



A Novel Association of HbQ India Trait with Sickle Cell Anemia: a New Insight in Hemoglobinopathies

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Accepted: 15 December 2021

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Abstract

HbQ India is a rare α -chain structural hemoglobinopathy usually asymptomatic and presents in the heterozygous form or co-inherited with β -thalassemia trait. Herein, we are reporting the third case of novel association of HbQ India with HbS trait hemoglobinopathy in a 30-year-old young male presented with chief complaints of yellowish discoloration of sclera since 5 years with raised serum bilirubin levels along with pedigree analysis of the family.

Keywords HbQ India · Hemoglobinopathy · Sickle cell trait · HPLC

Introduction

HbQ India is a rare hemoglobinopathy [1]. Identification of these hemoglobinopathies is crucial for prognostication, treatment, genetic counselling, and preventive strategies formulation. HbQ India (HbA1:c. 193 G > C) is an uncommon α -chain structural hemoglobin variant. The structural changes at codon 64 of the $\alpha 1$ -globin gene cause substitution of histidine for aspartic acid. HbQ India usually presents in the heterozygous form or co-inherited with β -thalassemia trait [2]. We are reporting the third case of HbQ India with HbS trait hemoglobinopathy in a 30-year-old young male presented with chief complaints of yellowish discoloration of sclera along with pedigree analysis of the family. To the best of our knowledge, only two index cases of co-inherited, HbQ India/HbS, hemoglobinopathy has been reported previously by Parab et al. [3] in the English literature.

Case Report

A 30-year-old young male presented with flu-like symptoms at COVID center of our hospital. Patient's oropharyngeal and nasal swab samples were taken for the RTPCR which came positive for COVID-19 infection and he was admitted to the isolation ward. He also complained of persistent yellowish discoloration of the sclera since 5 years. In view of Chhattisgarh being endemic state for sickle cell anemia (SCA) and his belonging to "Sahu community" which is a common ethnic group in the region for development of SCA, his detailed past medical history was also inquired. It was found that patient had yellowish discoloration of sclera with raised bilirubin levels (total bilirubin, 6.56 mg/dl; direct bilirubin, 1.02 mg/dl; and indirect bilirubin, 5.54 mg/dl) since 5 years. In 2018, patient was diagnosed to have sickle cell trait along with mild splenomegaly. His sickling test was positive, while direct and indirect Coombs tests were negative. Except mildly deranged bilirubin levels, other liver function tests (LFT) were within normal limits. His hemogram showed slightly decreased RBCs count: $3.98 \times 10^6/\mu\text{l}$; however, other parameters were normal. Peripheral blood smear showed predominantly normocytic normochromic RBCs. No schistocytes, pencil cells, or nRBC were found. At present admission, a high performance liquid chromatography (HPLC) was done for characterization of the hemoglobinopathy which revealed two peaks of 41.8% and 9.1% at retention time 4.14 and 4.60 corresponding to HbS and HbQ India, respectively, suggestive of sickle

This article is part of the Topical Collection on *Medicine*

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HPLC analysis of patient and his daughter

