

HEMOGLOBIN H DISEASE IN THE AL-QATIF REGION OF SAUDI ARABIA

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Background: The Al-Qatif region in the Eastern Province of Saudi Arabia has the highest prevalence of α -thalassemia genes in the Kingdom. Hemoglobin H (Hb H) disease, however, has been rarely reported. We decided therefore to verify the rarity of the disease, and characterize the presenting features in cases identified.

Patients and Methods: All patients seen in Qatif Central Hospital between September 1988 and November 1990 with low red cell indices were screened for Hb H disease, and those found positive had clinical data compiled from their hospital records and analyzed.

Results: Thirty-nine cases of Hb H were diagnosed. The mean age of the patients was 18 years. The mean hemoglobin was 13.5 g/dL for neonates and 7.6 g/dL for the others. The mean Hb Bart's level was 27.5% in neonates and the mean Hb H level in others was 11.1%. In addition to low red cell indices, all patients had a high red cell distribution width (RDW) mean of 25.6%. The main clinical signs were jaundice and hepatosplenomegaly. Concurrent glucose-6-phosphate dehydrogenase (G6PD) deficiency was seen in 28.2% of patients.

Conclusion: Hemoglobin H disease is not uncommon in the Al-Qatif region of Saudi Arabia. The red cell indices may mimic iron deficiency, which should be excluded by the presence of jaundice and organomegaly. The condition often co-exists with G6PD deficiency.

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Key Words: α -thalassemia, hemoglobin H, hemoglobin Bart's, red cell indices, G6PD deficiency.

Hemoglobin H (Hb H) disease is one of the α -thalassemia syndromes and is characterized by chronic hemolytic anemia of variable severity and a clinical picture of thalassemia intermedia.¹ Although the genetic basis of the disease is diverse, the condition generally results when the total output of alpha (α) genes is equivalent to one functional gene. In most cases, this anomaly results from the interaction of α^+ and α^0 -thalassemia genes. The loss of three genes results in a severe imbalance in the production of globin chains, with α/β globin chain synthesis ratios ranging between 0.20 and 0.40.² The excess β globins form homotetramers which constitute Hb H.

Hb H disease is widely found in South East Asia, parts of the Middle East and in Mediterranean populations.³⁻⁶ It also occurs sporadically in almost every racial group.² The occurrence of α -thalassemia in Saudi Arabia has been recorded since 1969,⁷ and the distribution of the genes in the Kingdom has since been studied extensively.⁸⁻¹⁰ The Eastern Province where Al-Qatif is located has the nation's highest frequencies of both α^+ and α^0 variants.¹¹ The severe form of nondeletion α -thalassemia (α^T) has also been found

in the Province.¹² Until recently, reports on Hb disease in the Kingdom were anecdotal,¹³ and the condition was presumed to be rare,¹⁴ however, a recent paper from Dammam¹⁵ shows that it is not uncommon. This paper seeks to confirm that the disease is not as rare as it was presumed to be, particularly in the Eastern Province of Saudi Arabia.

Patients and Methods

Between September 1988 and November 1990, patients who were sent to the Hematology Department at Qatif Central Hospital for evaluation and were found to have low red cell indices on a Coulter S+ IV or S+ VI (Coulter Electronics Inc., Florida, USA) profile had a peripheral blood film and reticulocyte count done. The peripheral blood films were stained with May-Grunwald-Giemsa, and the reticulocytes were stained supravivally with brilliant cresyl blue. The staining procedures were done using standard techniques.¹⁶ Those with significant numbers of Hb H inclusion bodies in the reticulocyte preparation had hemoglobin electrophoresis done to quantify the Hb H and/or Hb Bart's level. Patients with Hb H or Hb Bart's level of 20% or more on scanning had their hospital records reviewed for information regarding age, sex, presenting symptoms, nationality, address, history of blood transfusion, size of spleen and liver (in centimeters below the left and right costal margins, respectively), and other

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TABLE 1. Mean values of hematological parameters.

