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Hemoglobin H Disease*

A Case Report

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Thalassemia was the first recognized hemoglobinopathy. It is well known that considerable heterogeneity exists in the group of disorders known as thalassemia.[1] It is now generally accepted that the thalassemia are mainly due to a reduced rate of synthesis of either the alpha or the beta chain of hemoglobin A (Hb. A), which is designated as α-or β-thelassemia respectively.

β - thalassemia syndromes in which no abnormal hemoglobin could be shown are much more common throughout the world that α - thalassemias. The last type is seen relatively more frequently among Chinese and Greeks. Although delta[2,3] and gamma thalassemias are also described, they are much rarer forms of the disease.

Hemoglobin H disease, α type of a - thalassemia, has been reported in this country previously.[5-8] In this communication we would like to report another patient with this disease.

Methods

Hemograms were obtained using standard techniques. Hb concentration was determined by the cyanmethemoglobin method. The micro hematocrit was used for measuring packed cell volume. The starch gel electrophoresis was performed according to the method of Smithies[9] and the agar gel according to Robinson et al.[10] Fetal hemoglobin value was determined by the alkali denaturation method of Singer et al[11] and quantitative estimation of HbA_2 was obtained by chromatography on diethyl amino ethyl cellulose (DEAE).[12]

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Case Report

K.I. a 25 year-old female, Turkish Cypriot was brought to our attention since she was told during a routine examination in another hospital that she had some kind of thalassemia. She did not have any complaints referable to possible hemolytic anemia but became pale a month later with a mild grippal infection. Although her mother's peripheral smear was very much compatible with thalassemia syndrome, no permission was obtained for familial studies.

Physical examination revealed a well developed female without jaundice or hepatosplenomegaly. Other physical findings were also within normal limits. Hb: 11.6 gr/100 ml; leukocytes 8000/cmm, reticulocytes 2.6 percent with normal differential. The stained peripheral smear (Figure 1) revealed marked, anisocytosis, polychromasia, poikilocytosis, microcytosis, hypochromia and target cells. Platelets were adequate on the smear. The sickling test, made with 2 % sodium metabisulphite was negative. Intraerythrocytic precipitates of Hb H was shown with 1% of brilliant cressylblue stain. Osmotic fragility of the erythrocytes was markedly decreased.

