The First Documented Case of Hb South Florida Variant in Portugal

O Primeiro Caso da Variante Hb South Florida em Portugal

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ABSTRACT

We present a 39-year-old male, previous smoker, with no other known cardiovascular risk factors. He was referred to Internal Medicine for study of thrombophilia, because of repeated deep vein thrombosis. Multiple diagnostic tests were undertaken where HbA1c assay was included. The result was 14.6%. The patient did not have a prior diagnosis of diabetes and denied any symptoms. Fasting blood glucose and blood count did not reveal any changes. A further analysis of hemoglobin subtypes showed the presence of an unclassified variant. The sample was sent to a Portuguese reference center and, through molecular biology, an *HBB* mutation in heterozygosity was identified, coding for an hemoglobin variant - Hb South Florida (c.4G > A; p.Val2Met), which was for the first time documented in Portugal. We emphasize the importance of considering the presence of hemoglobin variants when HbA1C values are discrepant from the clinical presentation.

Keywords: Diabetes Mellitus; Glycated Hemoglobin A; Hemoglobins, Abnormal

RESUMO

Apresenta-se o caso de um homem de 39 anos, ex-fumador, sem outros fatores de risco conhecidos. Foi encaminhado à consulta de Medicina Interna para estudo de trombofilia por tromboses venosas profundas de repetição. Foi realizado estudo etiológico, onde o doseamento da HbA1c foi incluído. O resultado foi de 14,6%. O doente não apresentava diagnóstico prévio de diabetes *mellitus* e negava sintomas compatíveis. A glicemia em jejum e o hemograma não revelaram alterações. O estudo por eletroforese das hemoglobinas revelou uma variante não classificada. Num centro de referência português foi identificada, por biologia molecular, uma mutação em heterozigotia no gene *HBB* associada a uma variante de hemoglobina - Hb South Florida (c.4G > A; p.Val2Met), sendo a primeira vez que é documentada em Portugal. Salienta-se a importância de, na presença de valores de HbA1C discrepantes da apresentação clínica, considerar a presença de variantes de hemoglobina.

Palavras-chave: Diabetes Mellitus; Hemoglobina A Glicada; Hemoglobinas Anormais

INTRODUCTION

South Florida hemoglobin (Hb) is a rare variant of Hb that causes, depending on the methodology used, an erroneous elevation of glycosylated hemoglobin (HbA1c). Since its first description in 1986,[1] six cases have been reported in the world literature. This article shows a review of the seventh case in the world, and the first in Portugal.

CASE REPORT

A 39-year-old male with repeated deep vein thrombosis was referred to an internal medicine clinic for the investigation of possible thrombophilia. He had a great left saphenous vein thrombosis, a few years ago, for which a surgery was performed. Six months later he had a new event, with thrombosis of the left popliteal vein. In this context, treatment with rivaroxaban was started.

He had obesity, treated with bariatric surgery over 10 years ago and since then, had a normal weight; he also had a history of prior smoking habits. No other cardiovascular risk factors were known, as well as any related family conditions.

Diagnostic tests were requested including the HbA1c assay. The result was 14.6% (provided by the ion-exchange high performance liquid chromatography – HPLC), although the patient had no previous symptoms suggestive of diabetes such as hyperglycemia, weight loss, polydipsia, polyuria or tiredness (normal range of HbA1C is 3.4% - 5.8% by HPLC). He denied taking medicines other than rivaroxaban. He had no known condition that increased the life of red blood cells, such as anemia due to iron deficiency, asplenia or high levels of urea. He reported no recent episodes of bleeding or blood transfusions. Fasting blood glucose and a simple blood count were normal. His creatinine level was 1.0 mg/dL, and no uremia was noted. The remaining blood tests showed: an Hb of 13.9 g/dL, a hematocrit of 41.4 %, a slight microcytosis (MCV 78.9 fL, normal range 80 - 96 fL) with hypochromia (MCH 26.5 pg, normal range 28 - 34 pg); bilirubin and lactate dehydrogenase levels were normal.