Parameter	Adults and children	Neonates
RBC x 10 ¹² /L	4.23±1.13	6.15±0.78
Hb g/dL	7.6±1.8	13.5±0.53
Hct	0.254±0.06	0.47±0.43
MCV (fl)	61.0±5.7	76.6±3.5
MCH (pg)	18.1±1.9	22.1±2
MCHC (g/dL)	29.8±1.8	28.6±1.6
RDW %	25.6±5	28.5±2.7
HbH %	11.1%±8.5	–
Hb Bart's %	6.4%±4.6	27.5%±4.0
Hb A2%	0.75%±1.0	–

relevant clinical data like hemoglobin level and G6PD status. The hemoglobin electrophoresis was done on cellulose acetate plates at pH 8.6, using commercial reagents and equipment from Helena Laboratories (Beaumont, Texas, USA). The method used was that recommended by Wood.¹⁷

Results

The number of patients who had detectable Hb H or Hb Bart's level of 20% or more was 39, comprising 24 females (61.5%) and 15 males (38.5%). Their ages at the time of diagnosis ranged from 1 day to 36 years, with a mean of 18.0±11.5 SD. Five patients were newborns (1-2 days old), 17 were children (4 months – 12 years), and the remaining 17 were adolescents and adults (13-36 years). Thirty-eight of the patients (97.4%) were Saudis from the Eastern Province and all but three came from the Al-Qatif area. The only non-Saudi patient came from Bahrain.

Table 1 shows the hematological parameters of the patients. They all had low red cell indices and high red cell distribution width (RDW). The mean hemoglobin level in the adults and children was 7.6±1.8 g/dL and the corresponding figure for the newborns was 13.5±0.53 g/dL. The mean Hb H level was 11.1±8.5% for adults and children, and the mean Hb Bart's level was 27.5±4.0% for the newborns.

Of the 14 patients (35.9%) who presented with clinical jaundice, four were newborns. The total bilirubin ranged from 3-15 mg/dL in the neonates and 1.7-6.6 mg/dL in the others. The prevalence of splenomegaly was 56% and hepatomegaly was noted in 41% of the patients. The splenic size ranged from 1-13 cm and the liver size from 1-6 cm. Twenty-two patients (56.4%) presented with features of anemia, i.e., pallor and fatigue, with or without jaundice, and five of them were pregnant at the time of diagnosis. Thirteen patients (33.3%) presented with complaints unrelated to anemia and four infants (10.3%) presented with neonatal jaundice. Only two of the patients had had the diagnosis made previously.

Information regarding previous transfusion was obtainable from 36 patients. Ten patients (27.8%) had no history of transfusion and all the newborns were in this

group. Eleven patients (30.6%) had been transfused once, 10 (27.8%) had been transfused twice, one (2.8%) had received transfusion on three occasions, and four (11.1%) had been transfused on more than three occasions. All five pregnant patients had had previous transfusions, mainly during pregnancy. Eleven patients (28.2%, 8 males and 3 females) had concurrent G6PD deficiency.

Discussion

Symptomatic α -thalassemia syndromes are characterized by hypochromic red cells with marked reduction in mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV). Typical values for MCH are in the 20-25 pg range, and those for the MCV are in the 60-70 fl range.² The mean values for MCV, MCH, MCH concentration and RDW in our patients were 61 fl, 18.1 pg 29.8 g/dL and 25.6%, respectively, and were similar to those found in the patients from Dammam in the study by Qadri et al.¹⁵ The definitive diagnosis of Hb H disease is based on the presence of Hb H inclusion bodies in a reticulocyte preparation and a detectable Hb H band on hemoglobin electrophoresis,² and these were the criteria used in diagnosing our patients. In newborns, an additional criterion in the absence of a Hb H band was the presence of 20% or more in Hb Bart's level on hemoglobin electrophoresis.¹⁸

False-positive Hb H bands are seen in preleukemic states, and false-negative results may occur when the blood samples are not properly handled on storage or the lysates are shaken violently with organic solvents.² None of our patients showed any hematological or clinical features of preleukemia, and false-positive results were therefore unlikely. However, there was a possibility of false-negatives in some of the patients excluded since the laboratory had no control over the handling of blood samples before their reception by the technical staff. Moreover, owing to staff constraints, hemoglobin electrophoresis was done in batches and not daily. It is therefore conceivable that samples with low Hb H content could have precipitated out during storage, thereby leaving undetectable quantities in the red cells. None of our patients with Hb H inclusion bodies showed discordant results on hemoglobin electrophoresis.