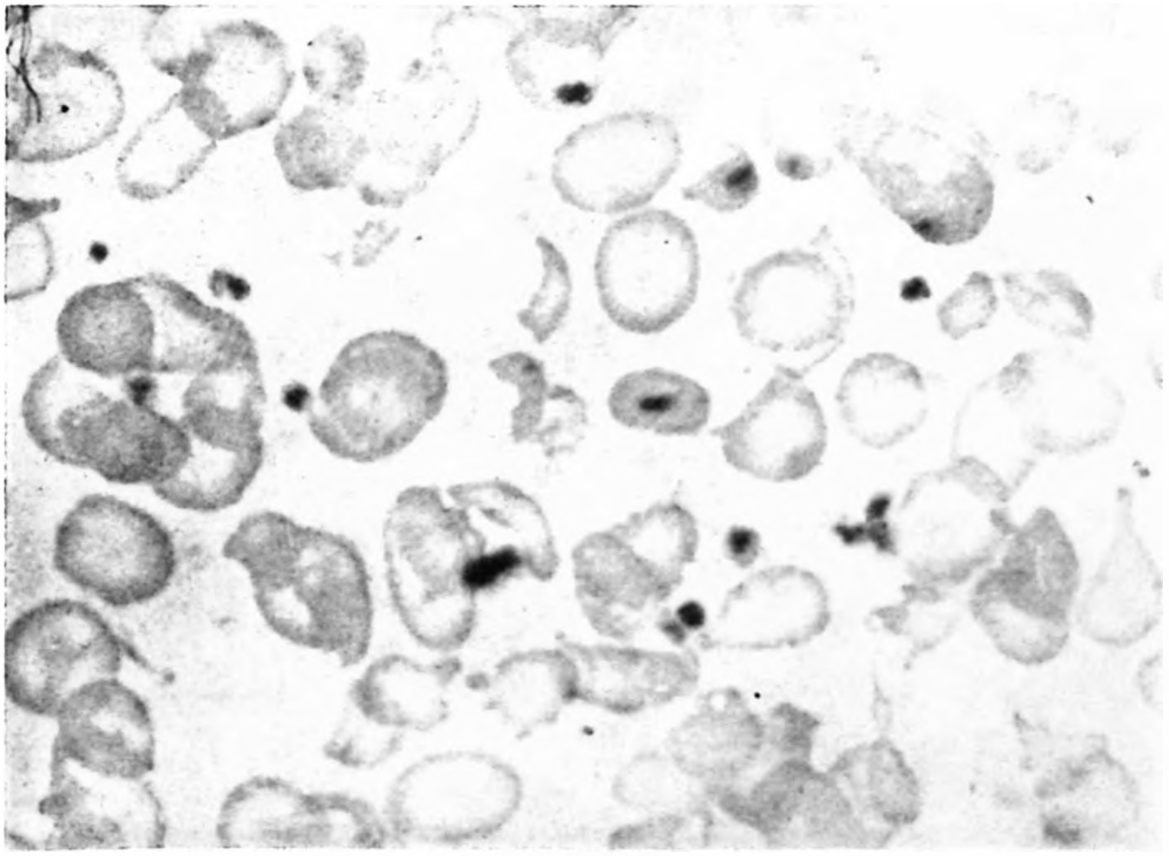

Figure 1

Peripheral smear of the patient anysocytosis, poikilocytosis and hypochromia are marked.

Hb electrophosesis of fresh hemoglobin solution on agar gel (at pH: 6.45) was normal (Figure 2) but showed decreased A_2 and fast moving component by starch gel electrophoresis at pH: 8.6 (Figure 3).

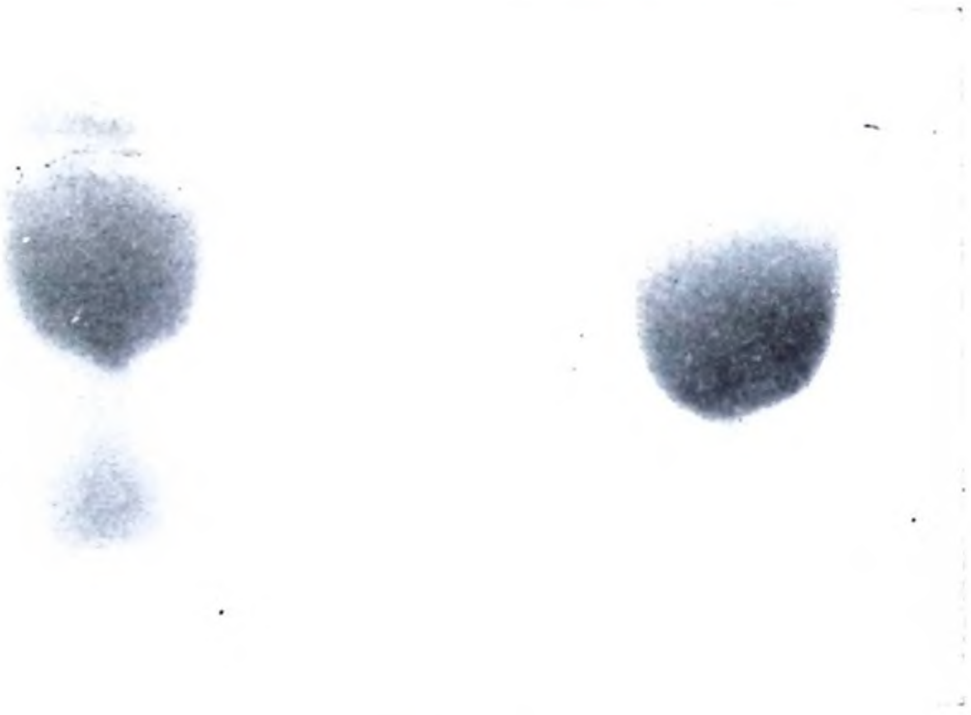

Figure 2
Agar gel electrophoresis at pH. 6.45 does not show any abnormality.

