Case Report

HbQ India variant in an epileptic patient – a rare case report

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ABSTRACT

Thalassemias and structural variations such as HbS, HbE, and HbD, as well as Hb Lepore, HbD-Iran, Hb-H illness, and HbQ India, are examples of inherited hemoglobin disorders. North and West India are home to the rare alpha-chain structural hemoglobin type known as HbQ India. The majority of patients are asymptomatic, and they frequently exhibit heterozygosity or co-inherited beta-thalassemia. We present the case of a 30-year-old Indian male epileptic patient coexisting with beta-thalassemia and HbQ India heterozygous variant. This case highlights the importance of screening hemoglobin variants in beta-thalassemia, interpreting normal HbA2 in coexisting iron deficiency anemia, and recognizing anti-seizure drug effects on hematological profiles. To measure different hemoglobin, a complete blood count, peripheral blood smear analysis, and cation exchange high-performance liquid chromatography (HPLC) were performed. The HPLC chromatogram showed hemoglobin of 22.5% and a retention time of 4.39 min. The normal HbA2 despite beta-thalassemia was attributed to iron deficiency anemia. HbQ India is a rare structural variant of hemoglobin. Despite being asymptomatic, it could make diagnosing beta thalassemia in the compound heterozygous state more challenging. HPLC provides a quick, precise, and reproducible method for screening this condition, enabling the identification and guidance of affected individuals.

Key words: Beta thalassemia, Epilepsy, HbQ India, High-performance liquid chromatography, Structural variant

Hemoglobinopathies are inherited abnormalities of hemoglobin caused by structural changes in the alpha or beta globin chain production [1]. Identifying these hemoglobinopathies is crucial for prognostication, treatment, genetic counseling, and formulation of preventive strategies [2]. Thalassemia (alpha and beta) is a commonly prevalent inherited hemoglobin disorder in India. Other structural variants include HbS, HbE, and HbD Punjab and their compound heterozygous states. Hb Lepore, HbD-Iran, HbJ-Meerut, Hb-H disease, and HbQ India are less commonly found hemoglobin variants [3]. The prevalence of thalassemia and hemoglobinopathy varies by geographical location. In India, there are an estimated 0.37 cases of hemoglobin-related disorders per 1,000 fetuses [1]. HbQ India (HbA1:c.193 G > C) is a rare α-chain structural hemoglobin variant. It usually presents in the heterozygous form or is co-inherited with beta-thalassemia. The HbQ India variant has a substitution mutation of histidine for aspartic acid at the 64 codon region of the alpha 1-globin gene [2,4]. Most individuals with HbQ are asymptomatic, with diagnoses often made incidentally during family studies or population screening [4]. A broad range of hematologic conditions, from minor thrombocytopenia or neutropenia to severe anemia, red cell aplasia, or bone marrow failure, are linked to anti-seizure medications (ASMs). Although the exact mechanism is unclear, immune-mediated pathways and drug interactions are believed to contribute [5].

We present a case of a 30-year-old Indian male epileptic patient coexisting with beta-thalassemia and HbQ India heterozygous variant. This case highlights the importance of screening hemoglobin variants in beta-thalassemia, interpreting normal Hb A2 in coexisting iron deficiency anemia, and recognizing anti-seizure drug effects on hematological profiles.

CASE REPORT

A 30-year-old Indian male epileptic patient visited our pathology laboratory for routine blood work complete blood count (CBC). He had been on anti-epileptic medications (Phenytoin 100 mg: TDS; Sodium valproate: 60 mg/kg/day) for the past 10 months and was

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under regular monitoring due to thrombocytopenia. The patient presented with pallor and mild anemia for the past 1 year. Hb electrophoresis was advised due to his recent marriage for thalassemia and Hb variant screening.

Routine tests and high-performance liquid chromatography (HPLC) electrophoresis revealed an abnormal hemoglobin peak at RT 4.39, indicating HbQ India heterozygosity. The patient's hematological profile revealed a hemoglobin concentration of 13.5 g/dL and a red blood cell (RBC) count of 5.96 × 10^6/µL. The mean corpuscular volume (MCV) was 70.3 fL, indicating microcytosis, while the mean corpuscular hemoglobin (MCH) and MCH concentration were 22.6 pg and 32.1 g/dL, respectively. Notably, the HbQ variant constituted 18.0% of the total hemoglobin on electrophoretic analysis, suggesting the presence of a significant hemoglobin variant component.

Peripheral smear showed microcytic hypochromic RBCs. WBCs were adequate with no immature cells. Platelet counts were reduced, confirming thrombocytopenia.

Mentzer Index = MCV/RBC Count = 70.3/5.96 = 11.9, suggestive of beta-thalassemia. The normal HbA2 despite beta-thalassemia was attributed to iron deficiency anemia. Fig. 1 shows the unknown peak (arrow) with hemoglobin of 22.5% and a retention time of 4.39 min. Minor post-HbQ and S window peaks are also seen.