The anemia of Hb H disease is of variable severity and simulates the clinical picture of thalassemia intermedia.¹ The hemoglobin values commonly range between 7-10 g/dL.² The hemoglobin values in our non-neonatal patients ranged between 3.0-11.2 g/dL, and were similar to the range reported from Greece by Kattamis et al.,¹⁹ however, the hemoglobin values in our patients did not correlate with the hemoglobin H values as reported in their study. Our patient with the highest Hb level (11.3% g/dL) had a Hb H value of 24%, while the patient with the lowest Hb (3.0 g/dL) had 10.3% Hb H. The report from Greece used transfusion requirement as one of the indicators of severity.

Using this criterion, 26 of our patients (66.7%) would be classified as having severe disease. Most of the transfusions were carried out in other hospitals and the specific indications were not known. We therefore preferred to classify the severity of the disease in our patients according to the hemoglobin values. The range of hemoglobin levels in Hb H was given as 7-10 g/dL.² Any level within this range we regarded as moderate, those above as mild and those below as severe. Three patients (8.8%) were thus classified as mild, 20 (58.8%) as moderate and 11 (32.4%) as severe. The newborns were excluded from this categorization because no established hemoglobin range was found in the literature.

Splenomegaly is common in Hb H disease.^{19,20} The prevalence of 56% in our patients was higher than in the study of Chinese patients by Hsu et al.,²⁰ but was lower than that found among the Greeks.¹⁹ Hepatomegaly was found in 41% of our patients, compared to 14% in the Chinese study,²⁰ while it did not seem to occur in other series.¹⁹

Why the Hb H disease in most of our patients was not diagnosed earlier is open to conjecture. The existence of Hb H disease in the Eastern Province has been known since 1971,¹³ and α -thalassemia in this country has since been studied extensively.^{11,14} Hospital-based studies are few, however,^{12,15,21} and therefore the index of suspicion of Hb H at the time of this study had been low. This is confirmed by the observation that a sizeable number of our patients had had previous contacts with hospitals in the area. Twenty-six patients (66.7%) had had blood transfusions before they were diagnosed as having Hb H disease. One of them had been labeled as "thalassemia, type unknown," implying that Hb H had not been considered, otherwise specific tests for the diagnosis would have been requested.

Another possible cause of underdiagnosis of Hb H in Saudi Arabia is that the diagnostic band on electrophoresis may be faint and therefore missed in the interpretation of the strip or plate. One of the patients in this series reported at another clinic in the Eastern Province with anemia, and his Hb electrophoresis was reported as Hb AA. A repeat electrophoresis in this hospital showed that he had a Hb H band which must have been missed at that hospital.

The upsurge in the reporting of Hb H in this part of the Kingdom may be due to the presence of this hospital in the Qatif area. Qatif Central Hospital was commissioned in 1988 as a referral hospital for the inhabitants who are ethnically homogenous and practise consanguineous marriages.²² This practice increases the chances of interaction between the various thalassemia genes and, in particular, homozygosity of the α^T variant.

A close correlation has been found between the severity of Hb H disease and the genotypes.^{19,20,23} The severe phenotype is associated with the nondeletion genotypes, while the mild ones are associated with the deletion genotypes.^{19,20} The common α -thalassemia genes found in Saudi Arabia are the deletion variants α^+ and α^0 and the

nondeletion variant α^T -Saudi.^{2,11} The variability seen in our patients may, therefore, be related to the interaction between these three genes, and should be elucidated in the future by the use of gene probes.

In conclusion, we confirm that hemoglobin H disease is not uncommon in the Eastern Province of Saudi Arabia. The pattern of presentation suggests that the disease should be considered in patients with microcytic hypochromic anemia with high RDW,²⁵ especially if there is jaundice and organomegaly. Furthermore, G6PD-deficient patients with low red cell indices, chronic jaundice and organomegaly should be screened for concurrent Hb H disease.

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