Are we PREPAREd? Concerning the "PREemptive Pharmacogenomics Testing for Preventing Adverse Drug Reactions (PREPARE) Study"

Estamos PREPARados? A Propósito do Estudo "Concerning the "PREemptive Pharmacogenomics Testing for Preventing Adverse Drug Reactions (PREPARE)"

Keywords: Drug-Related Side Effects and Adverse Reactions; Pharmacogenomic Testing; Genomic Medicine
Palavras-chave: Eficácia Medicamentosa; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos; Medicina Genômica; Testes Farmacogenómicos

Dear Editor,

As a multidisciplinary research team in Personalized Medicine, we read the paper recently published in Lancet by Swen JJ *et al*[1] with special interest.

Pharmacogenomics (PGx) significantly contributes to optimizing drug prescribing, improving patients' clinical outcomes, and mitigating adverse drug reactions (ADR).[1,2] Moreover, the efficacy rates of different drugs can vary widely, ranging from 25% to 80%.[2] ADRs account for about 6% of adult hospital admissions, and are one of the top ten leading causes of death and illness in developed countries, with a 10% increase in healthcare expenditures.[3,4] Currently, approximately 50% of commonly prescribed drugs already have an identified PGx profile, which is valuable for preemptive genotyping and brings clinical benefit to patients.[3]

The aforementioned article describes an open-label, multicenter, controlled, cluster-randomized, crossover implementation study of a 12-gene pharmacogenetic panel, considering 39 drugs. The study was conducted in 18 hospitals**,** nine community health centers, and 28 community pharmacies in seven European countries. It outlines the advantages of a PGx panel strategy combined with the guidelines developed by the Dutch Pharmacogenetics Working Group. Participants (6944) were randomly assigned either to genotype-guided doses [3342 (51.9%)] or standard care [3602 (48.1%)]. The authors reported a 30% reduction in clinically relevant ADR incidence, using a preemptive PGx panel.[1] This study provides further evidence to support a personalized medicine approach, with the added value of testing a panel of preemptive PGx in a multitude of healthcare institutions. It unveils certain limitations like potential bias in ADR reporting from an awareness effect and enhanced treatment monitoring. Furthermore, in real-life scenarios, polymedicated patients with comorbidities exhibit increased variability in drug response.

The European 1+Million Genomes Initiative and the Portuguese Strategy for Genomic Medicine (PT_MedGen) reflect the global interest in the implementation of genomic medicine in healthcare systems, promoting personalized approaches in rare diseases, oncology, and PGx. The United Kingdom, the Netherlands, and other countries are increasingly integrating PGx into their healthcare systems, allowing patients to receive personalized prescriptions. This new reality can improve treatment efficacy and patient safety, empower healthcare professionals in personalized care, and reduce costs for healthcare systems. The wider implementation is also crucial for real-world studies that consider the unique national frameworks and healthcare systems, by providing support with evidence-effective implementation plans. In Portugal, PGx is maturing and gaining momentum with the launch of the PT_MedGen strategy for genomic medicine.[5] Therefore, now is the time to prepare our clinical practice for PGx integration.

AUTHOR CONTRIBUTIONS

ACC: Conceptualization, literature review, and manuscript redaction.

MLC: Literature review and manuscript revision.

AV: Manuscript revision.

PROTECTION OF HUMANS AND ANIMALS

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Ana de CARMO CAMPOS[1,2], Maria Luís CARDOSO[2,3], Astrid VICENTE[2,3]
1. Serviço de Medicina III. Hospital Pulido Valente. Centro Hospitalar Universitário de Lisboa Norte. Lisboa. Portugal.
2. Departamento de Promoção da Saúde e Prevenção de Doenças Não Transmissíveis. Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA). Lisboa. Portugal.
3. BioISI, Instituto de Biossistemas e Ciências Integrativas. Faculdade de Ciências da Universidade de Lisboa. Lisboa. Portugal.
✉ **Autor correspondente:** Ana de Carmo Campos. decarmo.c@gmail.com
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Hyperventilation Syndrome Following an Asymptomatic COVID-19 Infection

