Low Glycosylated Hemoglobin Despite Poor Control of Diabetes

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ABSTRACT

Glycosylated hemoglobin (HbA1c)is a commonly used test in day to day practice to evaluate for long term control of type 1 and type 2 diabetes mellitus. Most of the therapeutic decisions are guided by patients HbA1c levels. HbA1c is also a recommended tool for the diagnosis of diabetes mellitus1. The treating physician should be aware about any caveats associated with the interpretation of the test leading to falsely low or falsely high values.

We report a case of a 33 year old gentleman with type 1 diabetes for past 27 years and with persistently low HbA1c.

Introduction :

Hemoglobin A (HbA) is the major component of total hemoglobin in healthy adults. HbA in turn comprises of HbA0, HbA1aHbA1b,and HbA1c. In presence of hyperglycemia glyco-hemoglobin or HbA1cis formed due to non-enzymatic glycation of N-terminal valine on the β chain of hemoglobin. This process of glycation occurs over the lifespan of erythrocytes. The lifespan of erythrocytes is approximately 120 days. Hence, laboratory assessment of HbA1c is an invaluable tool to determine long term glycemic control. However, several factors such as genetic, hematological, comorbid conditions can falsely elevate or lower HbA1clevels[2]. In general, any factor that reduces erythropoeisis will falsely elevate HbA1c.On the contrary, factors leading to increased reticulocytosis will falsely lower HbA1c[2].According to most of the standard guidelines HbA1c of less than or equal to 7% is desirable for majority of patients[3]. However, HbA1c below 7% does not necessarily mean that patient's glycemic control is good. One needs to be aware about the fallacies in HbA1c assessment. We present a case of a patient with Type 1 Diabetes with unusually low HbA1c secondary to underlying hemoglobinopathy HbQ India.

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Case :

33 year old gentleman hailing from Sindhi community, resident of Nagpur came to our Clinic for his regular follow up visit in June 2015. He was asymptomatic on the day of his clinic visit. Apart from Type 1 Diabetes he had no other comorbid conditions.

He was detected with type 1 Diabetes at the age of 5 years in 1987 with a classical presentation of weight loss, hyperosmolar symptoms, high blood glucose levels and ketoacidosis. Following his initial

diagnosis, he was started on three injections of insulin per day including regular and long acting insulin. At the age of 9 years in 1991, patient developed an acute febrile illness associated with severe Anemia (hemoglobin : 6.9 gm/dl). Further work-up for anemia revealed G6PD deficiency and an abnormal band on hemoglobin electrophoresis ***(Figure 1).*** The febrile illness was treated with antibiotics, antipyretics and supportive care. His hemoglobin levels improved with oral iron supplementation. During follow up over past 20 years patient had persistently normal HbA1c levels ***(Table 1).*** On the contrary, his corresponding blood glucose levels were raised i.e. therem was a disparity between HbA1c levels and blood glucose levels.

In March 2014 his hemoglobin electrophoresis was repeated to reevaluate and identify abnormal band of hemoglobin. The characteristic pattern on hemoglobin electrophoresis was suggestive of Hemoglobin Q-India ***(Figure 2).*** During this visit his HbA1c was 5.5% estimated with ion exchange high pressure liquid chromatography (HPLC) ***(Figure 3).*** His hemogram was normal with hemoglobin level of 13.6 gm/dl, MCV value 91.5, normal platelet and whole blood cell count.

In view of hemoglobinopathy, this patient was advised to frequently monitor his blood glucose levels rather than rely only on glycosylated hemoglobin.

Discussion :

HbQ India is a rare variant involving chain of hemoglobin molecule. It is characterized by replacement of aspartic acid by histidine at codon 64. It was first described by Sukumaran in 1972 in association with thalassemia. In most patients it remains asymptomatic and sometimes may give rise to low mean corpuscular volume (MCV), mild anemia but clinically significant disease is rare[4,5]. However, presence of HbQ India may interfere with estimation of HbA1c and give rise to falsely low values.

Similarly, various other hemoglobin variants such HbS, HbC, HbD Punjab, HbE, HbF, thalassemia may also interfere with HbA1c estimation. Some of these variants may be asymptomatic in heterozygous carriers or manifest clinically with severe anemia and multisystemic involvement[6]. Apart from hemoglobin variants other factors may give rise to false HbA1c reports.

Genetic factors include increased permeability of erythrocyte membrane to glucose in predisposed individuals; lifespan of erythrocytes can differ amongst individuals in absence of any hematological abnormalities[2].

Hematological abnormalities include common conditions such as iron deficiency, vitamin B12 deficiency, etc. These are associated with reduced erythropoeisis and hence a falsely high HbA1c value. On the other hand, hemolytic anemia is associated with increased reticulocytosis. Presence of young circulating red blood cells (RBC's) will reduce the mean lifespan of RBC's thus resulting in falsely low HbA1c values[7].