A detailed study of hemoglobin subtypes by Hb electrophoresis was performed. The patient' results revealed: Hb A2 = 2.5%, F = 0.1%, A1c = 3.4%, and the presence of a variant not classified by the methodology (93%). The blood sample was sent to a Portuguese reference center for the study of hemoglobinopathies and it was possible, through molecular biology and DNA screening, to identify that the patient was heterozygous with a beta chain Hb variant. He was found to have the South Florida variant (c.4G > A; p.Val2Met), which for the first time was described in Portugal. His family members have not been screened for

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this type of mutation.

As for the thrombophilia study, only a heterozygous mutation for the *MTHFR* gene (mutation C677T) was detected. He had no recurrence of thrombotic episodes while maintaining anticoagulant therapy.

DISCUSSION

Hb South Florida is a recently identified clinically silent hemoglobin variant that migrates with hemoglobin A, on ion exchange chromatography.[3] In the Hb South Florida, the Hb structure seems to function normally. This variant is characterized by the replacement of a neutral amino acid for a charged one, with valine substituted by methionine.[2] The only evidence for the presence of Hb South Florida was the finding of amounts of glycosylated hemoglobin in non-diabetic samples.[3] Normally, the healthy adult hemoglobin consists of approximately 97% HbA, 2.5% HbA2 and 0.5% HbF,[2] with other variants not specified if having no pathological significance. Aberrant HbA1c readings secondary to Hb variants seem to be an uncommon occurrence, and the exact incidence is unknown.[4]

Therefore, the frequency of this hemoglobin variant is unknown and rare. More than 1500 individual families have been evaluated and do not have hemoglobin South Florida.[3] There are only six cases reported in the literature, and, to our knowledge, no case has been reported in Portugal until now.

Certain conditions are known to misleadingly lower HbA1C, such as: bleeding, hemolytic disease, haemoglobinopathies and myelodysplastic disease; while others can give falsely high HbA1C levels such as: chronic anemia, renal failure and uremia (that can have high concentrations of carbamylated hemoglobin, resulting in aberrantly high HbA1C).[5]

Due to the high importance of HbA1c monitoring, more than 300 analytical methods have been developed for its analysis, such as immunoassay, high pressure liquid chromatography, spectrophotometry, ion-exchange and affinity chromatography, electrophoresis, boronate affinity chromatography, colorimetric methods, and mass spectroscopy. Ion-exchange chromatography is the method commonly used to measure the total rapidly migrating fraction of hemoglobin A, but only the molecular biology method is able to identify this hemoglobin variant.

Hb South Florida has been described six times in the literature, but there are other clinically silent Hb variants that can present with falsely elevated HbA1C values. Some are Hb Santa Juana (Beta 108 Asn → Ser), also known as Hb Serres, that has been widely reported in Greek and Mexican populations; Hb Takamatsu (Beta 120 Lys → Gln); Hb G-Szuhu (Beta 80 Asn → Lys) and Hb Camperdown (Beta 104 Arg → Ser).[6, 7]

However, these variants do not correlate with any symptoms or clinical disorder; as such, our patient's thrombotic events could not be attributed to this genetic finding.

The HbA1c test remains an essential tool in monitoring glucose control in patients with diabetes mellitus, and it has been widely recommended as a diagnostic test for diabetes.

It is important for clinicians to interpret the results of HbA1C on a clinical context and be aware of discrepancies. When there are inconsistencies between a patient's blood glucose monitoring and laboratory measured HbA1c, a falsely elevated or lowered HbA1c result should be suspected. It is also important to know that there are many other Hb variants in the population, some of which are clinically silent but can interfere with routine laboratory tests. Such subtle changes in the amino acid sequence, may explain, in part, the great variation of human response to the same environmental agents.[3]

These aspects should lead to further investigation for abnormal Hb variants, in order to prevent the misdiagnosis and inadvertent treatment of diabetes.

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AUTHORS CONTRIBUTION

MBM: Concept and design of the paper, draft of the manuscript, approval of the final version

LD, VG: Concept and design of the paper, draft of the manuscript.

CR: Critical review.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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