances, interstitial lung disease, anemia, depression, anxiety, osteoporosis and arthritis.[26]

Disease severity measures

The rarity of GPP and its heterogeneous cutaneous and extracutaneous manifestations pose a challenge for implementing comprehensive and precise disease measures in routine clinical assessment and follow-up of the patients.[7] Modified psoriasis disease measures, such as the GPP Physician Global Assessment (GPPGA) and GPP Area and Severity Index (GPPASI), have been developed and validated.[28,29]

The GPPGA was designed to evaluate the overall disease activity in the skin, corresponding to the average of the extent and intensity of the three subscores, namely pustulation, erythema and scaling/ crusting. It typically ranges from 0 to 4, with higher scores indicating more severe disease, respectively clear (0), almost clear (1), mild (2), moderate (3) and severe (4). For GPPASI, the score for each body region is determined by calculating the product of the GPPGA and its corresponding body surface area (BSA) score. This product is then multiplied by a weighting factor specific to each body region. The total GPPASI score is obtained by summing the individual scores from all body regions. However, these scores only assess the severity of skin manifestations and do not consider systemic involvement or overall disease burden. Also, its use in routine clinical practice will depend on its inclusion into hospital protocols or future guidelines. Establishing consensus on scoring systems for assessing disease burden, as well as on objective outcome measures and clinical endpoints, is essential for uniform application in clinical trials, enabling better comparisons between therapies.[28,29]

Establishing treatment goals in generalized pustular psoriasis

Treatment goals in GPP are not well defined primarily due to the rarity of the condition, its heterogeneous clinical manifestations, and the lack of uniform treatment protocols and therapeutic monitoring approaches. Proposed treatment objectives can be broadly categorized into immediate and long-term goals.[10]

Generalized pustular psoriasis is a potentially life-threatening condition that requires prompt diagnosis and intervention.[30] During a flare, the primary short-term goals are to rapidly control the cutaneous manifestations by halting and preventing pustule formation, reducing the burden of systemic signs and symptoms, and preventing the development of complications. In particular, timely management of GPP flares during pregnancy is crucial to avoid complications that could negatively affect both mother and fetus. Recently, rapid control of skin symptoms within one week of treatment has become a feasible goal with the use of IL-36 receptor inhibitors.[7,10,24,31]

Long-term management of GPP should focus on preventing flare-ups and managing associated comorbidities. Although specific long-term goals are not well defined in clinical trials, data from a survey of Corona Registry dermatologists suggested that over 80% of GPP patients experience persistent symptoms between flares, and many treatments fail to prevent recurrence. This highlights the need for comprehensive real-world studies to evaluate existing and emerging therapies, with the aim of establishing clear long-term goals for improving patient outcomes. Proposed long-term objectives include maintaining a low and stable GPPGA score between 0 and 1, ensuring the absence of systemic inflammation, and employing effective clinical monitoring approaches to identify and reduce the recurrence of flares.[7,10]

Disease management

Managing GPP can be complex and typically requires a multidisciplinary approach. Treatment for acute GPP flares depends on the severity of skin and systemic involvement but overall includes a combination of topical therapies, systemic medications, and supportive care, often provided in a tertiary hospital inpatient setting. For severe cases, this may include hospitalization for fluid balance, electrolyte management, and systemic antibiotics if bacterial infection is suspected. Topical therapies, such as corticosteroids, vitamin D analogs, calcineurin inhibitors and emollients, are used as adjuncts to systemic treatments to provide

symptomatic relief and improve skin barrier function. Analgesics, antipyretics and antihistamines may be administered to control the respective signs and symptoms.[7,10,24,31]

Conventional systemic therapies and phototherapy

Acitretin, cyclosporine, and methotrexate are commonly used non-targeted systemic therapies for GPP, although the evidence supporting their efficacy is limited, primarily relying on case reports and small retrospective studies. Acitretin plays a role in chronic GPP management, particularly when immunosuppressive therapies are unsuitable. Despite its effectiveness, it has a slower onset of action and is associated with significant side effects, including hyperlipidemia and liver toxicity. Cyclosporine offers rapid immunosuppressive effects but is limited by serious long-term side effects, such as nephrotoxicity and hypertension. It is typically reserved for short-term management, with patients transitioning to safer long-term therapies once their condition is stabilized. Methotrexate may be cost-effective for long-term management, but its effects may take weeks to manifest, making it unsuitable for acute flares. While these therapies have been historically utilized off-label as first-line systemic treatments for GPP, they are constrained by limited effectiveness and potential toxicities. Also, none of these treatments specifically target the underlying pathophysiology of GPP.[7,10,24,31]

Psoralen ultraviolet A phototherapy can be considered a second-line treatment for adults, but it is not recommended for acute forms of pustular psoriasis.[13] None of the previously mentioned therapies are safe during pregnancy, with the exception of cyclosporine. Systemic corticosteroids are generally avoided due to the risk of rebound flares, except for specific cases of impetigo herpetiformis.[7,10,24,31] Reports have also been published on the treatment of GPP with other agents, including the antineutrophil agent dapsone[32] and the small molecule phosphodiesterase-4 inhibitor apremilast.[33]

Biologic therapy

Various biologic agents approved for moderate to severe plaque psoriasis, such as TNF inhibitors (infliximab, adalimumab, certolizumab), IL-12/23 inhibitors (ustekinumab), IL-23 inhibitors (guselkumab and risankizumab) and IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) have emerged as potential options for the treatment of GPP, with several being licensed in Japan (Table 3).[34–36] These agents have also been frequently used off-label to treat GPP flares in other countries, although evidence supporting their efficacy is mainly derived from case series and small open-label, single-arm trials.[24,31,35–37] In a recent systematic review on the use of these biologics for GPP, secukinumab and ixekizumab had the highest rates of complete resolution (57.7% and 57.6%, respectively).[38] There are also case reports of GPP exhibiting a positive response to IL-1 inhibition with anakinra, canakinumab and gevokizumab.[13,39,40]

Over the last decade, advancements in understanding the molecular mechanisms underlying GPP pathogenesis, especially the key role of the IL-36 pathway, have driven the development of targeted therapies specifically for this condition. Spesolimab is a humanized monoclonal IgG1 antibody that binds strongly to IL-36R, inhibiting the ligands IL-36α, β, and γ from activating the receptor and consequently blocking the subsequent activation of IL-36-mediated proinflammatory and profibrotic pathways. Spesolimab became the first treatment to receive approval from the US Food and Drug Administration (FDA) in September 2022 and from the European Medicines Agency (EMA) in December 2022 for managing GPP in patients aged 12 and older.[11,34] The first evidence emerged from a phase I proof-of-concept study involving 7 patients experiencing a GPP flare. A single intravenous infusion of 10 mg/kg of spesolimab led to rapid, effective, and sustained clearance of skin symptoms, with no significant AE reported.[41] The Effisayil clinical trial program has been investigating the largest population of patients with GPP. The Effisayil 1 phase II trial, which included a multicentric cohort of 53 participants, further demonstrated the efficacy of spesolimab compared to placebo in clearing GPP lesions within one week and enhancing patient-reported pain, fatigue, quality of life, skin symptoms and systemic markers of inflammation.[42] For patients (aged 12 and older and weighing 40 kg or more) experiencing a flare, spesolimab should be administered as soon as possible as a single 900 mg intravenous infusion over 90 minutes. If flare symptoms persist, an additional dose may be administered one week after the initial infusion.[43]

The Effisayil 2 clinical trial assessed the use of spesolimab maintenance treatment to prevent GPP flares. In this multinational study involving 123 adolescents and adults with a history of GPP, high-dose spesolimab demonstrated a significant advantage over placebo in preventing GPP flare-ups over a 48-week period and in reducing the risk of a decline in quality of life, indicating its potential as an effective long-term treatment option for GPP.[44] The recommended dose of spesolimab for maintenance treatment is a subcutaneous loading dose of 600 mg, followed by 300 mg administered subcutaneously 4 weeks later and every 4 weeks thereafter. A subcutaneous loading dose is not required following treatment of a GPP flare with intravenous spesolimab.[43] The efficacy of spesolimab does not seem to be affected by the *IL36RN* mutational status.[41,42,44] Spesolimab was shown to be safe and well-tolerated by GPP patients, with most adverse events being non-serious, non-severe, and not leading to treatment discontinuation.[41,42,44] In the one-week placebo-controlled period of Study Effisayil

Table 3 – Overview of the main treatments for generalized pustular psoriasis[7,8,13,24,25,31,34]

Treatment	Mechanism of action	Efficacy in GPP	Potential safety issues	Indication for GPP
Cyclosporine	Calcineurin inhibitor	Effective in rapid control of acute GPP flares, but typically for short-term use.	Nephrotoxicity, hypertension, gengival hyperplasia, increased risk of infections and malignancies.	Off-label
Methotrexate	Antimetabolite that inhibits folate-dependent enzymes	Moderate efficacy, especially in chronic cases or when combined with other treatments.	Hepatotoxicity, bone marrow suppression, lung toxicity, gastrointestinal toxicity, increased risk of infections.	Off-label
Acitretin	Retinoid (oral)	Effective in chronic management of GPP; slower onset of action.	Teratogenicity, mucocutaneous dryness, hypertriglyceridemia, hepatotoxicity	Off-label
Corticosteroids	Broad immunosuppressive effects	Effective in short-term control of acute GPP flares, but not recommended for long-term use.	Adrenal suppression, weight gain, hypertension, hyperglycemia, osteoporosis, risk of rebound flares.	Off-label
Adalimumab	TNFinhibitor	Clinical efficacy demonstrated in case reports of GPP	Increased risk of infections, malignancies, injection site reactions, cardiovascular risks.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Infliximab	TNFinhibitor	Rapid onset of action (pustule clearance 1–3 days)	Infusion reactions, infections (e.g., tuberculosis), heart failure, hepatotoxicity.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Secukinumab	IL-17A inhibitor	Sustained clinical efficacy demonstrated in case reports and several small open-label phase 3 trials in GPP	Nasopharyngitis, upper respiratory infections, candidiasis, exacerbation of inflammatory bowel disease.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Ixekizumab	IL-17A inhibitor	Clinical efficacy demonstrated in case reports of GPP	Infections, hypersensitivity, exacerbation of inflammatory bowel disease, injection site reactions.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Brodalumab	IL-17 receptor antagonist	Clinical efficacy demonstrated in case reports of GPP	Risk of suicidal ideation and behavior, infections, neutropenia, hypersensitivity reactions.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Ustekinumab	IL-12/IL-23 inhibitor	Variable efficacy; less effective in controlling GPP compared to IL-17 inhibitors.	Increased risk of infections, malignancies, hypersensitivity reactions, reversible posterior leukoencephalopathy.	Off-label
Risankizumab	IL-23 inhibitor (p19 subunit)	Clinical efficacy demonstrated in case reports of GPP	Upper respiratory infections, headache, fatigue, injection site reactions, arthralgia.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Guselkumab	IL-23 inhibitor (p19 subunit)	Clinical efficacy demonstrated in case reports of GPP	Infections, upper respiratory tract infections, headaches, injection site reactions, gastrointestinal symptoms.	On-label for GPP flares in Japan. Off-label in Europe and United States.
Spesolimab	IL-36 receptor antagonist	Sustained efficacy in treating GPP flares and controlling the disease relapses in the long-term	Infections, hypersensitivity reactions.	On-label for GPP flares. Approved by FDA for the treatment of GPP and EMA for prevention of flares.

EMA: European Medicines Agency; FDA: Food and Drug Administration; GPP: generalized pustular psoriasis; IL: interleukin.

1, 14% of subjects receiving spesolimab experienced infections, compared to 6% of those on placebo. Among these, a serious infection, specifically a urinary tract infection, occurred in one subject (3%) treated with spesolimab, while no such infections were reported in the placebo group.[42] Since it is not possible to exclude that IL-36 inhibition may confer higher vulnerability of the host to infections, spesolimab is not recommended for those with active significant infections, and screening for tuberculosis is advised before treatment.[34,43] The safety and effectiveness of spesolimab in pediatric patients younger than 12 years of age or weighing less than 40 kg have not been established.[43]

Imsidolimab is another monoclonal antibody that targets IL-36 signaling. It demonstrated efficacy in an open-label study involving eight patients experiencing a GPP flare and is currently advancing to a phase III clinical trials.[45]

While significant progress has been made in developing targeted therapies for GPP, challenges remain in establishing clear guidelines for treatment success and failure and optimizing treatment for specific populations. There is a critical unmet need for effective and safe treatments for GPP in pregnant women and children, conditions that are even rarer. For impetigo herpetiformis, certolizumab may be a reasonable and safer option, as it exhibits minimal placental transfer. Currently, the dosages of biologics used for juvenile GPP, including etanercept, adalimumab, ustekinumab, ixekizumab, and secukinumab, are based on those approved for pediatric plaque-type psoriasis.[35,46] Ongoing research into biologic therapies for GPP will continue to improve patient outcomes and expand treatment options.

CONCLUSION

Generalized pustular psoriasis is a serious and potentially life-threatening condition that requires accurate diagnosis and prompt treatment. Understanding the IL-36 pathway's role as a critical inflammatory axis in GPP pathogenesis has paved the way for novel therapeutic strategies. Spesolimab has been shown to be effective in the management of GPP, both in the rapid control of the flares and in preventing their recurrence in the long-term, while maintaining a favorable safety profile. By addressing key unmet needs in GPP treatment, spesolimab is antecipated to become the standard of care for this rare orphan disease. Ongoing research and clinical implementation will be fundamental in refining treatment approaches and enhancing patient outcomes in GPP.