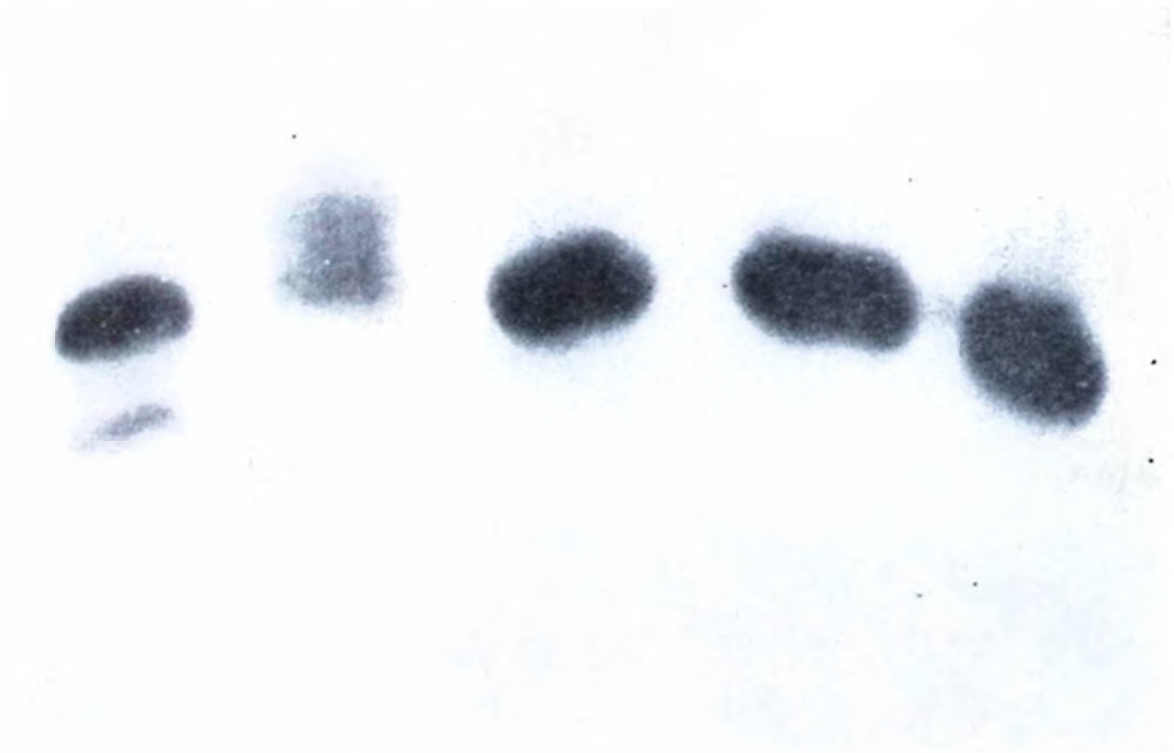

Figure 3
Starch gel electrophoresis at pH: 8.6 from top: sickle-cell trait, the patient's hemolysate: A_2 is barely seen, and a fast moving component is well separated, other three: normal controls.

Starch gel electrophoresis at pH: 7 showed a minor fraction moving toward anod (Figure 4). Hb A_2 and fetal hemoglobin levels were found to be 0.5 and 1.6 percent respectively, Hb H was found to be 260 per cent by the Sundermans method.[13]

