Further Cases of Hb Q-H Disease
(Hb Q-\alpha Thalassemia)

By LIE-INJO LUAN ENG, R. P. PILLAY AND V. THURAISSINGHAM

HEMOGLOBIN Q-H DISEASE is rare, and thus far only three cases have been described.\(^1,2\) It has been thought to result from a combination of the gene for Hb Q and the gene for \(\alpha\)-thalassemia.\(^2,3\) In the three cases mentioned, occurring in two Chinese families, clinical and hematologic findings were reported. However, the case described by Vella et al.\(^1\) was complicated by hookworm infection, and in the two described by Lie-Injo and Hart\(^2\) the red cell indices of the patients were determined after splenectomy and analyzed from samples transported from Brunei to Kuala Lumpur.

In this paper we present four additional cases of Hb Q-H disease, also in two Chinese families. Hematologic examinations were made of freshly drawn blood in three cases, and none of the patients were splenectomized.

METHODS

Morphologic examinations followed standard methods; hemoglobin level was estimated by the cyanmethemoglobin method in a photoelectric colorimeter, using standard solutions provided by Davis and Keeler, Ltd., London; electrophoresis of hemolysates was performed on both paper\(^4\) and starch gel\(^6\) and column chromatography in IRC-50;\(^7\) the alkali-resistant hemoglobin was measured by the method of Singer et al.\(^7\) Study of polypeptide chains of hemoglobin was by starch-gel electrophoresis in a urea-barbital system at pH 8.0\(^8\).

CASE REPORTS

Patient #1, Y. K. N., a 26-year-old Chinese woman, was admitted to the General Hospital, Kuala Lumpur, in February 1964 with chronic anemia of obscure origin. She was known to have had jaundice several years previously. On admission she was pale and slightly icteric. The spleen and liver were palpable three fingers below the costal margin. Blood analysis revealed: Hb, 7.6 Gm./100 ml.; RBC, 3.7 million/cu. mm.; PCV, 26.0 per cent; MCV, 70.5 cu. \(\mu\); MCH, 20.6 \(\mu\)g.; MCHC, 29.2 per cent; reticulocytes, 5.6 per cent;

From the G. W. Hooper Foundation and the Hematology Unit, Department of Medicine, University of California Medical Center, San Francisco, Calif.; the General Hospital, Kuala Lumpur, Malaysia; and the General Hospital, Penang, Malaysia.

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*Detailed analysis of hemoglobin in the individual cases is discussed under “Hemoglobin Studies.”

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Fig. 1.—Blood smear of Patient #1 showing numerous target cells and thin cells.

WBC, 8700/cu. mm., with PN 75 per cent; Ly. 22 per cent; Mo, 3 per cent; platelets, 130,000/cu. mm.; anisocytosis and poikilocytosis. Many target cells were seen (Fig. 1). Red blood cell fragility in hypotonic saline solutions was much decreased. Hemolysis started at 0.36 per cent and was complete at 0.12 per cent. Intracellular crystals, usually seen in red blood cells containing Hb H, were clearly seen in brilliant cresyl blue preparations. Alkali-resistant hemoglobin was 5.7 per cent of the total amount of hemoglobin. Plasma bilirubin of the indirect type was increased. Serum iron was normal, and the direct Coombs' test was negative. Malarial parasites were not seen. The urine contained increased amounts of urobilin and urobilinogen. No ova were found in the feces. The patient was discharged from the hospital but readmitted in April of the same year. Her clinical and hematologic findings were essentially the same as upon her first admission. X-ray examination of the skull, long bones, pelvis, and spine revealed no abnormalities.