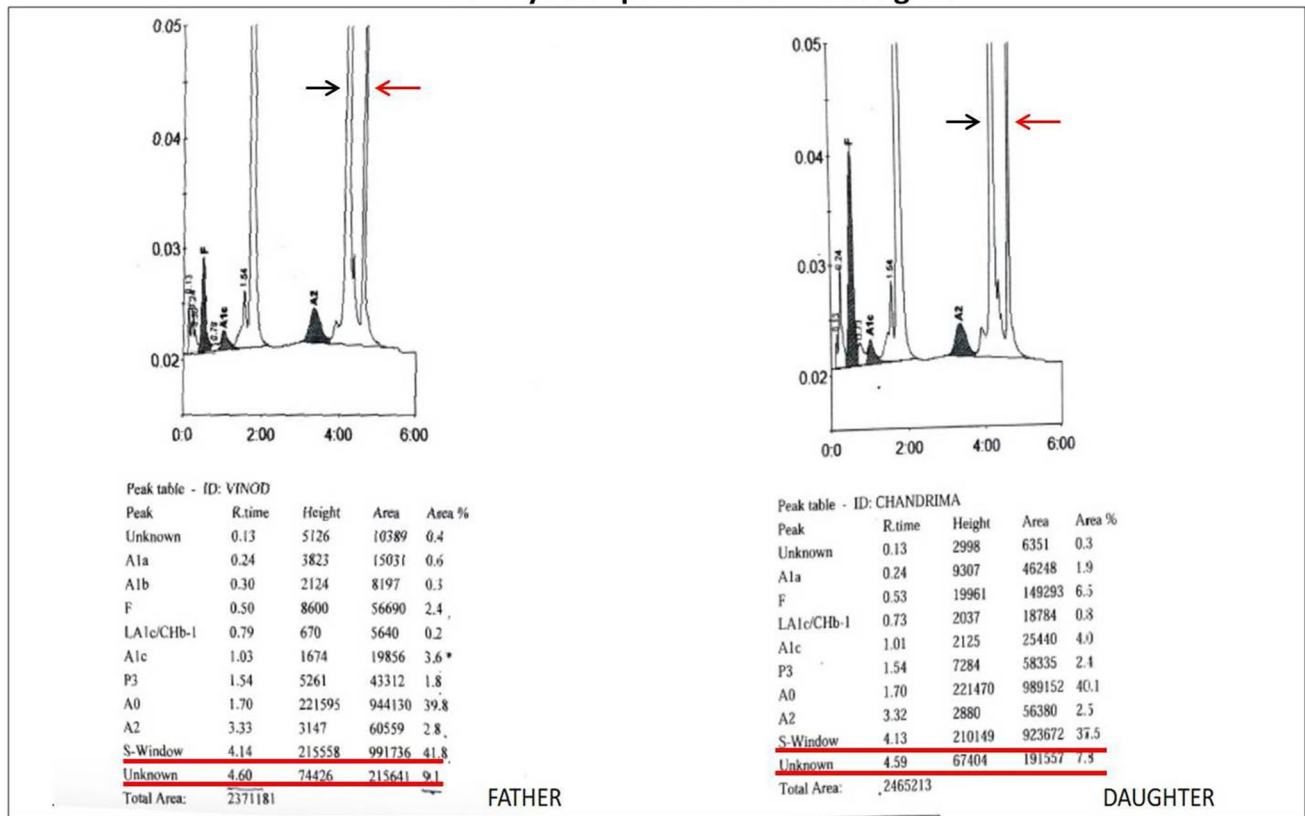


Fig. 1 High performance liquid chromatography analysis of patient and his daughter showing two peaks corresponding to HbS (black arrow) and HbQ India (red arrow) respectively

