Erroneous Diabetes Diagnosis: A Case of HbA1c Interference

A 66-year-old Caucasian female was referred for specialist follow-up of her treatment-refractory type 2 diabetes. The diagnosis was made based on two consecutive HbA1c results >6.5% (48 mmol/mol) in accordance with the Canadian Diabetes Association and the American Diabetes Association guidelines (1,2). Fasting glucose was normal and hyperglycemic symptoms were absent at diagnosis. The patient’s hematological indices were normal and she was unaware of any family history of hemoglobinopathy. Her glycemic control proved difficult to manage, with persistently elevated HbA1c (10.8–11.2% [95–99 mmol/mol]) despite treatment with metformin and, eventually, insulin glargine. Further, with treatment, the patient began to experience symptoms of episodic hypoglycemia.

A fasting glucose of 84.6 mg/dL (4.8 mmol/L) obtained at the same time as an HbA1c of 11.2% (99 mmol/mol) triggered suspicion of interference. As all of the HbA1c results were obtained by high-performance liquid chromatography (HPLC) (VARIANT II TURBO HbA1c Kit – 2.0; Bio-Rad), the analysis was repeated by immunoassay (DCA 2000+, Siemens Healthcare Diagnostics), which showed a normal result of 5.2% (33 mmol/mol).

The ordering physician was contacted and treatment withheld. The patient’s blood glucose remained within normal limits with cessation of hypoglycemic symptoms. Hemoglobinopathy investigation revealed the presence of the α-globin chain mutant hemoglobin (Hb) Wayne. Carriers of one affected α-globin gene (αα/αα Wayne) are clinically normal with unremarkable hematological indices (3). Hb Wayne was previously reported to interfere with Bio-Rad VARIANT II HPLC HbA1c measurements (4). Hb Wayne results from a frameshift mutation in the HBA2 gene (HBA2:c.420del) and exists as two isoforms, Hb Wayne I Asn and Hb Wayne II Asp. Each isoform comprises ~6–9% of total Hb and has different chromatographic properties on the VARIANT II TURBO HbA1c Kit – 2.0; Bio-Rad. Hb Wayne I coelutes with HbA1c, whereas Hb Wayne II coelutes with fetal Hb (Hbf). Because the immunoassay uses antibodies recognizing the structure of the β-N-terminal glycated amino acid, the measurement of HbA1c is more accurate.

Both HbA1c methodologies are certified by the NGSP as traceable to the Diabetes Control and Complications Trial (DCCT) as required by the recent “Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus” (5). All samples with Hbf >15%, HbA1c results <4% (20 mmol/mol) or >12% (108 mmol/mol) are verified by repeat testing and visual inspection of the chromatogram and evaluated for clinical concordance. However, HbA1c results from patients with Hb Wayne trait do not meet these criteria for further review.

Clinical practice guidelines recommend repeat testing by the same method to confirm a diagnosis of type 2 diabetes in asymptomatic patients. This approach led to diabetes misdiagnosis in this patient despite the availability of additional laboratory tests, such as fasting glucose. With this case, we aim to highlight that despite the usefulness of practice guidelines, their limitations must be recognized and sound clinical judgment should prevail. Like all laboratory tests, HbA1c measurement is subject to interferences, and results must be interpreted within the clinical context.

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