Patient #2, Y. A. C., an 18-year-old Chinese and brother of Y. K. N., was known to suffer from recurrent jaundice. When examined on April 8, 1964, he indeed appeared icteric and slightly anemic. The spleen was palpable three fingers and the liver two fingers below the respective costal margins; heart and lungs were normal. Hematologic data were: Hb, 10.8 Gm./100 ml.; RBC, 5.30 million/cu. mm.; PCV, 34.5 per cent; MCV, 65.1 cu. μ; MCH, 20.4 μg.; MCHC, 31.3 per cent; WBC, 15,000/cu. mm.; platelets, 315,000/cu. mm.; reticulocytes, 3.2 per cent. The red blood cells showed anisocytosis and poikilocytosis with target cells. Intracellular crystals were visible in the erythrocytes in brilliant cresyl blue preparations. Osmotic fragility of the erythrocytes to hypotonic saline solutions was decreased. Hemolysis started at 0.40 per cent and was complete at 0.12 per cent. Alkali-resistant hemoglobin was 4.7 per cent of the total amount of hemoglobin.

Patient #3, Y. H. S., a 14-year-old boy, another brother of Patient #1, also complained of weakness and pallor. Both spleen and liver were enlarged three fingers below the costal margin; other physical findings were normal. Hematologic data were: Hb, 10.0 Gm./100 ml.; RBC, 4.96 million/cu. mm.; PCV, 36.0 per cent; MCV, 72.6 cu. μ; MCH, 20.2 μg.; MCHC, 27.8 per cent; WBC, normal and differential count normal; platelets, normal; reticulocyte count, 4.0 per cent; with 2 normoblasts/100 leukocytes in the peripheral blood. Saline fragility of red blood cells was much decreased. Hemolysis started at 0.36 per cent and was complete at 0.12 per cent. Result of test for intracellular crystals was positive. Alkali-resistant hemoglobin was 1.6 per cent of the total amount of hemoglobin. Serum bilirubin of the indirect type was increased.

The father of these three patients was asymptomatic. His hemoglobin level was 12.1 Gm./100 ml.; microcytosis was definite; fragility of the erythrocytes was slightly decreased;
no intraerythrocytic crystals were seen. Electrophoresis did not show abnormal hemoglobin. The Hb A₂ component examined by paper electrophoresis was not increased; alkali-resistant hemoglobin was within normal limits. Serum iron and serum bilirubin were normal. The mother was also asymptomatic and not anemic. Spleen and liver were not enlarged. Hematologic findings were all within normal limits and intraerythrocytic crystals were not visible. Hemoglobin analysis by paper electrophoresis and chromatography revealed the presence of Hb A and Hb Q. Alkali-resistant hemoglobin and Hb A₂ were not increased; serum iron and serum bilirubin levels were normal.

Patient #4, T. C. L., a 31-year-old Chinese man, was known to have suffered for a long time from recurrent fever, jaundice and anemia, and had been repeatedly admitted to the General Hospital, Penang, for anemia, jaundice, and hepatosplenomegaly. His hemoglobin level on those occasions was around 30 to 40 per cent Sahli with reticulocytosis. Hemoglobin level when he was examined April 19, 1963 was as low as 3.2 Gm./100 ml. Peripheral blood repeatedly showed pronounced anisocytosis and poikilocytosis. Microcytosis, with hypochromia of the red blood cells and target cells, was evident. White blood cells and platelets were normal. Fragility of the red blood cells to hypotonic saline solutions was decreased. Coombs' tests gave negative results. Serum bilirubin usually was about 2 to 3 mg./100 ml. Serum iron examined May 21, 1964 was 280 μg./100 ml.; blood urea was normal; LE cells were not found. Bone marrow was hyperactive and normoblastic. The patient did not respond to any hematinic or to prednisolone and was given more than 10 pints of blood on different occasions. Therefore a blood sample was sent to the Institute for Medical Research, Kuala Lumpur, for further analysis.

Findings revealed: Hemoglobin level was 5.4 Gm./100 ml.; peripheral blood smear showed anisocytosis and poikilocytosis with target cells and normoblasts; reticulocyte count was definitely increased; alkali-resistant hemoglobin was within normal limits. Because of a small clot in the blood sample, no reliable hematologic indices could be obtained.

The patient had no siblings. His father had died, and his mother could not be contacted.