AUTHOR CONTRIBUTIONS

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

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Hereditary Hyperferritinemia-Cataract Syndrome: A Case Report

Síndrome Hereditária Hiperferritinemia-Catarata: Caso Clínico

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ABSTRACT

Hereditary hyperferritinemia-cataract syndrome is an autosomal dominant genetic disorder that is characterized by high serum ferritin levels without iron overload and early-onset cataracts. The authors describe the case of a 26-year-old woman with hyperferritinemia (1153.3 ng/mL, reference range 11.0 - 306.8 ng/mL), with no other abnormalities in iron metabolism, associated with cataracts diagnosed at the age of three. The diagnosis was confirmed by genetic testing with detection of a heterozygous variant in the *FTL* gene (c.-168G>T). It is important to recognise hereditary hyperferritinemia-cataract syndrome to avoid unnecessary medical procedures.
Keywords: Cataract/genetics; Hyperferritinemia; Iron Metabolism Disorders/congenital

RESUMO

A síndrome hereditária hiperferritinemia-catarata é um distúrbio genético autossómico dominante caracterizado por valores de ferritina sérica aumentados sem sobrecarga de ferro e por cataratas de início precoce. Os autores descrevem o caso de uma mulher de 26 anos com hiperferritinemia (1153,3 ng/mL, valor de referência 11,0 - 306,8 ng/mL), sem outras alterações na cinética de ferro, associada a cataratas diagnosticadas aos três anos de idade. O diagnóstico foi confirmado por estudo genético com a identificação de uma variante em heterozigotia no gene *FTL* (c.-168G>T). O reconhecimento da síndrome hereditária hiperferritinemia-catarata é importante para que seja possível evitar a realização de procedimentos médicos desnecessários.
Palavras-chave: Catarata/genética; Distúrbios do Metabolismo do Ferro/congénito; Hiperferritinemia

INTRODUCTION

Ferritin is a water-soluble protein that plays a key role in iron metabolism participating in iron detoxification and iron storage. Ferritin consists of 24 protein subunits of two different types: H-ferritin (heavy chain) and L-ferritin (light chain) that are encoded by genes located on chromosomes 11 and 19, respectively.[1] H- and L-ferritin have different functions, H-ferritin is responsible for iron storage and carries the ferroxidase activity needed to sequester iron while L-ferritin has a regulatory function with the presence of acidic groups that facilitate iron oxidation and hydrolysis.[2]

Iron homeostasis is mediated by iron-responsive elements (IREs) that are found within mRNA and by iron regulatory proteins (IRPs) that are cytoplasmic mRNA-binding proteins. A single functional IRE is found in the 5'-untranslated region (UTR) of mRNAs for the H and L-ferritin subunits, while multiple IREs are present in the 3'-UTR of the mRNA for the transferrin receptor. There are two iron regulatory proteins, IRP1 and IRP2, which are both capable of sensing cellular iron status and interacting with the IREs. Under conditions of intracellular iron depletion, both IRPs can bind IRE with high affinity and this interaction prevents translation of ferritin and eventually decreases ferritin protein levels. When iron concentration is high, IRP1 changes its conformation and loses its RNA-binding activity and activates its function as a cytosolic aconitase, an enzyme in the Krebs cycle. On the other hand, IRP2 is targeted for degradation by the proteasome. In the absence of a bound IRP, the ferritin transcript is readily translated, while the transferrin receptor transcript is rapidly degraded.[1]

Hereditary hyperferritinemia-cataract syndrome (HHCS), also known as Bonneau-Beaumont syndrome, arises from various point variants or deletions in the 5'-UTR of the *FTL* gene located in chromosome 19q13.3-q13.4, involving the IRE sequence. Mutations of the IRE element cause inhibition of the IRE-IRP interaction, with concomitant upregulation of FTL synthesis and accumulation of L-ferritin chains unrelated to the body's iron status.[3,4]

The authors describe the case of a 26-year-old woman with hereditary hyperferritinemia-cataract syndrome. This disorder is relatively harmless and can be misdiagnosed with other potential causes of hyperferritinemia. It is important to recognize it to avoid unnecessary medical procedures.

CASE REPORT

A 26-year-old woman was referred to the internal medicine clinic due to high serum ferritin levels and suspected hemochromatosis. The patient was born at term, and the pregnancy was unremarkable. Her history showed cataracts diagnosed when she was only three years old and she presented normal growth and psychomotor development. It was found that the patient had high serum ferritin levels.

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The family history revealed that the patient's 62-year-old father and 33-year-old brother also presented with early-onset cataracts and high ferritin levels, and both had already undergone cataract surgery. Also, other family members from the father's side had early-onset cataracts and high ferritin levels, including a 39-year-old cousin and a 56-year-old aunt. The patient also knew that her grandfather and great-grandmother, both from her father's side, had early-onset cataracts but were never assessed for hyperferritinemia (Fig. 1). From her mother's side there were no family members with early-onset cataracts or high ferritin levels.

Blood tests showed high ferritin levels with no other abnormalities in iron metabolism (Table 1); blood count, liver function and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were normal. Moreover, viral hepatitis and human immunodeficiency virus (HIV) were excluded as potential causes of hyperferritinemia. Genetic testing for hereditary hemochromatosis (*HFE* gene) was performed and was negative. Abdominal ultrasonography and magnetic resonance imaging were normal with an estimated hepatic iron concentration of 18 µmol/g (normal concentration up to 36 µmol/g) in the latter.

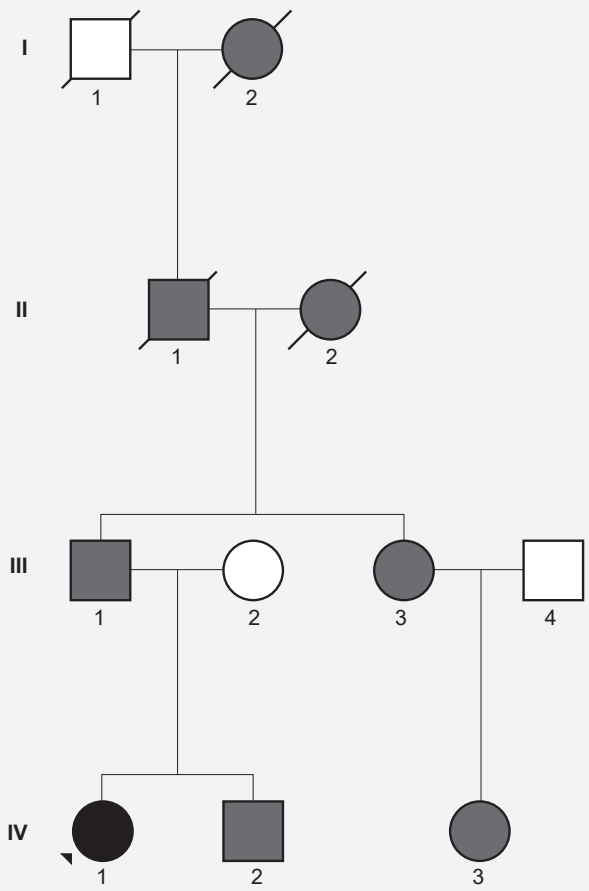

Figure 1 – Family tree. Squares indicate men, circles indicate women; slashed symbols indicate deceased individuals. Black-filled symbol indicate affected individual with HHCS; grey-filled symbols indicate suspected individuals.

Table 1 – Iron study

Blood tests	Results	Reference range
Iron	20.2 µmol/L	9.0 - 30.4 µmol/L
Transferrin	300.0 mg/dL	200.0 - 360.0 mg/dL
Transferrin saturation	29.0 %	7.4 - 64.7%
Ferritin	1153.3 ng/mL	11.0 - 306.8 ng/mL

Ophthalmological evaluation with slit-lamp examination revealed sutural and nuclear cataracts in both eyes (Fig. 2 and 3). Visual acuity was 5/10 on the right eye and 8/10 on the left eye.

After a review of the clinical case, hereditary hyperferritinemia-cataract syndrome (HHCS) was established as a diagnostic hypothesis. Genetic testing was performed with detection of a heterozygous variant in the IRE region of the ferritin light chain gene (*FTL* gene - c.-168G>T, classified as pathogenic). At the time of writing, the patient's father and brother were waiting for the genetic test for HHCS and the remaining family members did not want to be tested.

DISCUSSION

Hereditary hyperferritinemia-cataract syndrome is a rare autosomal dominant genetic disorder with an estimated prevalence of < 1/1 000 000.[4] The clinical manifestations are early-onset bilateral cataracts associated with hyperferritinemia without iron overload, and the cataracts are the only recognizable phenotypic manifestation. This disorder's cataract morphology is described as central and peripheral crystalline flecks in a radial pattern.[5] Although L-ferritin may accumulate harmlessly in other tissues, low protein turnover and containment by the capsule may cause ferritin crystals to accumulate within the eye's lens, disrupting light transmission. It is thought that the clinical severity of HCSS is correlated with the position of the *IRE* mutation.[4]

Since there is no iron overload, phlebotomy is not recommended and the only treatment needed is cataract surgery when patients suffer from visual impairment. Therefore, HHCS is considered a relatively harmless disease.

Most clinicians are not familiar with this disease. Since hemochromatosis is a relatively common disorder associated with hyperferritinemia, it could lead to misdiagnosis of HHCS. Hemochromatosis presents with high serum ferritin and high transferrin saturation levels, unlike HHCS that presents only with hyperferritinemia. Patients with HHCS who undergo phlebotomy rapidly develop iron deficiency anemia without significant change in ferritin serum levels.[1] Family history of hyperferritinemia and cataracts are important indicators of HHCS. The diagnosis is confirmed by genetic testing of the *FTL* gene.[6] Genetic counseling should be

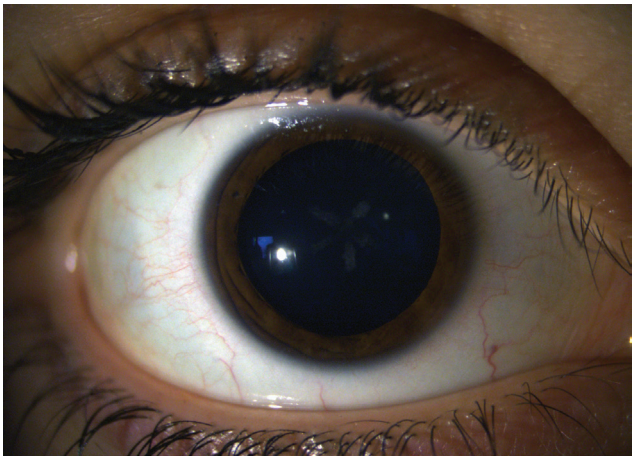

Figure 2 – Slit lamp examination of right eye

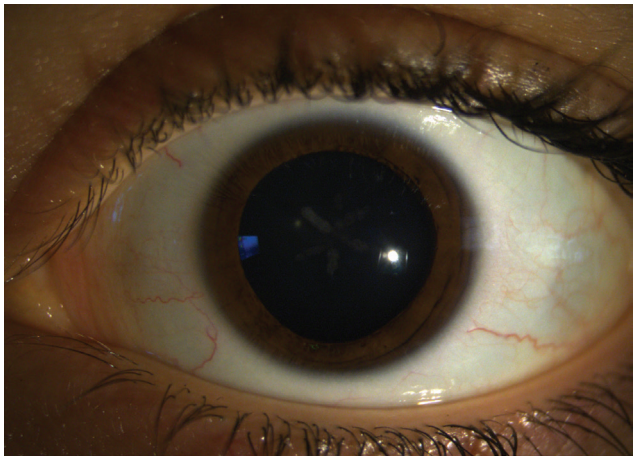

Figure 3 – Slit lamp examination of left eye

offered to the affected individuals so they can be informed about the chances of their future offspring being affected by the syndrome. In this case, the patient has a 50% risk of having an affected child with each pregnancy.

Hereditary hyperferritinemia-cataract syndrome should be considered in the differential diagnosis of hyperferritinemia, especially in the presence of normal transferrin saturation. It is important to recognize this entity to avoid unnecessary and even adverse medical procedures in patients with HHCS.

AUTHOR CONTRIBUTIONS

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

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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From Headache to Diagnosis: A Case of Pediatric Cerebral Abscess

Da Cefaleia ao Diagnóstico: Um Caso de Abcesso Cerebral Pediátrico

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Keywords: Brain Abscess/diagnosis; Child; Headache
Palavras-chave: Abscesso Cerebral; Cefaleia; Criança

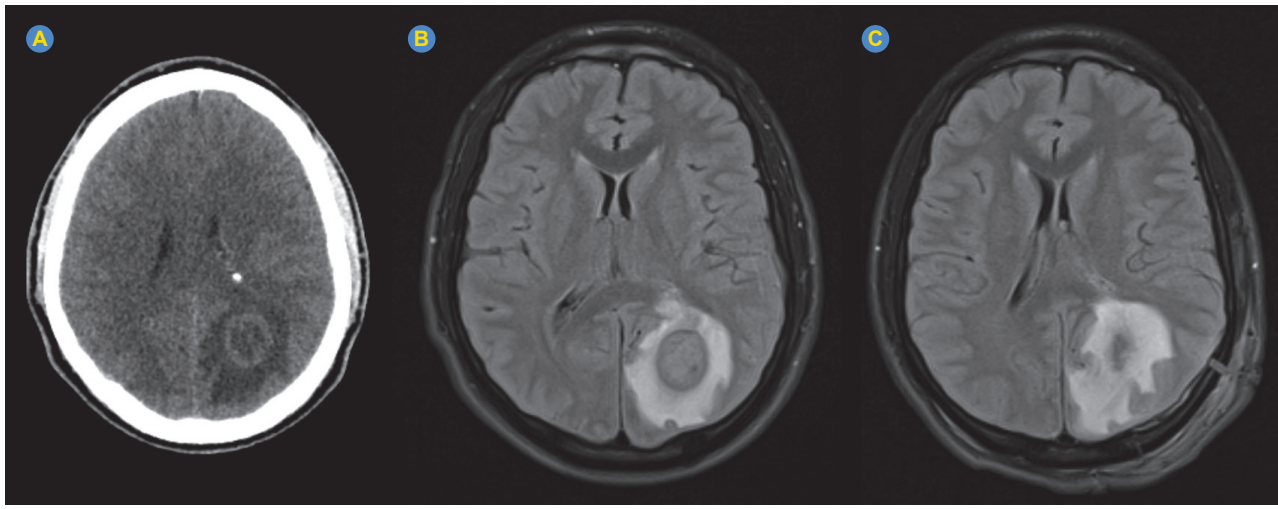

Figure 1 – Cerebral CT-scan revealing round lesion with mass effect and edema in the left occipital region (A). Cerebral MRI (T2/FLAIR) revealing a lesion with double rim sign highly characteristic of cerebral abscess (B). Cerebral MRI (T2/FLAIR) three days after surgical drainage (C).

