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LETTER TO JCP

Clinical phenotype of haemoglobin Q-H disease

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Seven patients of Chinese origin who had haemoglobin (Hb) Q-H disease were studied. They were found to have a similar clinical phenotype to that of patients with deletional Hb H disease, who have a near identical genotypic configuration. The complete absence of Hb A in Hb Q-H disease and the similar clinical phenotype to deletional Hb H disease lends support to the observation that Hb Q-Thailand shares similar functional properties with Hb A.

Take home messages

- Seven Chinese patients with haemoglobin (Hb) Q-H disease were found to have a similar clinical phenotype to that of patients with deletional Hb H disease, which has a near identical genotypic configuration
- The complete absence of Hb A in Hb Q-H disease and the similar clinical phenotype to deletional Hb H disease lends support to the observation that Hb Q-Thailand shares similar functional properties with Hb A

The haemoglobin (Hb) Q-Thailand mutation is an α globin chain variant that results from a point mutation (GAC → CAC; Asp → His) in codon 74 of the α1 globin gene on chromosome 16p with a leftward single α globin gene deletion ($-\alpha^{4.2}$).[1 2] Individuals who are heterozygous for Hb Q-Thailand usually show slight red cell microcytosis because the mutation is invariably linked to ($-\alpha^{4.2}$), and this mutation has been reported in subjects of Chinese, Thai, and Japanese origin.[3] In contrast, Hb Q-H disease, caused by the co-inheritance of Hb Q-Thailand and α^0 thalassaemia, has only been reported in Chinese families. The genotype of Hb Q-H disease is $--/-\alpha^Q$. Molecular analysis of Hb Q-H disease commonly shows that the ($--^{SEA}$) α-thalassaemia deletion (SEA deletion) is the α^0 thalassaemia determinant.[4] Hb Q-H disease manifests as chronic anaemia associated with jaundice and hepatosplenomegaly.[5] Affected individuals show a thalassaemic blood picture resembling Hb H disease, but Hb analysis shows absence of Hb A, with Hb Q-Thailand being the predominant fraction.[2] We report the clinical phenotype of seven unrelated patients with Hb Q-H disease, the largest series to date of this relatively uncommon thalassaemic disorder in the Chinese, diagnosed since 1995 at our laboratory, which receives referrals of Hb disorders from all over the territory.

> ''Haemoglobin Q-H disease manifests as chronic anaemia associated with jaundice and hepatosplenomegaly''

HAEMATOLOGICAL AND CLINICAL FINDINGS

Table 1 details the clinical and haematological data. All of the study subjects are Hong Kong Chinese, with patient number 7 being of Chinese descent from Thailand. Diagnosis was made on Hb pattern studies in all cases. Archival blood samples were of sufficient quantity for genotype determination in four individuals (patients 3, 4, 5, and 7). Genotyping revealed the Hb Q-Thailand mutation, as confirmed by direct nucleotide sequencing of the α1 globin gene, together with 4.2 kb single α globin gene deletion and SEA deletion, as detected by multiplex polymerase chain reaction. Hb A was absent and Hb Q-Thailand accounted for 93.9–97.9% of the total Hb. There was a high proportion of Hb H inclusion bodies, which were detected in 70–90% of red blood cells in these patients on supravital staining.

These seven patients were anaemic with steady state Hb concentrations ranging from 79 g/litre to 109 g/litre (mean, 97 g/litre). None of them required regular transfusions, although three of the seven had a history of infrequent blood transfusions. The other four had never been transfused. Four of the patients had splenomegaly, and splenectomy was performed in two as a result of hypersplenism. Two patients showed hepatomegaly. The six patients with iron studies available showed raised ferritin values, but none was put on iron chelation treatment.

DISCUSSION

Patients with Hb Q-H disease can be categorised under deletional Hb H disease, because genotypically they show deletion of three α globin genes.[6] Therefore, we compared the clinical features of Hb Q-H disease with those of Hb H disease caused by the ($--/-\alpha^{4.2}$) configuration in our archive, because their genetic configurations are almost identical. There appears to be no significant difference between the two groups with respect to clinical phenotype (table 1). Our results are entirely in accordance with the observation that Hb Q-Thailand shows normal oxygen affinity, Bohr effect, and cooperativity.[3] Thus, patients with Hb Q-H disease have similar clinical features to patients with deletional Hb H disease, even though Hb A is absent in the former condition.

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Abbreviations: Hb, haemoglobin; SEA deletion, ($--^{SEA}$) α thalassaemia deletion

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Table 1 Haematological and clinical profiles of patients with Hb Q-H disease

Patient	Sex	Age (years)	L	S	History of transfusion	Hb (g/l)	MCV (fl)	MCH (pg)	Hb H (%)	Hb A (%)	Hb A_2 (%)	Hb F (%)	Hb Q-Thailand (%)	Retic (%)	Bilirubin (μmol/l)	Iron (μmol/l)	Ferritin (pmol/l)	Transferrin saturation (%)
1	M	58	N	N	N	96	83.4	20.0	70	0	0.3	<0.3	97.9	–	–	39	5200	–
2	M	17	N	N	N	105	60.5	18.5	80	0	3.4	<0.3	93.9	–	–	–	–	–
3†	M	28	Y	Y	N	100	63.6	18.8	90	0	2.7	<0.3	95.6	9.2	90	32	1430	77
4	M	23	N	Y*	Y	105	59.7	18.4	89	0	2.4	<0.3	95.8	4.7	35	20	965	16
5	M	38	N	N	N	10.9	66.6	18.1	90	0	3.0	0.5	94.2	3.7	30	21	1530	38
6†	F	68	N	Y*	Y	79	70.2	18.9	70	0	2.1	<0.3	93.9	6.5	–	25	467	–
7‡	F	49	Y	Y	Y	84	77.2	21.7	85	0	1.2	<0.3	96.9	5.0	26	–	1907	–
HbH disease $--^{SEA}/-\alpha^{4.2}$ (n = 12)§		35	1 case	4 cases¶	3 cases, all transfusion independent	94	63.9	17.0	65	NA	NA	NA	NA	5.0	29.1	20	1108	41

*Splenectomy performed; †gallstones present; ‡hepatitis C carrier, liver biopsy showed chronic hepatitis and grade 2 iron overload (modified Scheuer grading); §mean values quoted for age and laboratory parameters in these 12 patients with deletional HbH disease as a result of $--^{SEA}/-\alpha^{4.2}$ configuration; ¶splenectomy performed in one patient.
Reference ranges: Hb, 130–180 g/l (men), 115–165 g/l (women); MCV, 80–96 fl; MCH, 27–32 pg; HbA_2, 2.3–3%; HbF<0.9%; reticulocytes, 0.2–2%; bilirubin, 7–19 μmol/l; iron, 9–33 μmol/l (men), 5–28 μmol/l (women); ferritin, 115–884 pmol/l (men), 15–331 pmol/l (women); transferrin saturation, 15–45%.
Hb, haemoglobin; Hb H, percentage of red cells with HbH inclusions; L, hepatomegaly; MCH, mean cell haemoglobin; MCV, mean cell volume; N, absent; NA, not applicable; Retic, reticulocytes; S, splenomegaly; Y, present; –, data not available.

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