Hemoglobin Studies

In patients 1, 2 and 3, hemoglobin analysis by paper electrophoresis at pH 8.6 showed a major component with the mobility of standard Hb Q and slightly slower than normal adult Hb A but definitely faster than Hb S, and a fast-moving minor component with the mobility of Hb H. At pH 6.5 the minor component was clearly separated from the major and migrated to the cathode; the major component did not separate from Hb A (Fig. 2). Ion-exchange chromatography, using IRC-50 and citrate buffer pH 6.0, revealed two com-
ponents, one major high up in the column and one minor that migrated downward, resembling the migration of Hb H; no Hb A was visible. When standard Hb A + Q was added to the hemolysate, a line in the position of Hb A appeared between the major and minor components, although the Hb Q in the added standard did not separate from the major component at the top of the column. The mobility of Hb G, an abnormal hemoglobin also found in the Chinese, resembles that of Hb Q on paper electrophoresis at pH 8.6, but on IRC-50 chromatography it is much greater than Hb Q and can easily be differentiated from Hb Q. Hb L has a mobility only slightly slower than Hb Q on IRC-50 column chromatography and slower than Hb Q on paper electrophoresis at pH 8.6. With ion-exchange chromatography it should have separated from the standard Hb Q in the addition experiment. We therefore concluded that the major and minor components in the patients were respectively Hb Q and Hb H. The presence of Hb H in the hemolysate is consistent with the finding of intracellular crystals in the red blood cells of the patients. Vertical starch-gel electrophoresis in discontinuous tris-citrate-borate buffer showed a major component resembling Hb Q in mobility and a fast-moving minor component having the mobility of Hb H. No Hb A was observed in cases 1, 2 and 3. Hb A2 was not visible but a slower component was demonstrated when the starch gel was stained with benzidine. Migration of this slow-moving component was as much behind Hb A2 as Hb Q was behind Hb A. Unfortunately, by the time our starch-gel electrophoretic method was established, the hemoglobin solutions kept in the freezer were rather old. Attempts to obtain new blood samples from this family failed. Old normal adult hemolysates of the same age, however, did not show this component, but the hemolysates of all four of our patients did. Analysis by paper electrophoresis and chromatography of the hemolysate of Patient #4 (T. C. L.) showed the presence of Hb A in addition to Hb Q and H. He was given a transfusion, however, shortly before blood examination. Starch-gel electrophoresis of a rather old hemoglobin solution kept in the freezer showed Hb A and Hb H in addition to Hb Q, also the slow-moving hemoglobin component that migrated behind Hb A2. Hb A2 was not at all or barely visible. Fortunately we later obtained a fresh blood sample from Patient #4, which was sent by airmail in acid-citrate-dextrose-inosine solution from Penang to San Francisco and arrived in good condition. This time, however, it was obtained long after any blood transfusion had been given, and starch-gel electrophoretic study of this sample did not show the presence of Hb A. A hemoglobin component slower than Hb A2 was clearly seen in this hemolysate as well as Hb Q and Hb H (Fig. 3). Its mobility at pH 8.6 was as much behind that of Hb A2 as Hb Q was behind Hb A. It was slightly more anodic than Hb B2 and had the same mobility as the slow-moving component seen in the older blood hemolysates of all four patients. This component is probably the same as that described by Dormandi et al. Hb A and Hb A2 were not visible. The alkali-resistant hemoglobin was 1.7 per cent of the total amount of hemoglobin. On starch-gel electrophoresis, using tris-EDTA-borate buffer pH 8.4, the fast-moving hemo-
Fig. 3.—Starch-gel electrophoresis in tris-EDTA-borate buffer pH 8.4 showing the hemolysate of case 4 compared with the hemolysates of normal adult controls, a Hb S trait carrier and a Hb B2 carrier. Note the slow-moving component in the patient which migrated behind Hb A2 and the absence of Hb A2 and Hb A. Benzidine stain.

globin appeared heterogeneous and consisted of a well-defined spot and another more cathodic diffuse spot (Fig. 3). The latter's mobility resembled that of “Bart’s” hemoglobin. This diffuse spot was clearly seen only after benzidine stain, indicating that the amount present was small. In addition to these components, a faint shadow appeared in front of the sharply defined spot. This pattern of the fast-moving hemoglobin complex was also noticed in a standard hemolysate from Hb H disease showing typical intracellular crystals not associated with Hb Q. It was noticed in all four patients that after the hemolysates were prepared and filtered a precipitate formed again, after standing, in the originally clear hemoglobin solution. This precipitate probably consisted of denatured Hb H.