A 17-year-old male patient presented to the emergency room with acute right retro-orbital and occipital headache worsened by cephalic movements and partially relieved with ibuprofen, along with vomiting and fever. The neurological assessment showed inferior-right quadrantanopia (not being able to see in one quarter of the visual field). A cerebral computed tomography (CT) scan showed a round lesion with mass effect in the left occipital region measuring 24 x 31 x 33 mm (Fig. 1A) raising suspicion of an abscess which was confirmed through magnetic resonance imaging (MRI) (Fig. 1B). Surgical draining was performed (Fig. 1C) and ceftriaxone and metronidazole were administered for six weeks. *Streptococcus intermedius* was identified in the pus. Evaluation by Otorhinolaryngology and Stomatology identified no signs of infection. Further investigation including a full-body CT-scan, echocardiogram, and immunodeficiency screening yielded no findings. At six-month follow-up, the patient was asymptomatic. Pediatric cerebral abscess is a rare life-threatening infection with an annual incidence of 0.5/100 000.[1,2] Assessing contiguous site infection, hematogenous seeding, and immunodeficiency is crucial.[3] However, in 20% of cases no etiology is identified.[1,3]

AUTHOR CONTRIBUTIONS

AAB: Study design, literature search, data acquisition, writing of the manuscript.

IIAM: Literature search, writing of the manuscript.

SM: Literature search, data acquisition, critical review of the manuscript.

AMM: Literature search, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

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AMP ACTA MÉDICA PORTUGUESA
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Gestão das Cefaleias em Portugal: Consenso das Sociedades Portuguesas de Cefaleias e Neurologia, Associação Portuguesa de Medicina Geral e Familiar e MiGRA

Headache Management in Portugal: Consensus among the Portuguese Headache and Neurology Societies, the Portuguese Association of General and Family Medicine, and MiGRA

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RESUMO

As cefaleias são uma causa significativa de incapacidade a nível global, com a enxaqueca a ocupar o segundo lugar entre as doenças com mais anos vividos com incapacidade. A maioria dos doentes com cefaleias, incluindo enxaqueca, podem e devem ser diagnosticados, tratados e acompanhados eficazmente nos cuidados de saúde primários. Isso não só reduz a incapacidade associada a estas patologias, mas também previne a progressão para formas crónicas ou o uso excessivo de medicamentos. A criação de uma rede eficiente de referenciação, envolvendo associações de doentes e profissionais de saúde além dos cuidados primários, é essencial para garantir o apoio necessário em casos mais complexos e para promover a saúde da população de forma ágil e atempada. Estas orientações para diagnóstico, terapêutica e referenciação resultam de um consenso entre a Sociedade Portuguesa de Cefaleias, Sociedade Portuguesa de Neurologia, Associação Portuguesa de Medicina Geral e Familiar, e a MiGRA Portugal, associação portuguesa de doentes com enxaqueca e cefaleias. Este documento foi elaborado para capacitar todos os médicos a contribuir de forma eficaz no tratamento destas patologias.

Palavras-chave: Cefaleias/diagnóstico; Cefaleias/tratamento farmacológico; Encaminhamento e Consulta; Perturbações da Enxaqueca/diagnóstico; Perturbações da Enxaqueca/tratamento farmacológico; Portugal

ABSTRACT

Headaches are a significant cause of global disability, with migraines ranking second of all conditions in terms of years lived with disability. Most headache patients, including those with migraine, can and should be effectively diagnosed, treated, and managed in primary healthcare settings. This approach not only reduces the disability associated with these conditions but also prevents progression to chronic forms or the development of medication overuse. The establishment of an efficient referral network, involving patient associations and healthcare professionals beyond primary care, is essential to ensure adequate support for more complex cases and to promote population health in a timely and effective manner. These guidelines for diagnosis, treatment, and referral are the result of a consensus among the Portuguese Headache Society, the Portuguese Society of Neurology, the Portuguese Association of Family Medicine, and MiGRA Portugal, the Portuguese association of migraine and headache patients. This document was designed to empower all physicians to contribute effectively to the management of these conditions.

Keywords: Headache/diagnosis; Headache/drug therapy; Migraine Disorders/diagnosis; Migraine Disorders/drug therapy; Portugal; Referral and Consultation

INTRODUÇÃO

Segundo a Organização Mundial da Saúde, a enxaqueca é a segunda causa de anos vividos com incapacidade, sendo a primeira em pessoas com menos de 50 anos, nas crianças e nos adolescentes.[1,2] Além da incapacidade e do sofrimento pessoal, tem custos socioeconómicos significativos, sobretudo indiretos, por absentismo e perda de

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produtividade laboral, já que atinge predominantemente as pessoas em idades de vida profissional ativa. Estes representam cerca de 70% dos custos totais relacionados com a doença. Em Portugal, com base num estudo realizado em ambiente laboral, estima-se que o custo indireto das cefaleias seja de mil milhões de euros por ano.[3]

Um estudo de prevalência nacional[4] estima que cerca de dois milhões de pessoas sofram de enxaqueca, 780 000 com episódios com incapacidade significativa e cerca de 750 000 adicionais com cefaleias crónicas (enxaqueca e outras). Aproximadamente 1,5 milhões de portugueses beneficiariam, assim, de acompanhamento médico, dos quais 90% deveria ter resposta nos cuidados de saúde primários.[5] Contudo, cerca de 40% das pessoas que vivem com cefaleias em Portugal não tem acompanhamento médico e mais de metade dos que o têm recorrem ao privado.[6]

A organização eficiente de serviços e tratamentos para cefaleias é custo-efetiva,[7] e a formação dos profissionais de cuidados de saúde primários em cefaleias melhora a eficácia clínica e diminui o desperdício de recursos.[8] Desta forma, torna-se essencial a atualização dos profissionais de saúde portugueses nas orientações de seguimento, terapêutica e de referenciação dos doentes com cefaleias. A referenciação adequada fará com que a inovação terapêutica eficaz seja acessível de forma eficiente, atempada e equitativa para os doentes resistentes e refratários[9,10] aos tratamentos convencionais.[11]

Neste consenso pretende-se sintetizar a mais recente evidência que levou às orientações de diagnóstico,[12] terapêutica[13] e de seguimento/referenciação[5] publicadas pela Sociedade Portuguesa de Cefaleias (SPC, www.cefaleias-spc.com) em relação à enxaqueca e outras cefaleias com foco na terapêutica farmacológica, e enquadrá-las nas mais recentes orientações das sociedades científicas internacionais. Não nos debruçaremos sobre as estratégias de terapêutica não farmacológica nem na neuroestimulação, disponíveis nas recomendações terapêuticas da SPC.[13]

ENXAQUECA: DEFINIÇÃO, INDICAÇÕES GERAIS DE TRATAMENTO, ORIENTAÇÃO E SEGUIMENTO

A enxaqueca é uma cefaleia primária que muito frequentemente motiva a procura de cuidados de saúde dada a incapacidade a que condiciona. A sua manifestação cardinal é a dor moderada a intensa (se não tratada), habitualmente unilateral e pulsátil. A dor nunca surge isolada, acompanha-se de anorexia e/ou náuseas com/sem vómitos, fotofobia e fonofobia, agravando-se com o movimento, esforço físico e esforço mental. Estes sintomas surgem progressivamente, associados ao aumento da intensidade da dor. A crise de enxaqueca é definida em quatro fases,[14] mas nem todas as fases ocorrem em todas as crises e/ou em todos os indivíduos. A primeira fase, prodrómica, que precede o aparecimento da dor em horas, é dominada por sintomas como a fadiga, bocejos, alteração do humor, retenção hídrica, compulsão alimentar, entre outros. Quinze a 20% das pessoas podem ter aura, que corresponde a fenómenos neurológicos transitórios, quase sempre manifestações visuais progressivas, como visão distorcida em ondas de calor, brilhos, cintilações, sensação de encandeamento, ou fenómenos complexos, como caleidoscópios ou linhas em *zig-zag* com brilho ou cor. Estes ocupam habitualmente um lado do campo visual (hemicampo) e regridem espontaneamente em 20 a 60 minutos. Em algumas pessoas podem ocorrer alterações da sensibilidade nos membros superiores e/ou face, boca e língua, assim como perturbações da linguagem (disfasia) em sequência – ou seja, um sintoma surge quando o anterior desvanece. A aura que incluí sintomas visuais, sensitivos e disfásicos sequenciais é designada por 'aura típica'. Quaisquer outros tipos de sintomas (perda de força, visão dupla ou outros) durante as auras são raros, devendo-se excluir outras patologias – é uma indicação formal para investigação etiológica urgente e/ou referenciação para a especialidade, de acordo com a apresentação clínica.[5] Após a aura, pode ou não ocorrer dor de cabeça, que pode ser tipo enxaqueca ou outro tipo de cefaleia. Se não houver dor associada, o evento designa-se por 'aura isolada'.[12] A fase da dor de cabeça (fase álgica) é a mais caraterística, contendo os sintomas que permitem o diagnóstico da doença. A dor surge e desaparece de forma progressiva e a crise termina com a persistência de alguns sintomas após o desaparecimento da dor – sonolência, desconcentração, fadiga, entre outros – o período posdrómico, que os doentes designam por 'ressaca'.

Uma forma rápida e eficiente de estabelecer o diagnóstico de enxaqueca é utilizar o instrumento ID-*Migraine*, traduzido e validado para a população portuguesa, autoaplicável e que consiste em três perguntas simples: "1. Sente-se enjoada(o) ou maldisposta(o) quando tem dor de cabeça?"; "2. A luz incomoda muito mais do que quando não tem dor de cabeça?"; e "3. As dores de cabeça limitaram a sua capacidade de trabalhar, estudar ou realizar as suas atividades normais durante pelo menos um dia nos últimos três meses?" Uma resposta afirmativa a duas dessas questões apresenta uma sensibilidade de 94% e um valor preditivo positivo de 80% para o diagnóstico de enxaqueca.[15]

Os episódios duram, por definição, entre quatro horas a três dias, recorrendo ciclicamente com frequência variável. Se, num período de três meses, a média de dias por mês (seguidos ou intercalados) com dor for igual ou superior a 15, a enxaqueca é designada como crónica; se forem 14 ou menos, designa-se por episódica.[12]

O tratamento farmacológico da enxaqueca é dividido em duas abordagens complementares: o tratamento agudo/sintomático das crises e o tratamento preventivo.

Tratamento farmacológico da crise (agudo)

O tratamento farmacológico agudo (ou abortivo) da crise de enxaqueca está sempre indicado, visando o rápido alívio da dor, dos sintomas acompanhantes e retorno à capacidade funcional normal. A administração da medicação deve ocorrer assim que o indivíduo reconheça os primeiros sintomas da crise. O fármaco ideal para cada doente é aquele cujo início de ação seja rápido, proporcionando alívio completo de todos os sintomas e evitando a incapacidade funcional. Deve ser eficaz numa única administração, prevenir o reaparecimento dos sintomas durante pelo menos 24 horas e ser isento de efeitos adversos.[16]

Existem várias classes de fármacos disponíveis com evidência de nível elevado no tratamento da crise de enxaqueca, dividindo-se em inespecíficos – que incluem os analgésicos e anti-inflamatórios não esteróides (AINEs) e os procinéticos – e os específicos, que incluem, triptanos, ergotamínicos e, mais recentemente, novas classes terapêuticas, como os ditanos e gepants (Tabela 1). Outros fármacos com efeito analgésico não são recomendados,

Tabela 1 – Fármacos e níveis de evidência e eficácia do tratamento da crise de enxaqueca[13,21,23,36-39]

