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Hemoglobin J-Chicago: about a discordant glycosylated hemoglobin

Hemoglobina J-Chicago: a propósito de una glicada discordante

Glycated hemoglobin (HbA1c) is the most widely used clinical test to estimate mean blood glucose levels and is used for both diagnosis and monitoring of diabetes treatment. When HbA1c values are unexpected or discordant with other information (especially glucose measurements), other factors such as anemia, kidney disease, or hemoglobinopathies should be considered.[1]

Hemoglobin (Hb) abnormalities are called hemoglobinopathies. The Hb molecule is a tetramer formed by 2 pairs of globin chains along with a heme group attached to each chain. Depending on the combination of globin types, different hemoglobins are synthesized, such as fetal hemoglobin (HbF), HbA, and HbA2. HbF is composed of 2 gamma (γ) chains and 2 alpha (α) chains, and transitions from being the major hemoglobin during gestation to representing less than 2%–3% at 6 months of age. HbA (formed by 2 α chains and 2 β chains), on the other hand, becomes the major hemoglobin after the 6th month of age. HbA2, formed by 2 α chains and 2 delta (δ) chains, is synthesized in small amounts from birth, maintaining a stable minor concentration after the 6th month.

Currently, more than 1200 structural variants of Hb have been described, mainly due to amino acid changes. One diagnostic method to assess the presence of Hb variants is capillary electrophoresis. This method allows for the detection of major Hb variants, as well as quantification of HbA2 and HbF.

Hb J is a rare variant of Hb and usually does not cause any disorders. It is characterized by a substitution of a glycine residue at position 16 of the β chain by an aspartic acid residue.[2] Currently, over 50 variants of Hb J have been documented; examples include Hb J-Ciudad del Cabo, Hb J-Buda, Hb J-Chicago, Hb J-Sardegna, Hb J-Toronto, Hb J-Camagüey, and Hb J-Singapore, among others. They are all characterized as ẗast-migrating hemoglobins,m̈eaning they have a faster electrophoretic mobility than HbA.[3]

We present the case of a 51-year-old Spanish white female patient with a history of grade 2 obesity, fibromyalgia, and microprolactinoma treated with low-dose dopamine agonists, monitored in endocrinology clinics for the past 9 years. During this follow-up, HbA1c was requested in 2022, resulting in 3.8% with baseline glucose levels of 97 mg/dL. The methodology used was ion-exchange chromatography in reverse phase with a dual-wavelength colorimetric method. Given these results, previous accumulations were performed, observing previous values between 3.9% and 4.1% since 2018. The patient reported nonspecific symptoms of vertigo syndrome, dysthymia, a strong craving for sweets, and occasional hypoglycemic sensations. For this reason, a capillary glucometer was provided, with no glucose levels <75 mg/dL obtained at any time. A comprehensive analytical assessment was performed in June of 2023, with the following notable results: Hb, 13.1 g/dL; glucose, 84 mg/dL; creatinine, 0.75 mg/dL; insulin, 10.2 μIU/mL (normal: 2.6–24.9); C-peptide, 2.7 ng/mL (normal: 1.10–4.40); HbA1c, 3.9%.

Given these discordant results, a hemoglobinopathy study was initiated. No signs of anemia or thalassemia were observed. Hb analysis in blood was performed by capillary electrophoresis, with the following results:

- Hb A 47.8% (N 96.8%–97.8%)
- HbF <0.5% (N up to 1%)
- Hb A2 1.8% (N 2.0%–3.5%)
- Other hemoglobins: presence of an anomalous fast-migrating Hb not identifiable (50.4%) (N absence)

An analysis of identification of anomalous hemoglobins by sequencing was performed, which revealed the presence in heterozygosis of a variant in the HBB gene [variant c.230C > A p.(Ala77Asp)] characterized by the synthesis of a hemoglobin J-Chicago. This gene is located on chromosome 11 of the human genome and encodes the beta globin polypeptide chain. Hemoglobin J-Chicago was first described in 1975 by Romain et al. in a 2-year-old black child from Chicago. This Hb variant shows no evidence of instability, alteration of oxygen affinity, or effect on hematological values.[4,5]

This hemoglobinopathy does not produce clinical consequences in patients, either in the homozygous or heterozygous state. Since hemolysis does not occur, disorders such as anemia, splenomegaly, or morphological abnormalities of erythrocytes are not produced. The average lifespan of red blood cells remains unchanged.[6] For this reason, in the event of anemia, it should not be tagged as a consequence of this hemoglobinopathy. Since most cases

of Hb J do not have clinical significance, they have been diagnosed by chance, as in our case.

Therefore, we can conclude that when there are discrepancies between HbA1c and calculated mean glucose, further exploration is required, as they may be suggestive of a disease or condition. If HbA1c is lower than expected, it is important to exclude reduced red cell survival, such as hemolysis or conditions where a disproportionate number of red blood cells are young, such as in erythropoietin treatment. A blood transfusion could also explain these results. On the other hand, although common hemoglobinopathies, such as sickle cell trait, do not interfere in most assays, it is important to consult with the laboratory to make sure that the assay used has not been affected. However, there are other hemoglobinopathies that can interfere with the result, such as in our case, Hb J, which invalidates the use of HbA1c in the patient.

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