Study of polypeptide chains in cases 1, 2 and 3 showed the presence of normal βA-chains and abnormal αQ-chains, without detectable αA-chains (Fig. 4). In Patient #4, study of polypeptide chains showed the presence of normal αA-chains as well as normal βA-chains and abnormal αQ-chains in the sample obtained after blood transfusion, but no αA-chains were demonstrable in the sample obtained after a long period without transfusion.

The hemolysate of the mother of Patients 1, 2 and 3, when examined by paper electrophoresis and by ion-exchange chromatography, showed the presence of Hb A and abnormal Hb Q. No increase of Hb A2 was found by paper electrophoresis. Alkali-resistant hemoglobin was normal. Hemolysate of the father contained only Hb A, no increase of Hb A2 or Hb F. The parents’
Fig. 4.—Starch-gel electrophoresis in urea-veronal buffer pH 8.0 of the polypeptide chains of the hemoglobin of Patients 1, 2, and 3, showing that the Hb Q in the patients had abnormal α-chains. The β-chains of Hb H were of the normal type and were found in the same position as normal β-chains of Hb A.

The hemolysates were not available for study when our starch-gel electrophoretic method was established.

**Discussion**

All four patients described showed symptoms of chronic hemolytic anemia with jaundice and hepatosplenomegaly. The reticulocyte count was increased and intracellular crystals were seen in the erythrocytes of all four. Hemoglobin analysis revealed the presence of Hb Q and Hb H and a component moving more slowly than Hb A₂. Hb Q was present in the mother of the three patients who were siblings, but no abnormal hemoglobin was detected in the father. Alkali-resistant hemoglobin and Hb A₂ were not increased in either parent. These findings correspond with those of previously reported cases of Hb Q-H disease, except that in the earlier cases electrophoretic studies were done on paper only, not on starch gel; therefore the component moving behind Hb A₂ at alkaline pH was not detected. A similar slow-moving hemoglobin component that migrated behind Hb A₂ and was called Hb Q₂ was described by Dormandi et al. in a child having Hb Q in association with Hb “Bart’s.”