	Classe	Princípios ativos (Nível de evidencia)	Efeito analgésico	Efeito antiemético	Uso parentérico	Uso na gravidez†	Evidência na Pediatria‡
Inespecíficos	Analgésicos	Paracetamol (B) Metamizol (B)	✓	Ø	✓ (EV, Retal)	Cat B	B§
	AINEs	AAS/ Ac. Lisina (A) Ibuprofeno (A) Naproxeno (A) Diclofenac (A) Ceterolac (A) Cetoprofeno (B)	✓	Ø	✓ (EV, Retal)	Cat C (Evitar > 32S)	CI A§ C Ø B Ø
	Procinéticos	Metoclopramida (B) Domperidona (B) Clorpromazina (B)	Ø	✓	✓ (EV)	Cat B	C
Específicos	Ergotamínicos	*Dihidroergatamina (A) #Ergotamina (B)	✓	Ø	✓ (EV, SC, Nasal)	CI	Ø
	Triptanos	Almotriptano (A) Eletriptano (A) Frovatriptano (A) Naratriptano (A) Rizatriptano (A) Sumatriptano (A) Zolmitriptano (A)	✓	±	✓ (SC, Nasal)	Cat C (Evitar 3ºT)	A (> 12) Ø§ Ø Ø A (> 6) A (> 12)§ A (> 12)
	Ditanos	*Lasmiditano (A)	✓	±	✓	Cat X	Ø
	Gepants	Rimegepant (A) *Ubrogepant (A) *Zavegepant (A)	✓	±	✓ (Nasal)	Cat X	Ø
Combinações	Naproxeno + Sumatriptano (A) Paracetamol + #Ergotamina + Cafeína + Beladona (B) AAS + Paracetamol + Cafeína (A)		✓	Ø	Ø	Cat X	B (> 12) Ø

✓ Indicado / existe evidência robusta;
± Indicado / existe alguma evidência;
Ø Não Indicado / não existe evidência ou existe evidência de baixa qualidade;
CI: Contra-indicado, com evidência robusta que não deve ser utilizado;
*: Indisponível em Portugal no momento da publicação.
#: Existe em Portugal um produto com este príncipio ativo associado a outros fármacos, sem evidência para a combinação.
†: Categorização da FDA (Food and Drug Administration) na GRAVIDEZ
Cat X: Categoria X – Contra-indicado; Cat C: Categoria C (estudos em animais não indicam risco para o feto e não existem estudos controlados em grávidas, ou não existem estudos animais ou humanos); Cat B: Categoria B (estudos em animais não demonstraram risco para o feto e não há estudos controlados em grávidas, ou estudos em animais demonstraram um efeito adverso, mas estudos controlados em grávidas não demonstraram esse risco).
‡: Nível de Evidência em ensaios em Pediatria;
§: Uso no aleitamento associado a baixo risco para o recém-nascido
AAS: ácido acetilsalicílico; Ac. Lisina: acetilsalicilato de lisina; EV: endovenoso, SC: subcutâneo.

devido à sua menor eficácia e ao maior risco de efeitos adversos – referimo-nos aos opióides e barbitúricos, sejam isolados ou em associação.[13]

A seleção de cada fármaco deve ser orientada pelo perfil do doente e pela existência de contraindicações ou precauções para o seu uso (Tabela 2); ou em determinados estados fisiológicos (como gravidez, aleitamento ou idade pediátrica); ou com determinadas circunstâncias da crise (como náuseas precoces). Excluídas estas situações, a eficácia dos fármacos utilizados deve ser o principal critério, sendo a primeira opção o mais eficiente, desde que desprovido de efeitos adversos significativos, identificado após uma estratégia de tentativa-erro.

A monitorização da eficácia e tolerabilidade da terapêutica abortiva de crise deve ser efetuada a cada avaliação médica, sendo relevante considerar os vários fatores que podem influenciar a resposta terapêutica – a toma tardia da medicação, a ocorrência de náuseas precoces que atrasam o esvaziamento gástrico e diminuem a eficácia terapêutica, a dosagem insuficiente, a necessidade de ajuste de dose de acordo com o peso corporal, as interações medicamentosas, a ocorrência de efeitos adversos ou o uso excessivo de medicação de crise.[17]

Se a administração de um fármaco está otimizada e, mesmo assim, não resulta numa melhoria significativa (definida como um alívio de sintomas que permita o regresso

Tabela 2 – Contraindicações e precauções no uso de fármacos com evidência no tratamento agudo da enxaqueca[13,21,36–40]

	Classe	Precauções	Contra-indicações
Tratamento de crise*	Analgésicos	Gravidez	Insuficiência hepática grave
	AINEs	Gravidez (até 32 semanas, períodos curtos) INDOMETACINA/ NAPROXENO: Aleitamento	Gravidez (> 32 semanas) Úlcera péptica, doença intestinal inflamatória, *bypass* gástrico, alergia ao AAS, insuficiência renal, uso concomitante de anticoagulantes. AAS: Aleitamento e Idade Pediátrica
	Procinéticos	Gravidez Efeitos extrapiramidais (excepto domperidona)	Aleitamento
	Ergotamínicos	Enxaqueca hemiplégica, com aura do tronco cerebral ou com aura prolongada	Preconceção, gravidez, aleitamento doença vascular periférica, doença coronária, HTA não controlada, AVC/AIT, insuficiência renal ou hepática.
	Triptanos	Gravidez, aleitamento (melhores eletriptano e sumatriptano), síndrome de Raynaud, enxaqueca hemiplégica ou com aura do tronco Risco de síndrome serotoninérgica Interações com metabolismo CYP3A4 (EXCETO sumatriptano e rizatriptano) RIZATRIPTANO: Interação propranolol	Doença vascular periférica, doença coronária, HTA não controlada, AVC, colite isquémica, insuficiência renal ou hepática graves Tratamento com IMAO (mais seguros eletriptano, naratriptano e frovatriptano) Alergia sulfonamidas (mais seguros rizatriptano, frovatriptano e zolmitriptano) ZOLMITRIPTANO: Síndrome Wolf-Parkinson-White
	Ditanos	Risco de sonolência – interdição de condução 8h após a toma Não há dados de administração concomitante com triptano ou gepants Risco de síndrome serotoninérgica Risco de bradicardia	Preconceção, gravidez, aleitamento
	Gepants	Interações com metabolismo CYP3A4 (ex.: claritromicina, itraconazol, ritonavir, diltiazem, eritromicina, fluconazol, fenobarbital, rifampicina, hipericão, bosentano, efavirenz, modafinil) Interações com metabolismo P-gp (ex.: ciclosporina, verapamil, quinidina)	Preconceção, gravidez, aleitamento Insuficiência hepática grave Doença renal terminal (CLcr < 15 ml/min)

*: Os ergotamínicos, triptanos, analgésicos não opióides e opióides e os anti-inflamatórios não esteróides (AINE) apresentam risco de desenvolvimento de cefaleia por uso excessivo de medicação aguda, se utilizados isoladamente ou em combinação por mais de 10 dias por mês (ou 15 dias, no caso dos AINEs), durante um período superior a três meses.[12] Em relação aos fármacos de mais recente introdução no mercado, existe evidência do risco de ocorrência deste fenómeno com os ditanos, mas não existe evidência em relação aos gepants, também utilizados como tratamento crónico (39).

AAS: ácido acetilsalicílico; AIT: acidente isquémico transitório; AVC: acidente vascular cerebral; CLcr: *clearance* da creatinina; HTA: hipertensão arterial; IMAO: inibidores da monoamino-oxidase; metabolismo P-gp: metabolismo da glicoproteína P.

à atividade normal em menos de duas horas, com benefício mantido pelo menos durante 24h), deve-se considerar a falência do fármaco e explorar alternativas. Como regra geral, os triptanos são tão ou mais eficazes que os AINEs, enquanto AINEs e analgésicos superam os ergotamínicos, além destes últimos terem mais efeitos adversos. Associar triptanos com AINES é mais eficaz que utilizar triptanos isoladamente.[18] Se a toma de uma dose de triptano não for eficaz, deve-se fazer pelo menos uma nova tentativa, após um intervalo de duas horas. Um indivíduo é considerado respondedor a um triptano quando este é eficaz em pelo menos três de quatro crises; caso contrário, é definido como um não respondedor a esse triptano. A ausência de resposta a um tripano não determina a ausência de resposta a outro; considera-se o indivíduo resistente aos triptanos após falha de pelo menos dois, e refratário quando ocorre falência com pelo menos três triptanos, incluindo a formulação subcutânea. Se existir contraindicação para o uso de triptanos, o indivíduo é inelegível para tratamento com estes fármacos.[9]

A eficácia dos novos fármacos específicos (ditanos e gepants) supera o placebo, porém numa meta-análise parecem ter eficácia equivalente ou inferior aos triptanos. Esses fármacos oferecem vantagens em perfis específicos, como em indivíduos com fatores de risco cardiovasculares ou em pessoas refratárias a tratamentos anteriores, devido ao seu mecanismo de ação distinto.[19]

Existem circunstâncias específicas em que se podem considerar alternativas; por exemplo, numa crise grave e incapacitante não controlada durante 72 horas (estado de mal de enxaqueca) são preferidas administrações por via intravenosa ou intramuscular, devido à rapidez de início de ação e à frequente presença de náuseas e/ou vómitos. As opções incluem sulfato de magnésio, valproato de sódio, clorpromazina, corticosteróides ou bloqueios anestésicos do nervo occipital com lidocaína, sendo a evidência de eficácia de qualquer dessas opções de baixa qualidade.[13] Outro exemplo é o tratamento dos sintomas de aura, geralmente não realizado, pois a maioria é autolimitada em menos de 30 minutos, dificultando a demonstração de eficácia terapêutica nesse período.

Tabela 3 – Fármacos e níveis de evidência e eficácia no tratamento preventivo da enxaqueca[13,21,23,27,41,42]

	Classe	Princípios ativos	Evidência da enxaqueca episódica	Evidência na enxaqueca crónica	Evidência na cef. uso exc. analgesicos	Uso na gravidez†	Evidência na Pediatria‡
Inespecíficos	Antidepressivos	Amitriptilina	A	Ø	B[1]	Cat B	B
		Venlafaxina	B	Ø	Ø		Ø
	Anticrises epiléticas	Topiramato	A	A	B[1]	Cat X	A
		Valproato de Sódio	A	B	C[1]		B
		Gabapentina	B	Ø	Ø		C
	Beta-bloqueantes	Propranolol	A	Ø	B[1]	Cat B	C
		Metoprolol	A	Ø	Ø		Ø
		*Nadolol	B	Ø	Ø		Ø
		Atenolol	B	Ø	Ø		Ø
		Bisoprolol	B	Ø	Ø		
	Antagonistas canais cálcio	Flunarizina	A	Ø	B[1]	Cat X	B
	Toxina	Onabotulínica A (SC)	Ø	A	A	Cat B	C
Específicos	Anticorpos monoclonais	Erenumab (SC)	A	A	A	Cat X	Ø§
		Eptinezumab (IV)	A	A	A		
		Fremanezumab (SC)	A	A	A		
		Galcanezumab (SC)	A	A	A		
	Gepants	Atogepant	A	A	Ø	Cat X	Ø§
		Rimegepant	A	Ø	Ø		

✓ Indicado / existe evidência robusta; ± Indicado / existe alguma evidência;
Ø Não Indicado / não existe evidência ou existe evidência de baixa qualidade;
CI Contra-indicado, com evidência robusta que não deve ser utilizado;
*: Indisponível em Portugal no momento da publicação;
1: Quando associado a suspensão da utilização excessiva de medicação
†: Categorização da FDA (Food and Drug Administration) na GRAVIDEZ
Cat X, Categoria X: Contra-indicado; Cat C: Categoria C (estudos em animais não indicam risco para o feto e não existem estudos controlados em grávidas, ou não existem estudos animais ou humanos); Cat B: Categoria B (estudos em animais não demonstraram risco para o feto e não há estudos controlados em grávidas, ou estudos em animais demonstraram um efeito adverso, mas estudos controlados em grávidas não demonstraram esse risco)
‡: Nível de Evidência em ensaios em Pediatria; apenas existe evidência em crianças > 12 A;
§: Ensaios em curso

Tratamento farmacológico preventivo

O tratamento preventivo da enxaqueca está indicado quando as crises comprometem a qualidade de vida, apesar do tratamento agudo otimizado (Tabela 3). Este visa reduzir a frequência, intensidade e duração das crises, diminuindo a incapacidade, o sofrimento e o risco de progressão para enxaqueca crónica e comorbilidades, como a cefaleia por uso excessivo de medicação, a ansiedade e a depressão. Esta abordagem também melhora a qualidade de vida, reduz os custos associados e capacita a pessoa na gestão da doença,[13,20,21] quando associada à literacia sobre a doença e educação para estilos de vida saudáveis.

A terapêutica preventiva é indicada para indivíduos com mais de quatro dias de dor por mês, sendo fortemente recomendada para quem usa medicação aguda 10 ou mais dias por mês e/ou tem 15 ou mais dias de dor de cabeça por mês (enxaqueca crónica), mesmo que nem em todos estes dias usem medicação aguda.[13,20-22]

Outros critérios para considerar profilaxia incluem: a incapacidade de controlar as crises (por falência ou limitações do uso de medicação aguda); crises com auras muito prolongadas ou muito incapacitantes; e a preferência do doente.[13,20-22]

O fármaco preventivo ideal é aquele que é eficaz a reduzir ou eliminar a ocorrência de crises e reduzir o impacto e intensidade de todos os sintomas das crises, com menos efeitos adversos. O início de ação rápido e uma posologia conveniente são preferências para tratamentos igualmente eficazes.[16]

Tal como para a terapêutica de crise, também para a prevenção dispomos de várias classes de fármacos com evidência de nível elevado, que incluem fármacos específicos, que atuam na via do péptido relacionado com o gene da calcitonina (CGRP), e inespecíficos, como os beta-bloqueantes, antidepressivos tricíclicos, antagonistas dos canais de cálcio, fármacos anticrise epilética (ACE), toxina botulínica, e os bloqueios anestésicos de nervo periférico (Tabela 3).