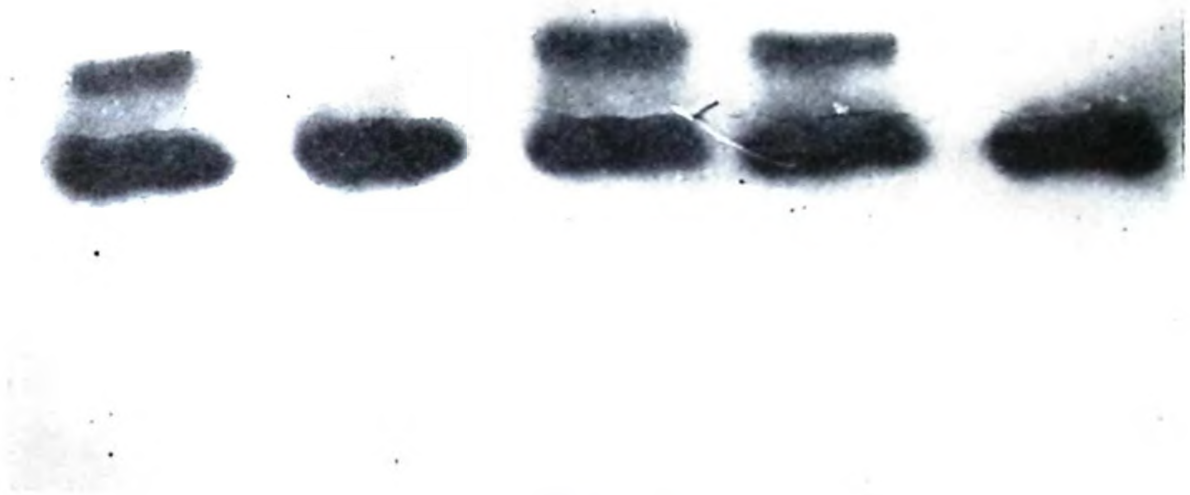

Figure 4
Starch gel electrophoresis at pH: 7, shows a minor fraction moving toward anod on the patient's hemolysate, (inserted 3 times and with controls).

Discussion

The hematologic findings and the hemoglobin electrophoresis result of this patient are consistent with the diagnosis of hemoglobin H disease. Although there are other hemoglobins like I, J.K. which are faster than hemoglobin A in starch gel electrophoresis at pH: 8.6, Hb H could easily be differentiated from them at pH: 7 on starch gel electrophosesis.

Hb A_2 is normal or decreased in hemoglobin H disease as in this case. Although another abnormal hemoglobin, Hb δA_2 which was considered as d tetramer,[14] is now accepted to have been the mixed tetramer $\beta_2 d_2$[15], has been isolated from some of the cases with hemoglobin H disease, we were not able to show it by electrophoresis and chromatography. Bart's hemoglobin, which is δ_4, could not be shown in fresh

hemolysate with the methods used. (However, when starch gel electrophoresis at pH: 7 was repeated a week later with frozen hemolysate, another component like Bart's slower than Hb H was shown).

Bart's hemoglobin is more alkali resistant than Hb A14 and alkali resistant fraction of this patient was found to be 1.6 per cent. Since alkali resistant Hb as measured by the technique of Singer et al includes not only HbF, but also some proportion of Bart's hemoglobin, it may also be interpreted that she did not have a considerable amount of Hb Bart's.

Although in some patients, the severity of the clinical symptomatology parallels the level of Hb H in the peripheral blood,[15] such a correlation has not been reported in other cases[17 18]. In spite of fairly high HbH concentration, the mildness of the symptomatology of our case may support the latter observations.

The distribution of Hb H and A in erythrocytes is not equal and intraerythrocytic inclusion bodies with cresylblue stain are seen in most but not all erythrocytes. These inclusion bodies are not only shown in erythrocytes but also in erythroblasts.[16]

The genetic of α - thalassemia remains a major problem in the thalassemia field because of the difficulty of identifying the carrier states in adult life. There are two major theories for the explanation of different clinical presentations of alpha thalassemias. Wasi et al postulated the presence of two different types of α - thalassemia trait.[20] One of these designated α - thalassemia trait which is recognised by slight thalassemic changes and the presence of traces of Hb H. The other type related to a silent gene which is called α - thalassemia$_2$ trait, normally causes no thalassemic changes in the adult but is associated with some Hb Bart's at birth. The combination of α - thalassemia$_1$, and α - thalassemia$_2$ genes causes Hb H disease, while the Hb Bart's hydrops fetalis syndrome represents the homozygous state for α - thalassemia$_1$. However, the presence of a minute amount of Bart's hemoglobin in the newborn period does not always indicate the genetic inheritance of α - thalassemia.[21]

Another theory postulated by Lehmann[22 23] accepts four thalassemia genes per individual, two per chromosome to explain the wide clinical spectrum of α - thalassemia. Only one α-thalassemia gene indicates the silent form; two genes, classical a-thalassemia; 3 genes; Hb H disease and four genes, Hb Bart's hydrops fetalis syndrome.

The alpha polypeptide chain sythesis, compared to β chain will give a better understanding of the genetics of alpha thalassemia. It is shown that even in silent carriers α-chain synthesis is under suppression[24] as it was proposed by Ingram and Stretton[25] in 1959. Since a familial study could not be accomplished we cannot explain the genetics of this case.

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