The human hemoglobin molecule consists of four polypeptide chains, of which each two are identical. Normal Hb A consists of two normal αₐ-chains and two normal βₐ-chains (Hb αₐβₐ); Hb F of two normal αₐ-chains and two normal γₐ-chains (Hb αₐγₐ); and Hb A₂ of two normal αₐ-chains and two normal δₐ-chains (Hb αₐδₐ). The synthesis of different polypeptide chains is controlled by separate structural genes in the chromosomes. Mutation can occur in each structural gene, resulting in the synthesis of an abnormal polypeptide chain and consequently in the formation of an abnormal hemoglobin. For instance, Hb Q is the result of a mutation of the gene for α-chain...
leading to the synthesis of abnormal \( \alpha^\text{Q} \)-chains. The \( \alpha^\text{Q} \)-chains combine with normal \( \beta^\text{A} \)-chains to form abnormal Hb \( \alpha^\text{Q} \beta^\text{A} \), i.e., Hb Q. Based on the idea of Itano,\(^9\) Ingram and Stretton\(^10\) put forward their amino-acid substitution hypothesis in which they proposed that thalassemia, in its typical form, is a mutation of the \( \alpha \) or the \( \beta \) gene of the adult series. However, the consequent amino-acid alteration does not change the electrophoretic behavior of the hemoglobin, or the alteration is so drastic that the particular chain is not made at all. Therefore they divided the thalassemias into two classes—\( \alpha \)-thalassemia and \( \beta \)-thalassemia—affecting the \( \alpha \) or the \( \beta \) gene. As an alternative they put forward the so-called “tap” hypothesis. This suggested that the defect in thalassemia is not a hidden amino-acid substitution but a defect in activating or inactivating of the \( \alpha \) or \( \beta \) chain genes. This results in deficient synthesis of the \( \alpha \) or \( \beta \) chains, although the \( \alpha \) and \( \beta \) chain genes in themselves are assumed to be perfectly normal. The defect in activating them might be expected to range from zero to complete shut off, producing a number of intermediate steps. In \( \alpha \)-thalassemia, then, the production of \( \alpha \)-chains is deficient; in \( \beta \)-thalassemia, the production of \( \beta \)-chains is deficient. Decreased production of \( \alpha \)-chains affects all three types of hemoglobin physiologically found in man—namely, Hb A, Hb F, and Hb A\(_2\), since all three contain \( \alpha \)-chains. Depression of \( \alpha \)-chain formation in the adult may lead to an excess of \( \beta \)-chains that form Hb \( \beta^\text{A} \), that is Hb H. In the heterozygous condition, however, depression is only slight, due to the presence of a normal gene in the normal chromosome, and can be entirely compensated. Hb H is therefore not found in the \( \alpha \)-thalassemia trait condition. Occasionally, intracellular crystals in the red blood cells are seen in \( \alpha \)-thalassemia trait carriers and are thought to represent denatured Hb H. In severe homozygous \( \alpha \)-thalassemia both genes that control the quantitative production of \( \alpha \)-chains are defective and the result is that in the fetal and neonatal periods a severe deficiency of \( \alpha \)-chain production leads to a large excess of \( \gamma \)-chains, because in this period \( \beta \)-chains are produced only in small amounts and \( \gamma \)-chains are the ones predominantly synthesized. This excess of \( \gamma \)-chains tetramerizes to form Hb \( \gamma^\text{A} \), known as Hb “Bart’s.” The latter seems unsuitable for the fetal period and is usually incompatible with life.\(^11\) In addition to the \( \alpha \)-thalassemia trait, which does not lead to the production of an appreciable amount of Hb H in the blood, and the severe homozygous \( \alpha \)-thalassemia that apparently leads to hydrops fetalis and to death in utero, cases of congenital hemolytic anemia have been described—the so-called Hb H disease associated with the presence of an appreciable amount of Hb H. The presence of this Hb H in the blood is apparently caused by a deficiency of \( \alpha \)-chain synthesis. In such cases the parents usually do not carry Hb H; the exact basis of inheritance of this disease is still obscure. Several possibilities have been put forward to explain this condition, for instance that Hb H disease may be the result of the interaction of two genes of a mild type of \( \alpha \)-thalassemia\(^10\) or the result of the interaction of a mild with a severe type of \( \alpha \)-thalassemia;\(^12\) that in Hb H disease, the \( \beta \) chains of the Hb H might have a nonelectrophoretic change such that production of this chain is increased or
such that, when the proportion is increased due to an α-thalassemia, the β\text{H}
chains polymerize preferentially.\textsuperscript{10}