A escolha do fármaco deve considerar as caraterísticas da enxaqueca (episódica, crónica com ou sem uso excessivo de medicação) e do indivíduo, como a idade, a fertilidade e doenças e condições associadas que possam limitar as opções terapêuticas (Tabela 4). A história prévia da utilidade e tolerabilidade dos fármacos é essencial, sobretudos os inespecíficos, cuja a taxa descontinuação atinge os 50% ao fim de um ano por falta de eficácia ou efeitos adversos.[23] A enxaqueca, episódica ou crónica, é considerada resistente se o indivíduo sofrer de oito ou mais dias de cefaleia debilitante por mês, durante pelo menos três meses, apesar do uso de pelo menos três classes de medicação preventiva ineficaz, intolerável ou contraindicada; será refratária se o mesmo ocorrer após terem sido experimentadas todas as classes terapêuticas.[9,10] Devem ser referenciados os doentes com enxaqueca episódica e/ou crónica não controlada (Tabela 5).

Os primeiros fármacos profiláticos específicos para a enxaqueca introduzidos em Portugal foram os anticorpos monoclonais anti-(r)CGRP, demostrando custo-efetividade no tratamento de adultos com pelo menos quatro dias de enxaqueca por mês, após falência de três ou mais terapêuticas preventivas. Consideraram-se como alternativas terapêuticas os fármacos preventivos orais e a toxina botulínica, quando indicada. São de dispensa hospitalar e o seu financiamento requer autorização e monitorização pela Comissão de Farmácia e Terapêutica de cada hospital.[24] Desde a sua introdução, a perceção da sua utilidade melhorou dada a evidência da sua eficácia e a segurança em estudos de vida real (RWE) e ensaios de fase IV. Em 2022, as orientações terapêuticas da European Headache Federation e, em 2024 da American Headache Society, passaram a considerar estes fármacos como alternativa terapêutica de primeira linha, devido ao seu melhor perfil de tolerabilidade e à evidência de ensaios comparativos e RWE que sugerem uma superioridade de eficácia.[25,26] O documento da American Headache Society inclui também os gepants, moléculas anti-rCGRP, como primeira linha terapêutica. Estas foram introduzidas no mercado europeu em 2023 e, uma delas, o atogepant, obteve o regime de comparticipação em Portugal em Janeiro 2025.[26]

Independentemente do fármaco, deve-se respeitar as condições de titulação e monitorizar trimestralmente a eficácia e tolerabilidade. Fatores como a dose, adesão, interações, uso excessivo de medicação aguda e controlo das comorbilidades podem influenciar a resposta à terapêutica. Perante resposta subótima, após correção destes fatores, pode-se alterar ou associar fármacos, embora a evidência para a associação seja limitada.

A duração do tratamento deve ser individualizada: com bom controlo sintomático, recomenda-se manter a dose por quatro a seis meses, podendo estender-se até aos 12 meses antes de considerar a sua suspensão, já que existe evidência de que o benefício pode manter-se após a suspensão. A retirada deve ser monitorizada e a terapêutica reinstituída, em caso de agravamento.[13]

OUTRAS CEFALEIAS: DEFINIÇÃO, INDICAÇÕES TERAPÊUTICAS, DE ORIENTAÇÃO E SEGUIMENTO

Cefaleia tipo tensão

A cefaleia tipo tensão (CTT) é a mais comum das dores de cabeça, estimando-se que a sua prevalência ao longo da vida possa chegar aos 78% da população, e a prevalência no último ano varia entre os 20% na Ásia e América até aos 80% na Europa. É mais frequente nas mulheres, com pico de incidência entre os 25 e os 34 anos,

relacionando-se com o *stress* e a má qualidade do sono.[27] A CTT carateriza-se por uma dor leve a moderada, descrita como sensação de pressão ou aperto, frequentemente comparada a uma faixa ou bandelete apertada. A dor é bilateral, não pulsátil e não é agravada pela atividade física. É incomum que se acompanhe de náuseas, embora possam ocorrer em alguns episódios, assim como fotofobia ou fonofobia ligeiras, sendo esta última mais frequente.

Tal como a enxaqueca, é classificada em episódica (< 15 dias/ mês), ou crónica (15 ou mais dias/ mês, durante pelo menos três meses). Ao contrário da enxaqueca, as crises podem ser curtas (30 minutos) ou muito prolongadas (até sete dias consecutivos), sendo habitual o agravamento vespertino.[12]

A abordagem terapêutica inclui tratamento agudo/sintomático e/ou preventivo, embora haja menos opções e evidência disponíveis, não existindo medicação específica para a CTT.

No tratamento agudo, são eficazes analgésicos (paracetamol e o ácido acetilsalicílico), AINEs (ibuprofeno,

Tabela 4 – Contraindicações e precauções no uso de fármacos com evidência no tratamento preventivo da enxaqueca[13,21,27,41,42]

	Classe	Princípios ativos	Precauções	Contra-indicações
Inespecíficos	Antidepressivos	Amitriptilina Venlafaxina	Hipertrofia prostática Mania/hipomania Obesidade, hipertensão ocular Obstipação, epilepsia Prolongamento QT (idosos, amitriptilina) Gravidez	Retenção urinária Glaucoma agudo
		Fluoxetina		
	Anticrises epiléticas	Topiramato Valproato de Sódio Gabapentina	Nefrolitíase (topiramato) Miopia grave e glaucoma (topiramato) Interação com COC Hiperandrogenismo e S.ovário poliquístico (valproato) Aleitamento Mulheres em idade fértil	Insuficiência hepática Pancreatite Trombocitopenia, pancitopenia e discrasias hemorrágicas. Gravidez e pré-concepção
	Antagonistas beta adrenérgicos	Propranolol Metoprolol *Nadolol Atenolol Bisoprolol	Asma e DPOC, Insuficiência cardíaca congestiva, S. Raynaud, doença arterial periférica Diabetes Gravidez Idoso, Depressão	Aleitamento (apenas atonolol e nadolol) BAV, bradiarritmia Insuficiência renal
	Antagonistas canais cálcio	Flunarizina	Depressão, obesidade, obstipação, insuficiência hepática, glaucoma, prostatismo	Parkinsonismo Gravidez, pré-concepção e aleitamento
	Toxina	Onabotulínica A (SC)	Gravidez, aleitamento Soluções continuidade crânio Antiagregação/anticoagulação	Doença da transmissão neuromuscular
Específicos	Anticorpos Monoclonais	Erenumab (SC) Eptinezumab (IV) Fremanezumab (SC) Galcanezumab (SC)	Doença cardiovascular e cerebrovascular, trombose venosa profunda Acima dos 65 anos (erenumab e galcanezumab), 70 anos (fremanezumab) e 75 anos (eptinezumab)	Gravidez, pré-concepção e aleitamento
	Gepants	Atogepant Rimegepant	Interações com metabolismo CYP3A4 (ex.: claritromicina, itraconazol, ritonavir, diltiazem, eritromicina, fluconazol, fenobarbital, rifampicina, hipericão, bosentano, efavirenz, modafinil) Interações com metabolismo P-gp (ex.: ciclosporina, verapamil, quinidina); Doença cardiovascular aguda	Pré-concepção, gravidez, aleitamento Insuficiência hepática grave Doença renal terminal (CLcr < 15 mL/min)

*: Indisponível em Portugal no momento da publicação.
CLcr: clearance da creatinina; COC: contracetivo oral combinado; DPOC: doença pulmonar obstrutiva crónica; IV: intravenoso; SC: subcutâneo.

naproxeno, diclofenac e cetoprofeno), e associações da cafeína aos analgésicos ou AINEs. A escolha deve considerar as caraterísticas individuais e frequência das crises.[13] Para o tratamento preventivo, os antidepressivos tricíclicos, especialmente a amitriptilina, são a primeira escolha. Alternativas incluem mirtazapina, venlafaxina, clomipramina, maprotilina e mianserina, alguns fármacos ACE, (gabapentina, topiramato) e a tizanidina (relaxante muscular).[13]

A resposta terapêutica costuma ser favorável; nos casos de CTT crónica, com falência no controlo da frequência e/ou intensidade após tratamento com dois preventivos há indicação para referenciação hospitalar (Tabela 5).[5]

Cefaleia em salvas

A cefaleia em salvas, a mais comum das cefaleias trigémino-autonómicas, é rara, com dados de prevalência ao longo da vida variando entre 124 a 381/100 000, sendo a prevalência anual entre 30 a 150/100 000, afetando mais homens e fumadores e tendo início entre os 20 e os 35 anos.[28] Carateriza-se por dor excruciante, estritamente unilateral e cuja intensidade máxima é na região ocular, periorbital, frontal e/ou temporal (território do nervo oftálmico, primeiro ramo do nervo trigémeo). A dor acompanha-se por um comportamento típico de inquietação/agitação e por sintomas autonómicos cranianos homolaterais, quer simpáticos (ptose e miose) quer parassimpáticos (rinorreia, obstrução nasal, lacrimejo, injeção conjuntival e edema palpebral). Estas crises, que duram 15 a 180 minutos, surgem diariamente (entre uma em dias alternados a oito/dia) com ritmo circadiano, muitas vezes à mesma hora do dia ou noite (predominância noturna). Em 80% dos casos, são episódicas, com surtos (fases com sintomas) que duraram entre sete dias a um ano, surgindo com ritmo circanual (na mesma época do ano) e remissões superiores a três meses. Se as remissões forem inferiores a três meses e a duração total dos surtos ultrapassar um ano, é classificada como cefaleia em salvas crónica.[12]

A exclusão de causas secundárias é essencial na manifestação, justificando referenciação prioritária para unidades de neurologia e/ou cefaleias (Tabela 5).[5] Devido à sua gravidade, exige sempre tratamento agudo e preventivo (de curta e/ou de longa duração), que deve ser instituído e monitorizado em unidades especializadas. É crucial instituir terapêutica abortiva das crises, dado que a intensidade da dor é tão disruptiva que há risco de suicídio.

O oxigénio normobárico a 100% (alto débito, 10 a 15 L/min, 20 minutos, por máscara facial com o indivíduo sentado), interrompe as crises em 60% a 80% dos casos, sendo alternativa os triptanos (resposta em 80% dos casos), quer o sumatriptano subcutâneo quer o zolmitriptano nasal; o zolmitriptano oral tem resposta mais tardia.

Para profilaxia de curta duração/transição, a prednisona oral é a opção mais utilizada, com ciclos de duração máxima de três semanas.[13]

Nevralgia do trigémeo

A nevralgia do trigémeo tem uma prevalência na vida entre 0,16% - 0,3%, e incidência anual de 4 - 29/100 000 pessoas-ano. É mais comum em mulheres e geralmente manifesta-se entre os 50 - 60 anos.[29] Apresenta-se com episódios de dor facial unilateral tipo choque elétrico ou 'esticão', intensa, súbita e de curta duração (alguns segundos a dois minutos), que podem ser desencadeados por mastigar, falar, ou tocar na face. Pode ocorrer várias vezes ao longo do dia, comprometendo a qualidade de vida e, frequentemente, a alimentação. Afeta mais frequentemente o nervo maxilar (segundo ramo do trigémeo), seguido do mandibular (terceiro ramo) e podendo ocorrer uma combinação de ambos; o território mais raro é o oftálmico onde pode associar-se a sintomas autonómicos oculares, fazendo diagnóstico diferencial com as cefaleias trigémino-autonómicas. O diagnóstico inaugural requer ressonância magnética crânio-encefálica, para excluir causas secundárias e/ou documentar contacto neurovascular, que pode favorecer a opção cirúrgica.[12] A terapêutica preventiva inicia-se com fármacos ACE, como a carbamazepina ou a oxcarbazepina.[13] A falta de controlo com estes fármacos justifica a referenciação para unidade especializada de neurologia e/ou cefaleias (Tabela 5).[5]

Organização da prestação de cuidados de saúde

Dada a elevada prevalência e impacto funcional das cefaleias, principalmente a enxaqueca, estas devem ser reconhecidas por todos os médicos, pois ocorrem em vários contextos clínicos – urgência, consultas de cuidados de saúde primários e consultas de especialidades hospitalares. Outros profissionais de saúde, como os farmacêuticos, devem estar capacitados para gerir a medicação não sujeita a receita médica nestes casos. A falta de conhecimento técnico foi identificada como o principal obstáculo para o cuidado efetivo dos doentes com cefaleias e enxaqueca a nível mundial.[30]

Os serviços de saúde devem estar eficientemente organizados para oferecer cuidados adequados e atempados, evitando desperdícios, dado que a maioria dos casos não necessita de cuidados especializados. As recomendações europeias relativas à organização destes serviços, bem como à qualificação necessária dos profissionais, foram adaptadas à realidade nacional,[5] sendo necessária a sua efetiva e eficiente implementação. Demonstrou-se que esta abordagem tem ganhos de efetividade e custo-eficácia (enxaqueca) ou proporciona economia de custos (cefaleia de tipo tensão e cefaleia por uso excessivo de medicação aguda), na perspetiva do prestador de cuidados de saúde,

ao longo de um e cinco anos, de forma consistente em diversos sistemas e contextos de saúde.[7]

De acordo com estas recomendações, 90% dos casos devem ser geridos pela Medicina Geral e Familiar,[5] seguindo critérios previamente definidos (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/22496/15649).

Após educação e orientação, a maioria das pessoas pode gerir autonomamente a sua patologia, estimando-se que 10% dos casos necessitarão de cuidados diferenciados e 1% de cuidados de elevada diferenciação. Um sistema de triagem efetivo deve assegurar uma referenciação eficiente entre os três níveis de cuidados, segundo critérios estabelecidos – Tabela 5.[5,31]

Neste modelo de serviços estruturados, pressupõe-se necessária a formação dos profissionais de saúde (farmacêuticos e médicos das especialidades de medicina geral e familiar, medicina do trabalho e neurologia), assim como a educação para a saúde da população.