DISCUSSION

HbQ India most often occurs in a heterozygous form and may co-occur with beta-thalassemia [6]. It was first reported in India in 1972 in Sindhi families by Sukumaran

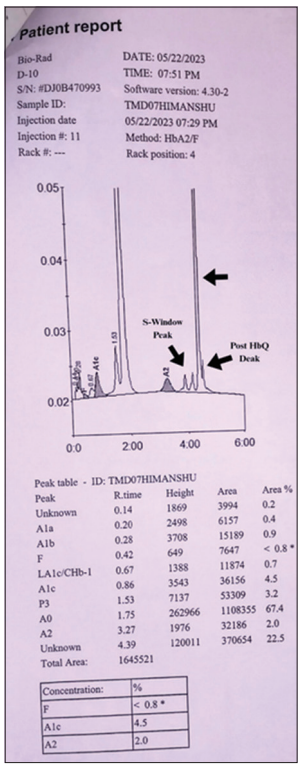

Figure 1: High-performance liquid chromatogram from the Biorad D10 instrument in an epileptic patient with HbQ India variant

et al. [7]. In a study by Phanasgaonkar *et al*., out of 64 cases, 22 had both HbQ India and beta-thalassemia [4]. Harrison *et al*. screened 7530 patients in North and West India and found 31 cases (0.4%) of HbQ India, with 6 being compound heterozygotes for beta thalassemia trait (BTT) and HbQ India [3]. All were asymptomatic, suggesting that HbQ India can go undetected without screening like HPLC, isoelectric focusing, polymerase chain reaction, and gene sequencing [8]. Typically, a single β-thalassemia allele raises HbA2 levels, but this may be masked by coexisting iron deficiency anemia, making HbA2 appear normal or borderline [9].

To the best of our knowledge, this is the only documented case of HbQ India in an epileptic patient with beta-thalassemia. This case underlines the importance of screening and interpreting variant results in patients on chronic medication or with unusual blood profiles.

Coinheritance of HbQ India with beta-thalassemia trait can complicate diagnosis, especially when concurrent iron deficiency anemia blunts the expected elevation in HbA2 levels, a key laboratory marker used for beta-thalassemia screening. In the present case, the patient was found to have normal HbA2 levels despite clear evidence of beta-thalassemia, a finding attributable to the iron-deficient state, as previously documented. Iron deficiency anemia can downregulate HbA2 synthesis, leading to diagnostic ambiguity and potentially missed beta-thalassemia carrier states if additional hemoglobin variant screening is not performed [10].

HbQ India is a structural alpha-globin variant resulting from the substitution of histidine for aspartic acid at codon 64 of the alpha-1 gene. This mutation produces a clinically silent phenotype in most cases, with affected individuals being largely asymptomatic and identified through population or familial screening rather than symptomatic presentation. Variants of HbQ, such as HbQ-Thailand and HbQ-Iran, share similar molecular mechanisms but have distinct epidemiological distributions. The presence of HbQ India in compound heterozygous states (such as with beta-thalassemia) has been associated with mild anemia, though clinical severity is generally less pronounced than that observed with other compound hemoglobinopathies [11].

Laboratory identification hinges on sophisticated methods – routine blood counts and red cell indices may be unremarkable, and conventional electrophoresis can misidentify HbQ due to its similar migration profile to HbS and HbD. The application of cation exchange HPLC is critical, as it produces an unknown peak at a distinctive retention time (4.39–4.77 min for Biorad D10 and Variant platforms), enabling accurate quantification and differentiation from other variants. Literature reports minor associated chromatogram peaks (split HbA2, post-HbQ, S-window) that require careful interpretation and sometimes molecular studies for confirmation [10].

Epilepsy management frequently involves long-term use of ASMs, such as phenytoin and sodium valproate. These agents can induce hematological side effects, ranging

from mild cytopenias to more severe red cell aplasia or bone marrow suppression. In this case, the patient demonstrated thrombocytopenia, which has known associations with ASM therapy, particularly sodium valproate. The interplay between chronic ASM exposure and underlying hemoglobinopathy may subtly alter the presentation and laboratory parameters, complicating the interpretation of hematological indices. Recent research emphasizes the importance of routine monitoring for hematological parameters in epileptic patients on polytherapy and advocates for vigilance in the screening process [12].

This case demonstrates the necessity for careful and targeted screening in populations with high hemoglobinopathy prevalence, especially among individuals with atypical hematological profiles, personal or family history of inherited disorders, or chronic medication use. The limitations of relying solely on CBC and electrophoresis for variant detection necessitate supplementing with advanced diagnostic modalities like HPLC and, when indicated, molecular testing. Comprehensive screening enables precise diagnosis, individualized counseling, and helps formulate preventive strategies, including genetic counseling for family planning, particularly in regions like North and West India, where such variants are more prevalent [13].

As per prior studies, most HbQ India cases, whether alone or in combination with beta-thalassemia, remain asymptomatic, although screening is crucial for identifying carriers and guiding medical decisions. The clinical presentation may be further masked in the presence of iron deficiency or medication-induced hematological changes, highlighting the need for multidisciplinary evaluation and holistic care pathways in similar scenarios [11].

In summary, the combination of HbQ India, beta-thalassemia trait, iron deficiency, and anti-epileptic drug therapy in this patient exemplifies the diagnostic nuances faced in current hematology practice. HPLC stands as the diagnostic gold standard for rare hemoglobin variants and should be incorporated into routine protocols for patients with unexplained anemia, those from high-risk ethnic backgrounds, or those with complex clinical histories such as chronic epilepsy management.

CONCLUSION

HbQ India is a rare structural hemoglobin variant that is often asymptomatic. However, when coexisting with other hemoglobinopathies, it may manifest clinically. Despite normal hemogram findings, HPLC is the gold standard for its detection. This case demonstrates the critical role of screening in accurately diagnosing such hemoglobinopathies, especially in populations at genetic risk or those on medications affecting hematopoiesis.

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