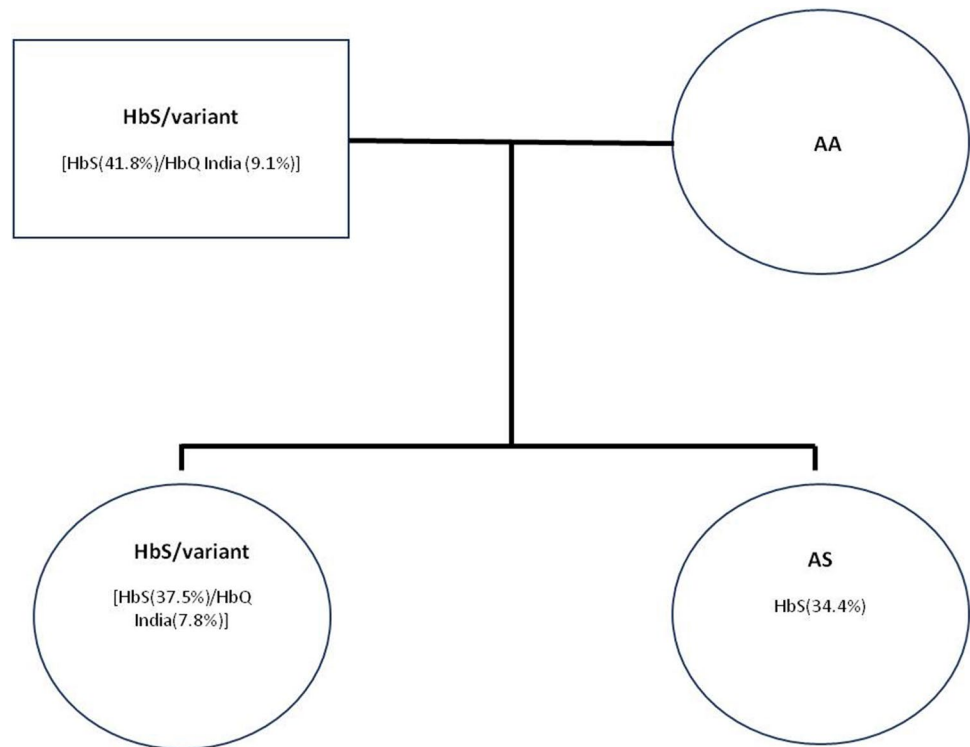
cell-HbQ India hemoglobinopathy (Fig. 1). Again, LFT delineated high bilirubin levels (total bilirubin, 5.69 mg/dl; direct bilirubin, 0.85 mg/dl; indirect bilirubin, 4.84 mg/dl) (Table 1). We also did a pedigree analysis of the family (Fig. 2) by HPLC and found wife carrying normal Hb pattern, while elder daughter (3 years) was sickle cell trait and younger daughter (1 year) was also having sickle

cell-HbQ India hemoglobinopathy. His both daughters were asymptomatic with normal hemogram. Patient was symptomatically treated for the COVID-19 infection and discharged after 7 days, when his COVID-19 RT-PCR report became negative. At 3 months of follow-up, patient is otherwise healthy and resumed his office, however still having persistent icterus.

Table 1 Hematological and Biochemical parameters of family members

Hematological parameters	Hb (g/dl)	RBC count (10 ⁶ /μl)	RETIC (%)	HCT (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	RDW-CV (%)
Father (HbQ/HbS)	13.1	3.98	0.44	36.5	91.7	32.9	35.9	13.2
Mother	13.5	4.24	1.79	39.0	92.0	31.8	34.6	12.1
Daughter (HbS)	12.3	4.18	1.21	34.8	83.3	29.4	35.3	13.7
Daughter (HbQ/HbS)	11.1	4.03	3.31	30.3	75.2	27.5	36.6	14.0
Biochemical parameters of patient								
	Total Bilirubin (mg/dl)	Direct Bilirubin (mg/dl)		Indirect Bilirubin (mg/dl)		AST (U/L)	ALT (U/L)	LDH (U/L)
Father (HbQ/HbS)	5.69	0.85		4.84		25	13	228