CONCLUSÃO

Este documento tem como objetivo servir como um resumo prático e sensibilizar os médicos, especialmente de Medicina Geral e Familiar, mas também outros profissionais envolvidos no tratamento de doentes com cefaleias e enxaqueca, para as alternativas terapêuticas disponíveis.

Tabela 5 – Critérios de referenciação dos doentes com cefaleias para consultas de especialidade de neurologia e/ou cefaleias[5]

Critério de referenciação para consulta de neurologia	Critério de referenciação para consulta/unidade especializada em cefaleias
• enxaqueca episódica não controlada (mais que duas faltas ao trabalho ou idas à urgência por ano e/ou falência de controlo das crises após tratamento com dois preventivos diferentes ou contraindicação para a sua utilização); • enxaqueca com aura atípica, prolongada, frequente ou com dúvidas de diagnóstico; • enxaqueca com aura hemiplégica, retiniana ou do tronco cerebral; • enxaqueca crónica não controlada, com ou sem cefaleia por uso excessivo de medicamentos (manutenção do padrão crónico após falência de tratamento com um preventivo, associada a medidas de controlo de ansiedade, sono e excesso de medicação); • cefaleia tipo tensão crónica ou cefaleia pós-traumática crónica não controladas (falência de controlo da frequência e/ou intensidade da dor após tratamento com dois preventivos); • todas as cefaleias trigémino-autonómicas e todas as outras cefaleias primárias; • nevralgia do trigémeo de difícil controlo (falência de controlo após tratamento com um antiepilético); • todas as outras nevralgias cranianas; • cefaleias desencadeadas por estímulos específicos; • cefaleias relacionadas com outras patologias neurológicas (do sono, vasculares, etc.); • qualquer cefaleia associada à existência de comorbilidades e/ou situações especiais (ex.: gravidez) que limitem a prescrição dos fármacos mais comuns; • suspeita de cefaleia secundária cujo diagnóstico e/ ou plano terapêutico necessitem de abordagem clínica e/ou recursos não disponíveis nos cuidados de saúde primários; • incerteza no diagnóstico.	• enxaqueca episódica resistente (falência de controlo das crises após tratamento com três preventivos em dose e duração terapêutica adequada e/ou limitação da utilização destes fármacos e controlo das comorbilidades associadas) e/ ou enxaqueca que condicione mais que duas faltas ao trabalho ou idas à urgência por ano); • enxaqueca crónica de difícil controlo, com ou sem cefaleia por uso excessivo de medicamentos (manutenção do padrão crónico após falência de tratamento com 2 preventivos, e/ou limitação da utilização destes fármacos, associada a medidas de controlo de ansiedade, sono e excesso de medicação e limitação do uso excessivo de medicamentos); • enxaqueca crónica com indicação para tratamento com toxina botulínica ou anticorpos monoclonais; • cefaleia por uso excessivo de medicação com indicação para suspensão em regime de hospital de dia e/ou internamento; • cefaleia tipo tensão crónica ou cefaleia pós-traumática crónica resistente (falência de controlo da frequência e/ou intensidade da dor após tratamento com três preventivos) e/ou limitação da utilização destes fármacos e controlo das comorbilidades associadas; • cefaleias trigémino-autonómicas e outras cefaleias primárias de difícil controlo (falência de controlo após 1 a 2 preventivos em dose e duração adequada e/ou limitação da utilização destes fármacos); • nevralgia do trigémeo de difícil controlo (falência de controlo após 2 fármacos antiepiléticos ou antidepressivos com efeito na dor e/ou limitação da utilização destes fármacos); • outras nevralgias cranianas com indicação para terapêutica por bloqueios anestésicos de nervos periféricos; • qualquer doente com cefaleias que beneficie de uma abordagem multidisciplinar para controlo sintomático ou que necessite de segunda opinião especializada; • qualquer doente com cefaleias primárias ou secundárias que necessite de abordagem por especialidades não disponíveis nos centros de nível III/IV.

Contudo, o enfoque aqui dado é exclusivamente nas alternativas farmacológicas, reconhecendo que existem abordagens complementares para a gestão das cefaleias assim como a importância da educação do doente, complementada com material informativo disponível no site da MiGRA Portugal (https://migraportugal.pt/category/materiais-de-apoio-ao-doente/). Reforça-se que este documento não substitui as recomendações oficiais da SPC (http://www.cefaleias-spc.com/publicacoes/).

As cefaleias, sobretudo a enxaqueca, continuam amplamente subtratadas, quer pela insuficiência no diagnóstico, como pela implementação inadequada das terapêuticas disponíveis. As principais barreiras à eficiente prestação de cuidados aos doentes com cefaleias incluem[32] a falta de conhecimento da população afetada sobre a sua condição e possibilidades de melhoria, que reduz a procura de ajuda, mesmo quando severamente impactados. Muitos dos que tomam a iniciativa de procurar ajuda, ao fazê-lo numa consulta generalista ou com outros profissionais de saúde (farmacêutico, fisioterapeuta, optometrista), muitas vezes são geridos no sentido excluir outras patologias, realizando exames ou tentando terapêuticas empíricas (ex.: óculos 'de descanso') que não proporcionam a solução esperada. Isso deixa os doentes num vazio diagnóstico, onde, apesar de "estar tudo bem", continuam a sofrer e não se vislumbra um caminho claro para o alívio.

Um diagnóstico correto e claro no primeiro contacto com os cuidados de saúde é fundamental, dado que a educação sobre a doença capacita a maioria das pessoas a viver a sua vida, apesar da enxaqueca. O diagnóstico é clínico, não requer exames complementares, e pode ser realizado com apenas três perguntas, se o contexto for adequado.[15] Qualquer profissional de saúde deve ter a capacidade de orientar o doente, e/ou encaminhá-lo para a MiGRA Portugal, que oferece um espaço de partilha de experiências e, sobretudo, informação sobre a doença, continuamente atualizada.

As duas restantes barreiras são de responsabilidade médica e incluem a subutilização da terapêutica disponível e a falta de seguimento adequado, de forma a otimizar a estratégia de tratamento.[32]

Um estudo europeu mostrou que apenas 10% a 40% dos doentes seguidos em cuidados de saúde primários recebeu uma prescrição de triptanos para tratamento agudo, subindo para 25% a 60% se seguidos por neurologia. Da mesma forma, a prescrição de preventivos a doentes com indicação é de apenas 0% a 15% entre médicos de cuidados primários, e 15% a 50% na especialidade.[33] Um inquérito da MiGRA revelou que, em Portugal, 40% dos doentes com enxaqueca e indicação para preventivos não tem seguimento médico regular e, entre os seguidos, apenas 54% recebiam terapêutica preventiva.[6] A dificuldade de acesso a tratamentos avançados, como anticorpos monoclonais apenas comparticipados nos hospitais públicos, condiciona a sua subutilização e impede o acesso dos doentes mais graves à terapêutica eficaz.[34]

O envolvimento de todos os profissionais de saúde é essencial para melhorar o acesso à medicação mais adequada. Os médicos de medicina geral e familiar desempenham um papel fulcral: diagnosticar corretamente, tratar as crises com medicação específica, introduzir atempadamente terapêutica preventiva e educar os doentes sobre a gestão da doença e/ou referenciá-los à MiGRA Portugal. Este é o apelo que fazemos, para que, em conjunto, possamos melhorar o acesso e a qualidade de vida dos doentes com enxaqueca e cefaleias.

CONTRIBUTO DOS AUTORES

RGG: Elaboração das tabelas e do fluxograma, redação e revisão crítica do manuscrito.

EP, IPM: Redação e revisão crítica do manuscrito.

IL, RMP, FP: Revisão crítica do manuscrito.

MP: Elaboração do fluxograma e revisão crítica do manuscrito.

Todos os autores aprovaram a versão final a ser publicada.

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RGG declara que recebeu, por atividades relacionadas com o tema do trabalho em consideração para publicação, honorários por conferências, atividades educacionais, consultoria e participação em ensaios clínicos de Allergan/Abbvie, AMGEN, Astra Zeneca, Almirall, Bial, Biogen, Bristol-Myers Squibb, CMBE, FLOAT, Lilly, Lundbeck, Merk, Novartis, Novo Nordisk, Organon, Pfizer, Roche, Sanofi, Tecnifar e Teva. Declara ainda que recebeu fundos para investigação na área das cefaleias da Fundação Ciência Tecnologia (Project 29675, MigN2Treat, 02/SAICT/2017), da Learning-Health, Luz Saúde (LiON, Luz Innovation on Neurosciences), da Novartis-Sociedade Portuguesa de Cefaleias e do Centro de Investigação Interdisciplinar em Saúde da Universidade Católica Portuguesa.

EP declara que recebeu, por atividades relacionadas com o tema deste trabalho, honorários por atividades educacionais, conferências, consultoria e participação em ensaios clínicos de Lilly, Novartis, Teva, Linde, Vitalaire, Abbvie, Pfizer, Lundbeck, Organon, Amgen, Astrazeneca, Almirall, Bial, Brainsgate, Sanofi, Lilly.

IPM declara que recebeu, por atividades relacionadas com o tema deste trabalho, honorários por atividades educacionais, conferências, consultoria e participação em ensaios clínicos de Allergan, Abbvie, Amgen, Astra Zeneca, Almirall, Eli Lilly, Lundbeck, Novartis, Organon, Pfizer, Tecnifar, Teva e Zambom.

IL declara que recebeu, por atividades relacionadas com o tema deste trabalho, honorários por atividades educacionais, conferências e consultoria de Abbvie, Angelini Pharma, Lundbeck, Organon, Bial e Teva.

RMP declara que recebeu, por atividades relacionadas com o tema deste trabalho, honorários por atividades educacionais, conferências, consultoria de Jaba, Abbvie e Ferrer.

MP declara que recebeu, por atividades relacionadas com o tema do trabalho em consideração para publicação, honorários por consultoria e despesas de deslocações para representação da MiGRA Portugal de Abbvie e Pfizer.

FP declara que recebeu, por atividades relacionadas com o tema deste trabalho, honorários por atividades educacionais, conferências, consultoria e participação em ensaios clínicos de Abbvie, Amgen, Pfizer, Lundbeck, Teva, Tecnifar, Organon, Novartis.

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Gravidez Ectópica Intersticial: Um Caso Raro

Interstitial Ectopic Pregnancy: A Rare Case

Palavras-chave: Gravidez Ectópica/diagnóstico; Gravidez Ectópica/tratamento; Gravidez Intersticial/diagnóstico; Gravidez Intersticial/tratamento; Laparotomia
Keywords: Laparotomy; Pregnancy, Ectopic/diagnosis; Pregnancy, Ectopic/therapy; Pregnancy, Interstitial/therapy; Pregnancy, Interstitial/therapy

Caro Editor,

Apresenta-se um relato de um caso de gravidez ectópica intersticial (GEI), numa nulípara de 35 anos de idade, com oito semanas de amenorreia, assintomática. Ecograficamente constatou-se GEI direita: saco gestacional de 42 mm, não comunicante com o endométrio, camada miometrial circundante residual e com embrião com atividade cardíaca, datação compatível com oito semanas e cinco dias. Analiticamente, apresentava β-hCG de 59311 UI/L. Não apresentava fatores de risco. Decidiu-se resolução cirúrgica, dado o tamanho do saco gestacional e experiência da equipa: resseção cornual e salpingectomia direita laparotómica (Fig. 1). A análise anatomopatológica confirmou o diagnóstico.

A GEI representa 2% - 4% das gestações ectópicas.[1-3] Trata-se de uma gravidez em que a implantação ocorre na porção intersticial da trompa de Falópio que, comparativamente com o segmento distal, tem uma capacidade significativamente maior de expansão antes da rotura acontecer.[2,4] Os fatores de risco são: cirurgia tubária, salpingite ístmica nodosa, anomalia estrutural da trompa causada por endometriose, leiomiomas ou malformações uterinas, infeção pélvica, tabagismo, gravidez ectópica prévia e uso de técnicas de procriação medicamente assistida.[1,2]

Clinicamente, manifesta-se com perda hemática vaginal e dor pélvica, podendo ser assintomática.[2] A sua localização leva, geralmente, a um atraso no diagnóstico, podendo condicionar um aumento da incidência de rotura (2% - 2,5%), frequentemente associada a choque hemorrágico e elevada taxa de mortalidade, devido à elevada vascularização do corno uterino.[3] Adicionalmente, o diagnóstico ecográfico pode ser desafiante: cavidade endometrial vazia, saco gestacional não comunicante com o endométrio e localizado a mais de um centímetro da porção mais lateral deste, com uma fina camada miometrial circundante.[4]

Ao contrário das outras gravidezes tubárias, na GEI não existem protocolos para orientar a decisão terapêutica, a qual acaba por se basear em estudos retrospetivos, pequenas séries e muitas vezes na experiência individual. Deve ter-se em conta a idade gestacional, as apresentações clínica e ecográfica, o desejo de preservação de fertilidade, entre outros.[1,5]

O tratamento cirúrgico é considerado primeira linha quando há rotura, instabilidade hemodinâmica, dor persistente ou saco gestacional > 40 mm, através da ressecção cornual ou cornuostomia laparoscópicas. A laparotomia constituía a abordagem tradicional, com resseção cornual ou histerectomia, estando atualmente indicada em caso de instabilidade hemodinâmica ou experiência da equipa.[3,5] Num diagnóstico precoce, com estabilidade hemodinâmica e níveis baixos de β-hCG, é possível optar pelo tratamento com metotrexato.[5]

