The Influence of Falsely Low HbA1c Levels in Diabetes Patients With Hereditary Hemorrhagic Telangiectasia: The Need for Alternative Diagnostic Approaches

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ABSTRACT

Introduction: Hereditary hemorrhagic telangiectasia (HHT) causes various age-related symptoms, including epistaxis, telangiectasia, and anemia. These symptoms often require a variety of treatments, including iron supplementation and blood transfusions. The resulting anemia can lead to atypical presentations of comorbidities, such as diabetes.

Case Presentation: A 46-year-old Hispanic woman with a history of HHT presented for diabetes evaluation due to asymptomatic, elevated nonfasting blood glucose despite normal hemoglobin A1c (HbA1c) levels. Following initiation of continuous glucose monitoring and metformin (500 mg twice daily), her blood glucose levels improved significantly.

Discussion: Patients with HHT are more likely to develop iron deficiency anemia and anemia secondary to chronic blood loss, rendering HbA1c levels unreliable for diagnosing diabetes.

Conclusions: Clinicians should consider the impact of HHT-related anemia when monitoring patients for diabetes. Alternative diagnostic methods are necessary to prevent delays in diagnosis and treatment.

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) (Renu-Osler-Weber syndrome) is an autosomal dominant vascular disorder affecting approximately 1 in every 5000 individuals.[1,2] The disease is characterized by vascular malformations primarily involving the skin, mucous membranes of the nose and gastrointestinal (GI) tract, and visceral organs such as the brain, liver, and lungs.[2] The most common symptoms include epistaxis and telangiectasia, which both have an age-related presentation.[2] Due to delayed symptom presentation and the rarity of the disease, diagnostic delay of HHT is common, averaging nearly 3 decades after disease onset.[1]

A major complication of HHT is anemia, including iron deficiency anemia and anemia due to chronic blood loss.[1] While the total burden of anemia among patients with HHT is unknown, the condition typically worsens with delayed diagnosis.[1,3] Patients frequently require chronic oral and intravenous iron replacement therapy and, in severe cases, blood transfusions.[3] Both anemia and blood transfusions can significantly impact hemoglobin A1c (HbA1c) levels, making the presentation of diabetes atypical and difficult to diagnose.[4] This case report highlights a patient with HHT, chronic blood loss anemia, and a delayed diagnosis of diabetes, illustrating the importance of exploring alternative diagnostic methods in patients with unique clinical presentations, including HHT.

CASE PRESENTATION

A 46-year-old Hispanic woman with a personal and family history of HHT since childhood, transfusion-dependent anemia secondary to chronic blood loss, and seropositive systemic lupus erythematosus (SLE) presented with asymptomatic elevated nonfasting blood glucose levels. At initial presentation, she was taking ferrous sulfate (325 mg every other day) for anemia due to chronic blood loss and iron deficiency anemia diagnosed in childhood. She had also begun receiving iron infusions 4 to 5 years prior.

On initial visit, the patient's vital signs and comprehensive physical examination, including a foot exam, were unremark

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able. Laboratory tests revealed a slightly elevated HbA1c level of 6.0%, increased from 4.5% and 4.0% recorded 10 months and 12 months earlier, respectively. An anti-islet cell antibody test was negative, and the urine microalbumin level was elevated at 23.5 mg/L, leading to a diagnosis of suspected type 2 diabetes. She was prescribed continuous glucose monitoring (CGM) (Freestyle Libre 3 Sensor Plus) and started on metformin, 500 mg twice daily. The CGM was recommended due to the inaccuracy of previous HbA1c readings. The patient was instructed to collect at least 2 weeks of glucose data for review at the next visit.

At the 1-month follow-up, the patient's blood glucose levels had improved significantly. Prior to metformin initiation, glucose levels ranged from 74 to 208 mg/dL; these stabilized to 142 to 151 mg/dL after 2 weeks of therapy. Continued dietary and activity modifications were advised, along with collecting 10 to 14 more days of CGM data and follow-up in 3 months.

DISCUSSION

Due to the angiodysplasia and arteriovenous malformations, anemia from iron deficiency and chronic blood loss is common in patients with HHT.[5] A 2018 study identified the prevalence of anemia among patients with HHT at 50%, with an average age at diagnosis of 38 years.[3] In contrast, the estimated global prevalence of anemia in 2010 was 32%.[3] Thus, it is crucial for physicians to continually monitor HHT patients for anemia and its confounding effect on other comorbidities.

Patients with HHT and anemia due to chronic blood loss may require both iron and blood transfusions. This can affect the formation and levels of HbA1c, resulting in missed diabetes diagnoses.[4,6] HbA1c is formed through the irreversible, nonenzymatic glycation of hemoglobin.[6] This process depends on the glucose concentrations present in red blood cells (RBCs), and levels are impacted by many factors, including the length of RBC lifespan.[6] In 2010, the American Diabetes Association (ADA) established an HbA1c level of 6.5% or higher as indicative of diabetes; since then, HbA1c has been heavily relied upon for diabetes diagnoses.[4]

Despite its widespread use, HbA1c is not an ideal disease indicator for all patients. Amenia has a significant impact on HbA1c levels due to its effect on RBC lifespan and treatment requiring frequent blood transfusions.[7] Any condition that shortens the lifespan of RBCs will result in a decreased HbA1c level, making this value ineffective for diabetes screening.[4] Furthermore, blood transfusions have been shown to lower HbA1c levels more significantly in patients with diabetes than in the general population.[8] Thus, it is crucial to recognize the impact that both HHT and chronic blood loss anemia have on patient HbA1c levels and utilize alternative methods for proper diabetes diagnosis and treatment.

In this case, once it was determined that the patient had undiagnosed diabetes of unspecified type, CGM was utilized. CGM is an increasingly reliable and efficacious alternative for diagnosing and monitoring diabetes.[9] These devices monitor interstitial glucose levels as frequently as every 5 minutes.[9] The frequency and accuracy of these values allow physicians to fine-tune treatment strategies more effectively than self-monitoring of blood glucose.[9] CGM is not typically a primary diagnostic tool due to the inconvenience of insertion and sometimes frequent calibration required.[10] Access to CGM is also limited by insurance coverage, which often requires a prior diagnosis of type 1 diabetes, a significant history of home glucose monitoring, or established insulin therapy.[11] However, when HbA1c is unreliable, CGM can provide the necessary data for proper diagnosis and management.[9] Beyond CGM, fructosamine assays may also be utilized to monitor glycemic control in these patients.[12]

Most people with type 2 diabetes experience diagnostic delays of 4 to 7 years following the onset of hyperglycemia.[13] A 2018 study found that of 18 356 adults studied with an elevated HbA1c level, 30.2% remained undiagnosed 1 year later.[13] This study also noted that individuals with lower initial HbA1c levels or prediabetes were more likely to remain undiagnosed.[13] While patients are frequently asymptomatic during this period, delays represent a lost opportunity to prevent complications.[13] Particularly when looking at delays in treating high blood pressure secondary to new type 2 diabetes diagnosis, it was found that even a 1-year delay can result in a significant increase in lifetime diabetes complications, including amputation, congestive heart failure, end-stage renal disease, ischemic heart disease, myocardial infarction, and stroke.[14]

CONCLUSIONS

It is crucial for physicians with patients with conditions that make HbA1c levels unreliable to monitor potential diabetes development using alternative methods. To prevent diagnostic delays and reduce long-term complications, clinicians should treat the individual clinical presentation rather than relying solely on standard diagnostic criteria.

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