Comorbid conditions such as chronic kidney disease has complex interactions with HbA1c levels. Patients with CKD have increased carbamylated hemoglobin which can interfere with various assays. Reduced erythropoeisis is a major underlying etiology for anemia in CKD patients, which can result in falsely high HbA1c values whereasuse of recombinant erythropoietin to treat anemia results in increased reticulocytosis with resultant reduction in erythrocyte lifespan and thus a falsely low HbA1c value. Patients hospitalized with critical illness may have a myriad problems such as hemolysis, bone marrow suppression, bleeding diathesis, etc which makes interpretation of HbA1c difficult[7].

Falsely elevated HbA1c can also be seen with alcohol intake, pregnancy, post-splenectomy status. Whereas, liver cirrhosis, hypersplenism, drugs like dapsone, antiretroviral agents, ribavirin may lead to falsely low values[2,8]. Very high triglycerides may cause falsely low values and elevated bilirubin may falsely elevate HbA1c2.

Different assays using various methods are available to measure HbA1c such as immunoassay, ion exchange high performance liquid

chromatography (HPLC), boronate affinity and direct enzymatic. Various hemoglobin variants, carbamylated hemoglobin may interfere with these assays and give rise to false HbA1c reports[6].

False positive and false negative HbA1c is a clinically significant problem. Suspicion should arise in patients with very low or very high values, when blood glucose values and HbA1c are contrasting. In type 1 diabetes persistent good control of diabetes over several years is uncommon and a false HbA1c should be suspected. In addition, an abnormal HbA1c value can also give a clue for an underlying undiagnosed hemoglobin variant. In such situations, glucometer based glucose monitoring and continuous blood glucose monitoring should be more frequently used.

References :

1. American Diabetes Association. Classification and Diagnosis of Diabetes: Diabetes Care 2017; 40 (Supplement 1) : S11-S24.
2. Gallagher E.J, Roith D.E, and Bloomgarden Z. Review of hemoglobin A1c in the management of diabetes : Journal of Diabetes 2009;1: 917.
3. Glycemic Targets American Diabetes Association. Classification and Diagnosis of Diabetes: Diabetes Care 2017; 40 (Supplement 1) : S48-S56.
4. Panigrahi I, Bajaj J, Chatterjee T, Saxena R, Mahapatra M, Pati H. Hb Q India: Is it always benign? American journal of Hematology 2005; 78: 245-6.
5. Bhimani R.K, Rathod B.G, et.al. Hb Q India : An uncommon hemoglobin variant diagnosed in two patients-case series. International Archives of Integrated Medicine 2014; 1: 68-74.
6. Randie R.L., William L.R. A Review of Variant Hemoglobins interfering with Hemoglobin A1C Measurement. Journal of Diabetes Science and Technology 2009; 3: 446-51.
7. Bazerbachi F, Shaban N, Alraiyes AH, Alraies MC. Is hemoglobin A1c an accurate Measure of glycemic control in all diabetic patients? Clevel and Clinic Journal of Medicine2014; 81:146-149.
8. Unnikrishnan R, Anjana RM, Mohan V. Drugs affecting HbA1c levels. Indian Journal of Endocrinology and Metabolism 2012; 16: 528-531.

Table 1 : **showing contrasting blood glucose and HbA1c values**

YEAR	FBS	PPBS	HbA1c
November 1999	226	249	9.9%
January 2001	230	275	7.5%
May 2003	131	217	4.7%
January 2005	162	284	5.3%
April 2006	67	216	6.3%
Feb 2008	245	290	5.5%
April 2008	400	431	5.8%
June 2011	235	309	5.6%
August 2012	264	300	5.4%
March 2014	171	320	5.5%