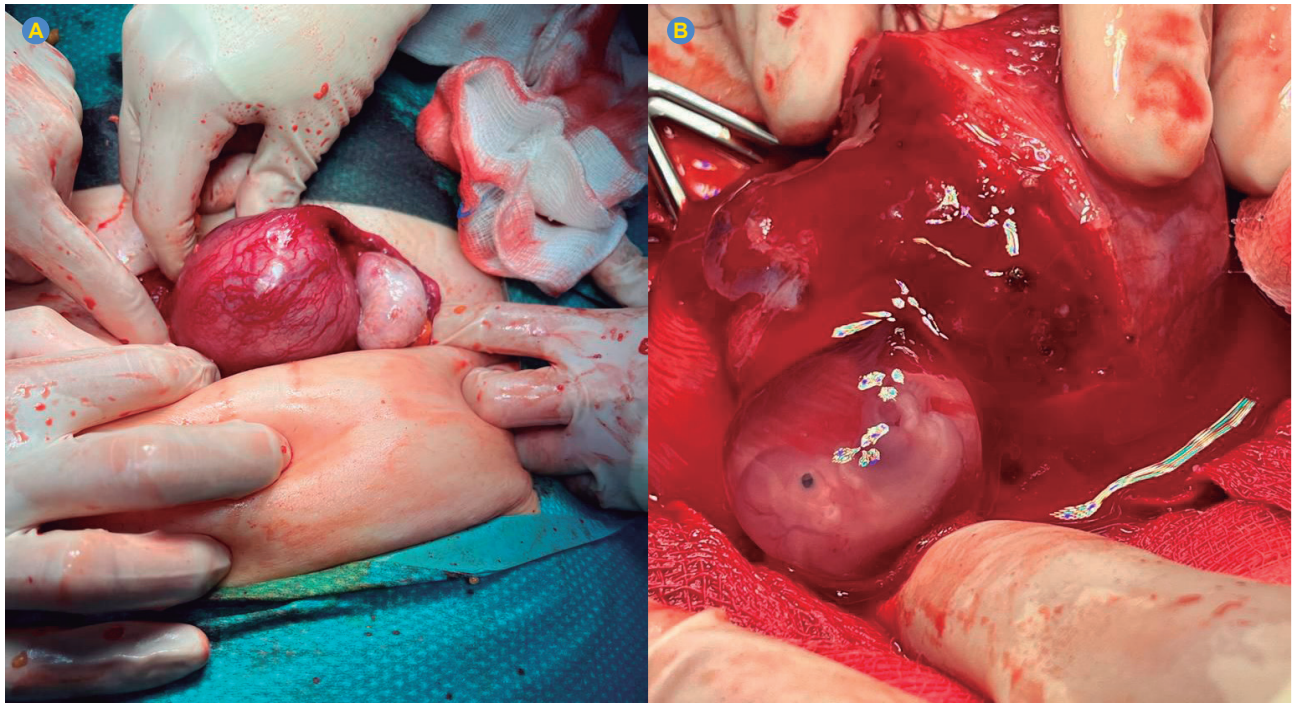

Figura 1 – Aspeto macroscópico de gravidez ectópica intersticial à direita (A), identificada pela seta preta; aparência cirúrgica do saco gestacional de gravidez ectópica intersticial durante resseção cornual laparotómica (B).

Em conclusão, a GEI é uma entidade rara cujo diagnóstico precoce é fundamental para o bom desfecho, sendo necessários mais estudos para orientar a decisão terapêutica.

CONTRIBUTO DOS AUTORES

IJ: Conceção e desenho do estudo, recolha de dados, redação do manuscrito.

HG: Conceção do estudo, revisão do manuscrito.

NA: Recolha de dados, revisão do manuscrito.

Todas as autoras aprovaram a versão final a ser publicada.

PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em outubro de 2024.

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 interesse relacionados com o presente trabalho.

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Paediatric Meningioangiomatosis PD-L1+: A Case Report

Meningioangiomatose Pediátrica PD-L1+: Um Caso Clínico

Keywords: Angiomatosis; Child; Immune Checkpoint Inhibitors; Meningioma
Palavras-chave: Angiomatose; Criança; Inibidores de Checkpoint Imunológico; Meningioma

Dear Editor,

It is now well established in the literature that immune checkpoints (including in particular PD-1, PD-L1 and CTLA4) play an important role in the 'molecular communication' between cells/tissues and the surrounding immune microenvironment, modulating the continuous function of self/non-self-recognition. This awareness has led to the increasingly widespread use of immune checkpoint inhibitors in oncology, with the aim of preventing the immunoescape of neoplastic cells and enabling the immune system's effector cells to recognize and fight them. However, the status of immune checkpoints in non-neoplastic and/or pre-neoplastic disease is still poorly explored: the case we present belongs to this context.

We present the case of a 6-year-old girl who was born at term with no perinatal problems except for the presence of a slowly growing midline occipital swelling. The ultrasound examination showed a swelling in the middle occipital area measuring 13 x 18 mm, without any vascular signal. A subsequent brain magnetic resonance imaging (MRI) (Fig. 1A) showed and confirmed the presence of a midline occipital meningocele with a large craniolacunia (cranial bone or skull bone discontinuity). Also noted were the presence of normotensive hydrocephalus, subcortical fronto-parietal ischemic lesions, probably occurring during pregnancy, resulting in severe atrophy of the corpus callosum. Other associated malformations included: cyst of the septum pellucidum and microgyria in the parieto-occipital regions, vermian hypoplasia and secondary right convex thoracolumbar scoliosis with hemispondilus at C2-C3 left and somatic fusion at C4-C5. This was associated with the presence of a meningocele at the level of the external occipital protuberance. Surgical *en bloc* excision of the lesion with removal of the dystrophic skin allowed histological examination: microscopy showed angiomatoid and fibrous/fibroblastic areas with scattered meningothelial cells in clusters or surrounding vessels, without atypia or mitosis or a significant presence of lymphocytes/macrophages around the lesion, immunohistochemically epithelial membrane antigen+, progesterone+ and PD-L1+ (Fig. 1B), leading to the diagnosis of meningioangiomatosis (MAM), PD-L1 positive (the positivity rate, calculated as the number of PD-L1-positive pathological cells out of the total number of pathological cells, was 10%). The patient underwent surgical, clinical/epileptological and radiological follow-up, with nothing to report two years after surgery.

Meningioangiomatosis is a lesion with almost 200 histologically confirmed cases, typically affecting children and young adults, often presenting with seizures, headaches, neurological deficits or developmental defects including meningocele and/or encephalocele.[1,2] Neuroimaging (MRI) can show cortical lesions, but a definitive diagnosis usually requires biopsy. Previously, MAM was widely considered in the literature to be a non-neoplastic lesion (although sometimes associated with neurofibromatosis type 2, as in meningiomas), a view we considered reliable at the time. However, recent findings by Tauziède-Espariat *et al* challenge this view and show that MAM may represent a pre-neoplastic or neoplastic lesion. Their study revealed genetic alterations, including 22q homozygous deletions, and epigenetic profiles that closely align MAM with pediatric meningiomas,

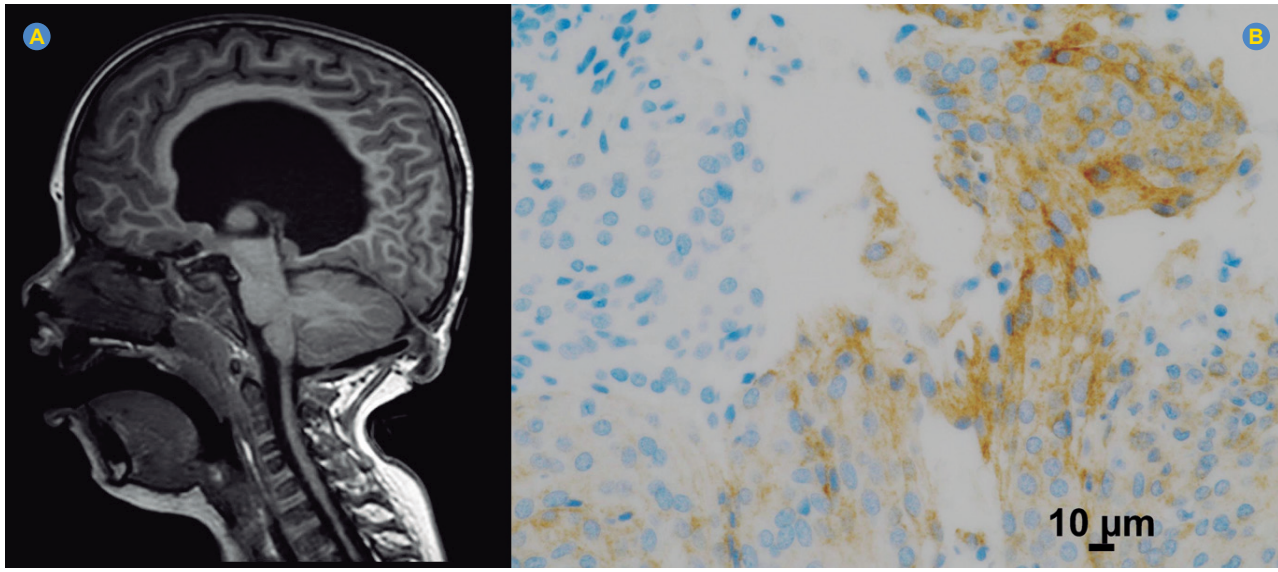

Figure 1 – Neuroimaging (MRI, sagittal plane, T1-weighted): defect of the occipital bone with herniation of mainly meningeal tissue (meningocele) with associated voluminous hydrocephalus (A). Microphotograph showing expression for PD-L1 in pathological cells (40x) (B).

suggesting a histomolecular continuum between these entities.[3]

To the best of our knowledge, this is the first described case of MAM/PD-L1+. Nevertheless, our observation of PD-L1 positivity could serve as an indirect confirmation of Tauziède-Espariat *et al*'s conclusions. Indeed, PD-L1 is an immune checkpoint associated with the immunoescape of many tumors, including meningiomas, which are targeted by specific therapies with anti-tumor effects,[4-6] thus supporting the hypothesis of a neoplastic potential in MAM. This raises important questions: does PD-L1 expression indicate that all MAM lesions have neoplastic potential, or does it identify a specific subset of MAM that may progress to a neoplastic state through mechanisms such as immune escape? These considerations highlight the need for further studies to delineate the molecular subgroups of MAM and to explore the role of PD-L1 as both a biomarker and a therapeutic target in such a disease, potentially broadening the ever-expanding landscape of lesions treatable with anti-immune checkpoints.

AUTHOR CONTRIBUTIONS

GG: Study design, data interpretation, literature search, writing of the manuscript.

SB: Data interpretation, literature search, writing of the manuscript.

AR: Data interpretation.

CM, MP: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

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COMPETING INTERESTS

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Chilblains as a Clue for the Diagnosis of Essential Thrombocythemia

Perniose como Pista para o Diagnóstico de Trombocitose Essencial

Keywords: Chilblains; Thrombocythemia, Essential/diagnosis
Palavras-chave: Pérnio; Trombocitose Essencial/diagnóstico

Dear Editor,

A 75-year-old man, Fitzpatrick's phototype II, with a past medical history relevant for atrial fibrillation, was referred to the Dermatology department due to actinic keratosis on his face. However, on dermatological examination, severe chilblain-like lesions on his fingers were also evident (Fig. 1). After detailed anamnesis, the patient mentioned these painful violaceous and ulcerated patches had lasted for two years, leading to nail dystrophy. In addition, these skin lesions worsened with cold weather. For this reason, the patient was previously examined at a private reumatology clinic with suspected perniosis and was treated with nifedipine, with no clinical improvement. The patient denied any other systemic signs or symptoms.

At this point, laboratory examination revealed a thrombocytosis of 772 000/mm^3, antinuclear antibodies (ANA) test of 1/160, negative extractable nuclear antigen antibodies (ENA) panel, negative cryoglobulins, negative rheumatoid factor, negative antiphospholipid antibodies and the serum protein electrophoresis did not yield any significant changes. Subsequently, the patient was referred to the Hematology department, where the diagnosis of essential thrombocythemia (ET) was established. The patient started treatment with hydroxyurea 500 mg every other day with a drop in platelets to 584 000/mm^3 and a slight improvement in skin lesions and pain.

Essential thrombocythemia is a myeloproliferative neoplasm defined by an increase in blood platelets and a predisposition to vascular events (both thrombotic and, less frequently, hemorrhagic).[1] Cutaneous lesions may be the first manifestation of ET[1,2] and generally include microcirculatory abnormalities such as erythromelalgia, (characterized by recurrent episodes of burning pain and erythema in the distal extremities, which is exacerbated by heat and exercise), acrocyanosis, hematoma, ecchymosis, petechiae, purpura, superficial thrombophlebitis, Raynaud's phenomenon, livedo reticularis, ulceration, and ischemic gangrene.[1] Recognizing dermatologic manifestations of ET may be a clue to its early diagnosis.