Síndrome de Hiperventilação Após uma Infeção COVID-19 Assintomática

Keywords: COVID-19; Hyperventilation
Palavras-chave: COVID-19; Hiperventilação

Hyperventilation syndrome (HVS) is characterized by a variety of symptoms induced by inappropriate breathing patterns, namely excessive ventilation.[1,2]

A 33-year-old woman with no comorbidities, occasional smoker, was evaluated at our clinic due to a six-month history of dyspnea (mMRC 3), chest tightness, and severe fatigue that started after the self-isolation period following an asymptomatic coronavirus disease 2019 (COVID-19) infection in January 2021. She also described episodes of anxiety, palpitations, lower limb paresthesia and blurred vision. On physical examination, the patient was tachypneic at rest (RR 32 - 36 bpm). She scored 35/64 in the Nijmegen questionnaire (a score above 23/64 is suggestive of hyperventilation syndrome).

The arterial blood gas analysis at rest revealed respiratory alkalosis (pH 7.506, pCO_2 23.6 mmHg; normal pH: 7.35 - 7.45, pCO_2: 35 - 45 mmHg). On the six-minute walk test (6MWT), she experienced severe dyspnea [end BORG dyspnea level (0 - 10): 10], chest tightness and lower limb paresthesias; the test was ceased at 3 minutes 27 seconds, after 168 meters, with no significant oxygen desaturation and normal cardiac response. Complete blood work – including autoimmunity testing, thyroid and kidney function, serum electrolytes, cardiac biomarkers, and HCG test – was normal. Pulmonary function tests and a chest radiograph revealed no significant changes. A thoracic computed tomography (CT) scan angiography excluded the presence of a pulmonary thromboembolism, and a ventilation/perfusion scan showed no significant mismatch. The patient performed an electrocardiogram which was unremarkable. A transthoracic echocardiogram was considered normal (LVEF 71%; PSAP 27 mmHg), as well as the myocardial perfusion scintigraphy and the cardiac magnetic resonance imaging (MRI). The patient also performed a cardiopulmonary exercise test, which revealed an exercise limitation (maximum VO2 7.1 mL/kg/min, 31% predicted), with an adequate gas exchange and cardiovascular response.

A diagnosis of post-COVID-19 HVS was suspected. The patient entered a pulmonary rehabilitation program, with aerobic exercises, respiratory muscle training, and psychological reconditioning. She experienced an improvement in her quality of life [initial EuroQoL (EQ)-5D 11/15; final EQ-5D: 7/15] and a satisfactory response on the last 6MWT performed – 462 m of distance walked (77% predicted). A re-evaluation arterial blood gas analysis performed at rest revealed a mild hypocapnia (pCO_2 33.2 mmHg; normal pCO_2: 35 - 45 mmHg). Due to the favorable response to the rehabilitation program, a referral to psychiatry assessment was not considered.

The combination of the Nijmegen score and Cardiopulmonary exercise is used to establish a diagnosis of HVS.[1] Following a COVID-19 infection, ruling out thrombotic lung disease and myocarditis is important.[3] Regarding pathophysiology, hypocapnia and anxiety seem to play an important role in the development of symptoms.[4] In patients with post-COVID-19 HVS, it has been suggested that inflammatory and/or microangiopathic changes in the pre-Bötzinger complex, a part of the ventral respiratory group of interneurons responsible for the control of breathing and the response to hypoxia, may lead to the dysregulation of the ventilatory drive. Respiratory rehabilitation is usually recommended for symptom management.

This is, to the best of our knowledge, the first report of a case of post-COVID-19 HVS in Portugal. As this is a rare disorder, clinical awareness is required to identify this often-missed manifestation of post-COVID-19.

AUTHOR CONTRIBUTIONS

IC: Writing of the manuscript.
AC, CR: Critical review of the manuscript.
FC: Conception and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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