Fig. 2 Flowchart showing pedigree analysis of the patient's family



Discussion

HbQ India is a very rare alpha-chain structural variant hemoglobinopathy with a prevalence of 0.4% in the Indian subcontinent [2]. Sachdev et al. in their HPLC-based study in northern India and Nepal reported a prevalence of 0.2% for HbQ India hemoglobinopathy [4]. HbQ is prevalent in South East Asia and shows three structural variants which includes HbQ India (alpha 64 Asp to His), HbQ Thailand (alpha 74 Asp to His), and HbQ Iran (alpha 75 Asp to His). HbQ India is clustered in western and northern India and more common in the Sindhi and Punjabi communities [5]. The earlier reported indexed cases by Parab et al. [3] were also belonging to Sindhi community but the present case is from Sahu community which is not identified as risk factor for the HbQ India hemoglobinopathy. Chhattisgarh is an endemic zone for sickle cell anemia; however, only two cases of HbQ India with HbS trait hemoglobinopathy are reported from this part of country by Parab et al. [3]. Phanasgaonkar et al. [2] in their study reported 64 patients of HbQ India which included 36 of HbQ India trait, 22 of HbQ India- β thalassemia traits, 3 of HbQ India- β thalassemia major, and 3 cases of HbQ India homozygous. The literature about HbQ India is very limited and only one of the earlier published paper by Parab et al. [3] reported co-inheritance of HbQ India with HbS trait. So, this is a third case of HbQ India-HbS trait. HbQ India trait and HbQ India- β thalassemia trait patients are usually asymptomatic, and sometimes show only mild hematological

parameters derangement and diagnosed incidentally during screening. Parab et al. in their index cases reported mild anemia in both mother and daughter (Hb 10.1 g/dl and 10.7 g/dl, respectively) with decreased mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) [3]. However, authors have not discussed any details about clinical presentation and liver function test in their cases. In present cases, patient presented with a long-term (about 5 years) persistent icterus with indirect hyperbilirubinemia, mild anemia, and decreased total RBCs count. Daughter of the patient was asymptomatic and showed mild anemia with slightly decreased MCH. Panigrahi et al. [6] in their series found jaundice in one patient, however which could be explained by concomitantly inherited G6PD deficiency. We assume that HbQ India in presence of co-inherited sickle cell trait is clinically symptomatic and more severe in comparison to other types of inheritance pattern and association. Since this is a case report, the exact mechanism and pathophysiology of icterus further needs to be elucidated. On physical examination, both father and the affected daughter showed mild splenomegaly. However, radiological examination were not done so exact size cannot be assessed. Jaundice and splenomegaly are unique findings in this particular case as the previous reported case does not mention them. Also, HbQ India in heterozygous form or with other hemoglobinopathies such as β thalassemia is usually silent clinically. The mutation $\alpha 64$ (E 13) involved in HbQ India is on the surface of the hemoglobin tetramer

and the charge changes at these positions do not affect the properties of the hemoglobin molecule leading to a clinically silent phenotype [7].

Mean corpuscular volume (MCV) and MCH levels reduce in patient showing co-inheritance of HbQ India with β thalassemia; however, in present case, these parameters were within normal range.

Harrison et al. [8] reported that HbQ India levels vary from 13.6 to 24.4% and 7.4 to 9.0% in patients with HbQ India trait and HbQ India with β thalassemia trait, respectively. In present case, HbQ level was 9.1% corresponding to an unknown post HbS peak at retention time 4.60 min. Parab et al. [3] in their case reported HbQ India peak at 4.55 min as well as a hybrid peak of HbS and HbQ India in HbC window at retention time of 5.08 min [3]. Harrison et al. [8] also reported minor additional peaks (post HbQ, Split HbA2, and HbS). In present, case hybrid peak or minor peaks were not found. In best of our knowledge, only two cases were reported, so it is still debatable if low production of HbQ India is capable to alter the HbS phenotype.

To conclude, HbQ India is a very rare hemoglobinopathy usually inherited in heterozygous form alone or in common association with β thalassemia trait in Sindhi and Punjabi community and remain silent. This is a first case of HbQ India co-inherited with sickle cell trait in Sahu community with chronic persistent jaundice.

Author Contribution 1. Dr Rakesh Kumar Gupta: Concept, design, definition of intellectual content, manuscript editing

2. Dr Kartavya Verma: Data acquisition, data analysis, literature search, manuscript preparation

3. Dr Gurmeet Singh: Manuscript editing, and manuscript review

Availability of Data and Material Yes.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication A written informed consent was taken for publication.

Competing Interests The authors declare no competing interests.

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