Chilblains are a prevalent dermatological condition that typically manifests during the winter months because of an abnormal immune response from exposure to cold temperatures. These lesions typically manifest as painful, edematous, erythematous or violaceous papules and plaques with associated pruritus, burning or pain. In addition, erosions, ulcerations, or blisters may be superimposed. The diagnosis can be established clinically.[3] Primary chilblains are uncommon in the elderly population and a systemic underlying cause should be investigated, particularly in severe cases,

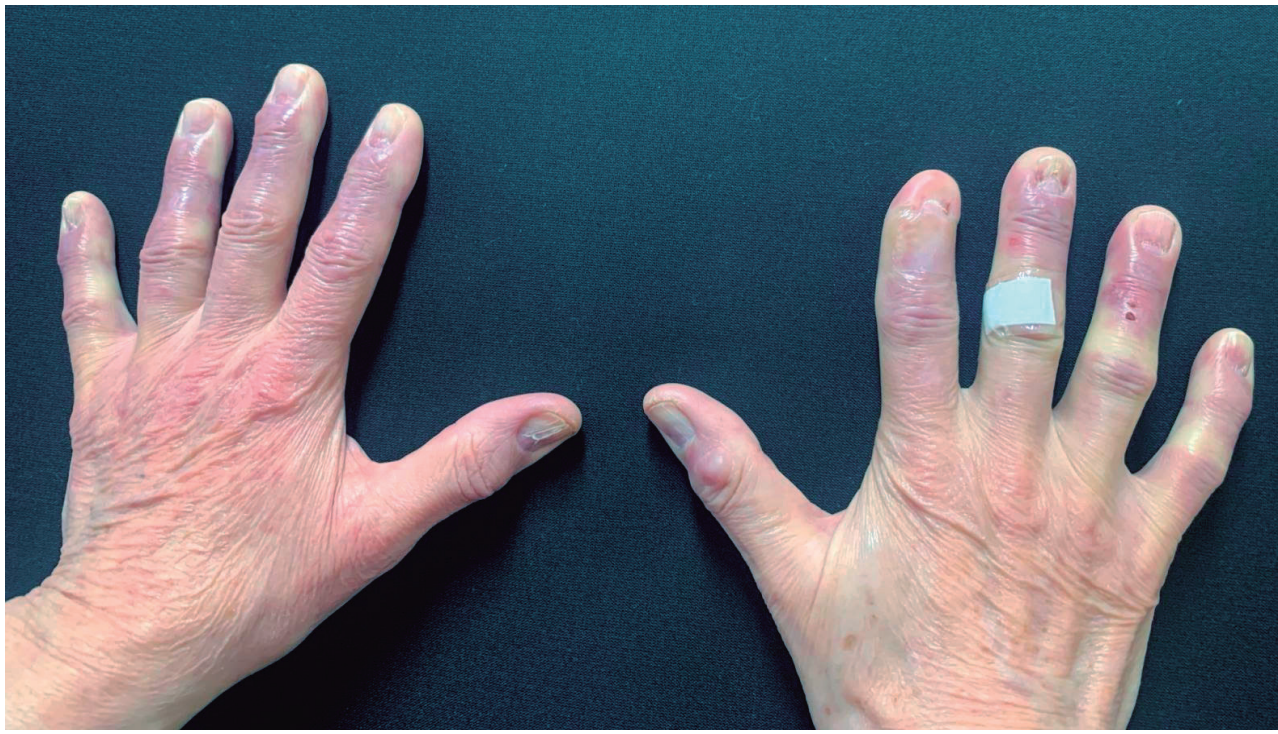

Figure 1 – Erythematous-to-violaceous plaques with ill-defined borders on the distal dorsal aspect of the fingers, accompanied by erosions and nail dystrophy, including dorsal pterygium, anonychia (absence of the nail plate), and onychorrhexis (longitudinal ridging and fragility of the nail plate).

or in those occurring outside of the typical seasonal period, or which are refractory to conventional therapy.[4]

Our clinical case highlights the importance of physical examination in modern medicine, not only in the cutaneous manifestation of systemic diseases but also in the identification of signs and symptoms that were not the initial reason for the appointment.

AUTHOR CONTRIBUTIONS

HL: Data collection, literature search, writing of the manuscript.

JR: Critical review of the manuscript.

AR: Data collection, critical review of the manuscript.

All authors approved the final version to be published.

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PATIENT CONSENT

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COMPETING INTERESTS

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Hiperferritinemia Hereditária: Um Desafio Diagnóstico

Hereditary Hyperferritinemia: A Diagnostic Challenge

Palavras-chave: Catarata/genética; Criança; Distúrbios do Metabolismo do Ferro/congénito; Hiperferritinemia/diagnóstico
Keywords: Hematology; Hospitals, Tertiary; Referral and Consultation; Portugal; Primary Health Care

A ferritina, proteína envolvida no armazenamento intracelular de ferro, é constituída por cadeias leves (L-ferritina) e pesadas (H-ferritina), codificadas por genes distintos. A hiperferritinemia é um achado comum na prática clínica. Na maioria dos casos não está associada a sobrecarga de ferro, sendo as principais causas a inflamação, etilismo, destruição celular e síndrome metabólica.[1] A investigação etiológica deve abranger: anamnese, antecedentes, análises com hemograma, reticulócitos, cinética de ferro, perfil lipídico e hepático, glicose, marcadores inflamatórios, e eventualmente haptoglobina, desidrogenase láctica (DHL), serologias víricas e ecografia abdominal. Na suspeita de sobrecarga de ferro, ponderar estudo genético do HFE e ressonância magnética (RM) hepática e cardíaca. Se persistirem dúvidas, considerar testes genéticos para causas raras de hiperferritinemia (Fig. 1).[1,2]

Descrevemos o caso de uma criança de três anos, referenciada à Hematologia por hiperferritinemia persistente (1000 – 2000 ng/mL). O restante estudo analítico – incluindo hemograma, cinética de ferro, parâmetros hepáticos, DHL e proteína C reativa – encontrava-se normal. Revendo os antecedentes familiares, averiguou-se que o pai, de 40 anos, tinha antecedentes de cirurgia às cataratas em idade jovem, histórico de hiperferritinemia (> 3000 ng/mL) e saturação de transferrina (ST) aumentada (50%). A avaliação laboratorial do pai revelou: ferritina 2756 ng/mL, ST 18% (VR: 20 - 50), hemograma e bioquímica sem alterações. A RM excluiu sobrecarga de ferro hepática ou cardíaca. A pesquisa de mutações da hemocromatose hereditária, doença da ferroportina e hepcidina foi negativa. O estudo genético, por sequenciação em larga escala, confirmou a presença da mutação *c.-168G>C* em heterozigotia, associada a síndrome hereditária de hiperferritinemia-cataratas (SHHC). Solicitou-se o estudo genético da criança, que revelou a mesma mutação. Referenciou-se a doente à Oftalmologia Pediátrica, para avaliação da acuidade visual e seguimento. Manteve-se acompanhamento na Hematologia e convocaram-se os irmãos para estudo.

A SHHC é uma causa genética rara de hiperferritinemia (~1/200 000),[3] de transmissão autossómica dominante. A mutação do gene *FTL* (L-ferritina) compromete a ligação das proteínas reguladoras do ferro, levando à síntese desregulada de L-ferritina sem elevação da ST ou sobrecarga de ferro. Manifesta-se por cataratas bilaterais precoces, por precipitação das cadeias L-ferritina no cristalino. Apresenta bom prognóstico, dado que a L-ferritina não se acumula noutros órgãos, não requerendo tratamento de espoliação de ferro. É recomendado o seguimento por Oftalmologia e intervenção cirúrgica se défice visual significativo.[3,4] Em 2017, foi descrito o primeiro caso numa família portuguesa.[5]

As autoras pretendem alertar para a importância da investigação etiológica adequada da hiperferritinemia para evitar terapêuticas ou exames invasivos desnecessários, com riscos para o doente.

CONTRIBUTO DOS AUTORES

MG: Colheita e interpretação de dados, conceção e redação do manuscrito.

FF: Colheita e interpretação de dados, conceção e revisão crítica do manuscrito.

Ambas as autoras aprovaram a versão final a ser publicada.

CONFIDENCIALIDADE DOS DADOS

As autoras declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

As autoras declaram não ter conflitos de interesse relacionados com o presente trabalho.

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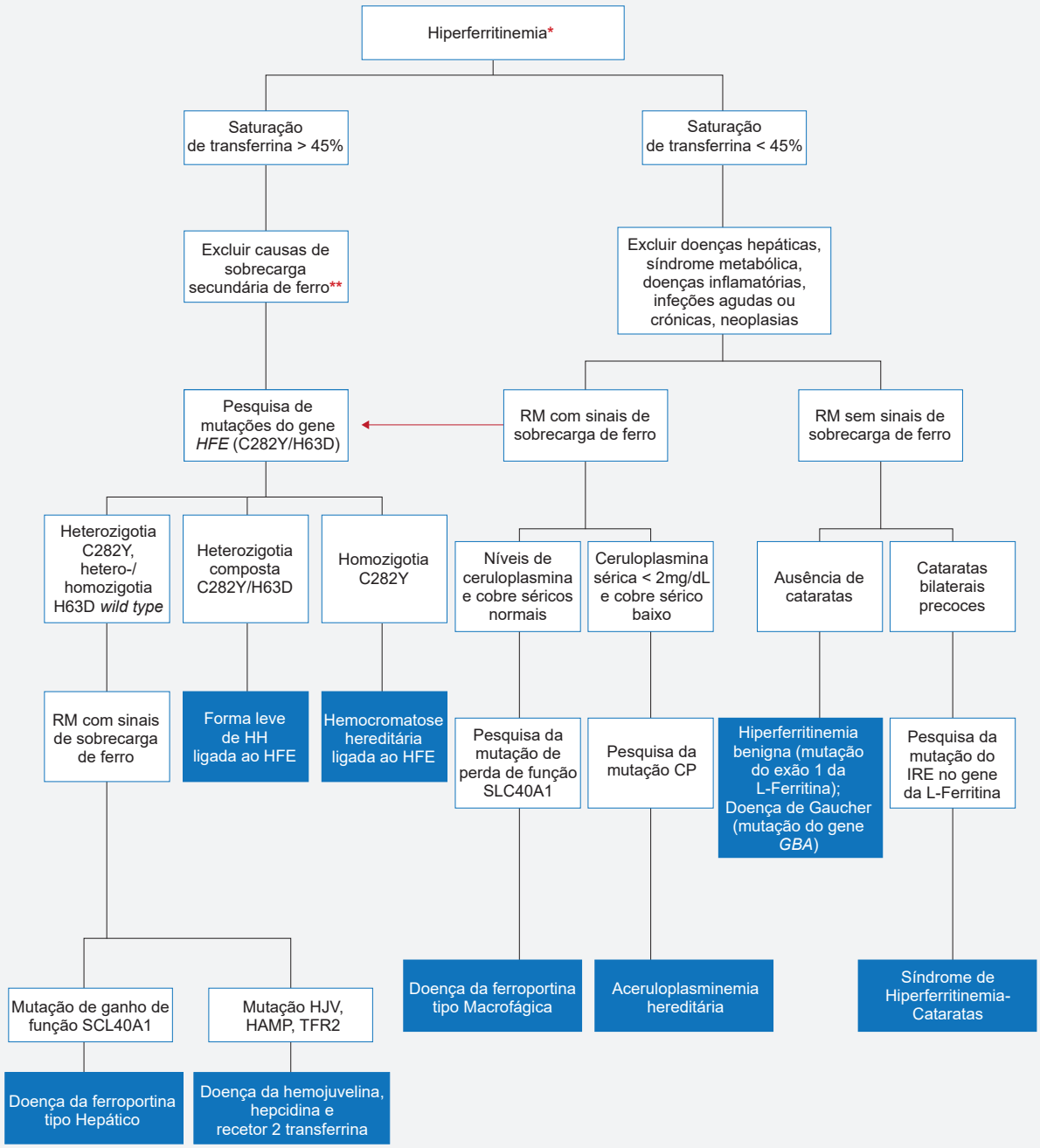

Figura 1 – Diagnóstico diferencial de hiperferritinemia

*: ferritina > 200 ng/mL nas mulheres e > 300 ng/mL nos homens (valores de referência dependem do laboratório);

**: suplementação com ferro, transfusões, porfiria cutânea tarda, doenças hematológicas e eritropoiese ineficaz (talassemia, síndrome mielodisplásica, anemia sideroblástica, etc.)

RM: ressonância magnética; IRE: elemento de resposta ao ferro; HH: hemocromatose hereditária

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Addressing Burnout and Enhancing Efficiency with Digital Health

Abordar o Burnout e Melhorar a Eficiência com Saúde Digital

Keywords: Artificial Intelligence; Burnout, Professional; Digital Health; Health Personnel; Portugal
Palavras-chave: Esgotamento Profissional; Inteligência Artificial; Pessoal de Saúde; Portugal; Saúde Digital

Dear Editor,

We are writing to discuss our concerns about the burnout of healthcare workers in Portugal and how digital health solutions can address this challenge. Limited resources, workforce shortages, and uneven workload distribution are significant contributors to this increasing problem. These issues are compounded by rigid hierarchical structures and inadequate communication, which hamper the work environment and decrease job satisfaction.[1]

Digital health solutions, such as artificial intelligence (AI)-powered automation, offer transformative potential to address these issues. Automation of routine administrative tasks like scheduling, prescribing, and data entry can reduce the burden on healthcare workers, allowing them to focus more on patient care.[2] Additionally, AI-driven chatbots and virtual assistants can provide round-the-clock support for patient queries, appointment scheduling, and medication reminders, further reducing the frontline staff workload. Wearable health monitoring devices also enable real-time tracking of patient metrics, facilitating early interventions and minimizing unnecessary hospital visits.

To ensure these tools are effective, input from healthcare professionals and patients, who understand the real-world challenges of clinical environments, must be included in their design. Integrating human judgment with AI systems guarantees proper application, minimizes risks of over-reliance, and fosters efficient decision-making. Moreover, explicable AI can empower patients by enhancing health literacy and promoting shared decision-making, transitioning from paternalistic care models to more collaborative approaches.[3]

In conclusion, leveraging digital health innovations is essential to address burnout and improve efficiency within Portugal's healthcare system. These solutions, combined with a commitment to participatory design and ethical governance, have the potential to create a more resilient and supportive work environment for healthcare professionals.

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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