Figure 1 : **Showing abnormal hemoglobin band**

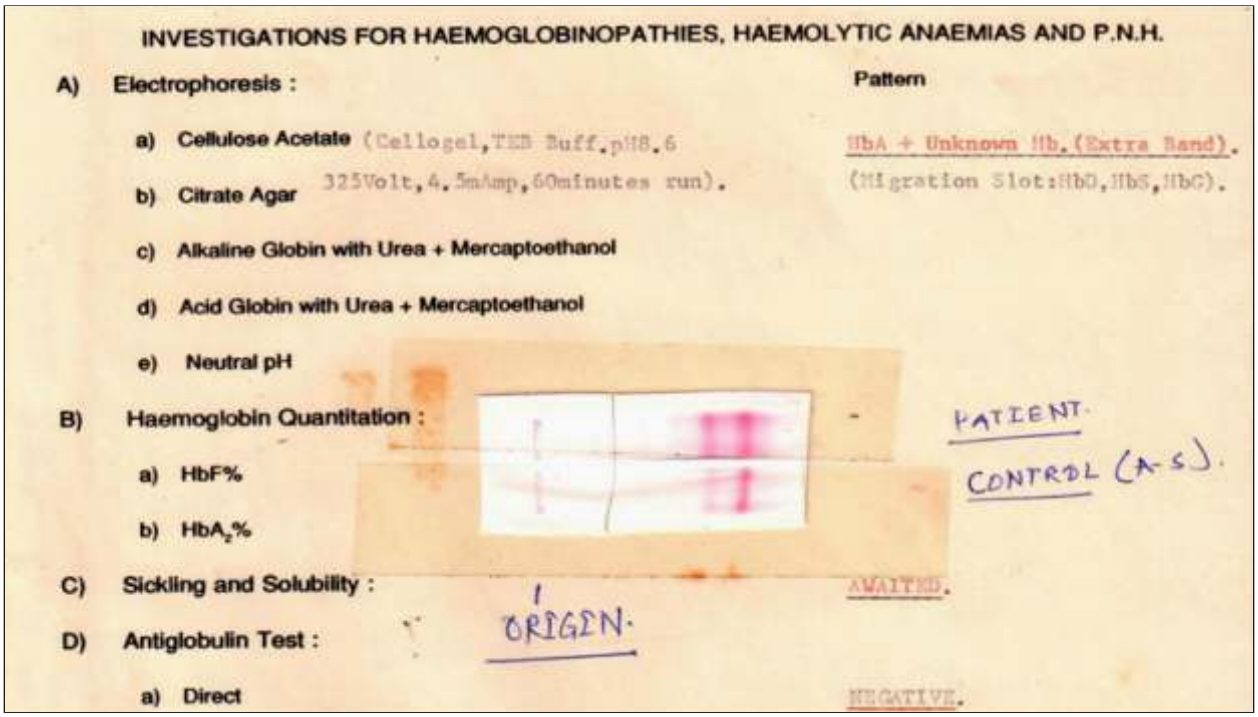
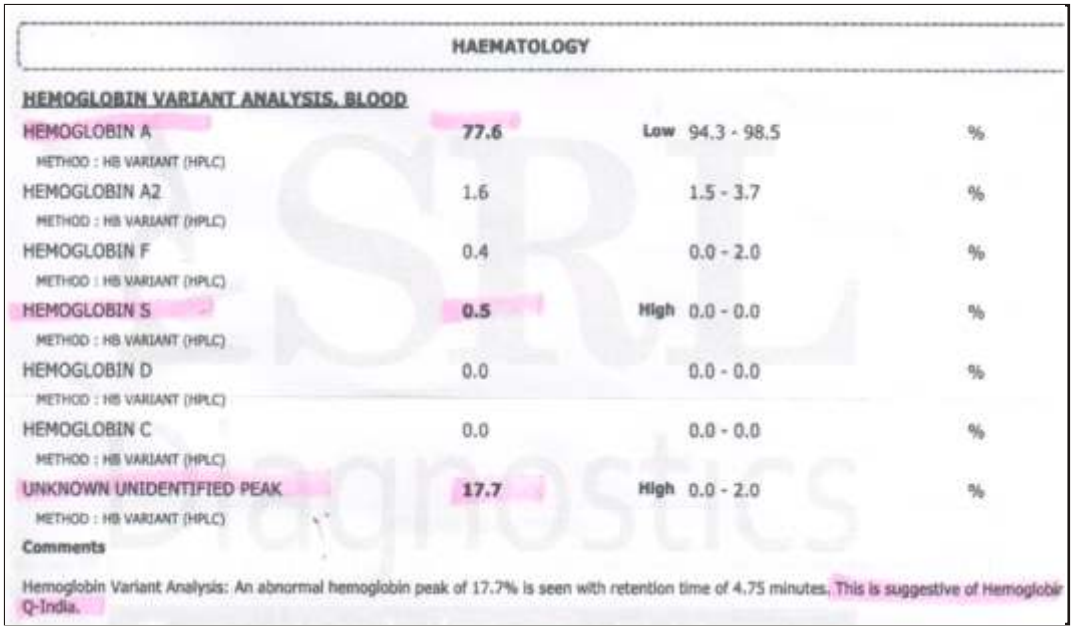


Figure 2 : **Hemoglobin electrophoresis showing unidentified peak with retention time of 4.75 minutes, consistent Hemoglobin Q-India**



HAEMATOLOGY

HEMOGLOBIN VARIANT ANALYSIS, BLOOD

HEMOGLOBIN A	**77.6**	**Low**	94.3 - 98.5	%
METHOD : HB VARIANT (HPLC)				
HEMOGLOBIN A2	1.6		1.5 - 3.7	%
METHOD : HB VARIANT (HPLC)				
HEMOGLOBIN F	0.4		0.0 - 2.0	%
METHOD : HB VARIANT (HPLC)				
HEMOGLOBIN S	**0.5**	**High**	0.0 - 0.0	%
METHOD : HB VARIANT (HPLC)				
HEMOGLOBIN D	0.0		0.0 - 0.0	%
METHOD : HB VARIANT (HPLC)				
HEMOGLOBIN C	0.0		0.0 - 0.0	%
METHOD : HB VARIANT (HPLC)				
UNKNOWN UNIDENTIFIED PEAK	**17.7**	**High**	0.0 - 2.0	%
METHOD : HB VARIANT (HPLC)				

Comments

Hemoglobin Variant Analysis: An abnormal hemoglobin peak of 17.7% is seen with retention time of 4.75 minutes. This is suggestive of Hemoglobin Q-India.

Figure 3 : **Showing patients HbA1c value of 5.5%**