As suggested in previous publications,\textsuperscript{2,3} Hb Q-H disease is probably the
result of heterozygosity for Hb Q, an α-chain variant\textsuperscript{4,18} and α-thalassemia.
α-thalassemia leads to deficient production of normal α\text{A}-chains and in the adult
a combination of the genes for Hb Q and α-thalassemia may result in complete
absence of normal α\text{A}-chains, and the available β\text{A}-chains may combine with
the α\text{Q}-chains to form Hb Q (α\text{2Q}/β\text{2A}). No Hb A is then found. α\text{Q}-
chains may be expected to combine with δ\text{A}-chains to form Hb α\text{Q}δ\text{A}.
The slow-moving minor hemoglobin component found in all four patients in
this study probably represents Hb α\text{Q}δ\text{A}. No Hb A and no Hb A\text{2} were
present in their blood unless blood transfusions had been given. The findings
in our patients and in the family of three of them therefore conform to the
pattern of Hb Q-α thalassemia. The fast-moving hemoglobin was not homo-
genous on starch-gel electrophoresis, and the more cathodic hemoglobin of the
fast-moving components had the mobility of Hb “Bart’s.” The same in-
homogeneity of the fast-moving hemoglobin was seen on starch-gel electro-
phoresis in a standard hemolysate from a patient with Hb H disease, with
typical intraerythrocytic crystals and not associated with Hb Q. Fessas\textsuperscript{14} and
Huelns et al.\textsuperscript{15} also observed inhomogeneity of the fast-moving hemoglobin in
Hb H disease by starch-gel electrophoresis. It consisted of Hb H and Hb
“Bart’s.” Whether the additional shadow in front of the more anodic compo-
nent is an artifact cannot be determined. Inhomogeneity of the fast-moving
hemoglobin can sometimes also be demonstrated on paper electrophoresis,
although this method is not always successful. Lack of α\text{A}-chains also may lead
to the formation of a small amount of Hb “Bart’s,” that is, Hb γ\text{t}. Theoretically
the possibility of α\text{Q}-chains to combine with γ\text{t}-chains to form Hb α\text{Q}γ\text{t}
and excess δ-chains to form Hb δ\text{t} might be expected, but we did not find evi-
dence of this. Study of the hemoglobin polypeptide chains in the four patients
demonstrated that Hb Q in these patients was indeed an α-chain variant. No
α\text{A}-chains were seen in the blood of the first three. Normal α\text{A}-chains were
present in the blood of the fourth patient after transfusion but only when the
transfusion was relatively recent. The mother had the Hb Q trait and the
father was heterozygous for α-thalassemia, as suggested by the microcytosis,
the diminished osmotic fragility of the erythrocytes, and the normal levels of
Hb A\text{2} and Hb F. As previously mentioned, deficiency of α-chain synthesis is
slight in the α-thalassemia trait and does not give rise to formation of an
appreciable amount of Hb H.

The previously reported cases of Hb Q-H disease had normocytic or slightly
macrocytic anemia. The patients of Lie-Injo and Hart had been splenecto-
mized and their blood samples had been transported a long distance prior to
examination. It is well known that after splenectomy the MCV of the erythro-
cytes increases. Furthermore, the possibility of changes in hematologic indices
during transport cannot be excluded. In the case reported by Vella et al.\textsuperscript{1}
the anemia was hypochromic normocytic. In the patients we now describe, on the
other hand, there was definite microcytosis. None had undergone splenectomy and in three of the patients hematologic examinations were made immediately after blood was drawn. Before common hematologic characteristics of this disease can be established, however, more cases must be studied.

Large, round and peculiar intraerythrocytic crystals that were thought to represent denatured Hb H have been observed after splenectomy in cases of Hb H disease\textsuperscript{16,17} and Hb Q-H disease.\textsuperscript{2} These particular large intracellular bodies were not seen in the cases reported in this paper, but only small intraerythrocytic crystals were present. Again this suggests that large round inclusion bodies occur only after splenectomy, probably due to the absence of the spleen capable of eliminating such cells from the circulating blood.

**Summary**

Case reports of four patients, all Chinese, with Hb Q-H disease—also called Hb Q-\(\alpha\) thalassemia—are presented. Three were siblings. Symptoms of chronic hemolytic anemia with jaundice and hepatosplenomegaly were present in all four subjects. The red blood cells were microcytic. Slight hypochromia was present in three of the cases. Poikilo- and anisocytosis with target cells and small intraerythrocytic crystals were found in the blood. Starch-gel electrophoresis revealed the presence of a large amount of Hb Q, a small amount of Hb H, and a minor slow-moving hemoglobin component with a mobility as much behind Hb A\(_2\) as Hb Q was behind Hb A. A small amount of Hb “Bart’s” was probably also present. The minor slow-moving component was thought to represent Hb \(\alpha_2^6\delta_2\alpha\) or Hb Q\(_2\). Hb A and Hb A\(_2\) were not seen except after recent blood transfusion. Study of hemoglobin polypeptide chains showed the presence of normal \(\beta\)-chains and abnormal \(\alpha\)-chains, without demonstrable \(\alpha\)-chains in the first three patients. In Patient #4 normal \(\alpha\)-chains were demonstrable only after recent blood transfusion. The mother of the three siblings was heterozygous for Hb A; the father had \(\alpha\)-thalassemia trait.

**Summario in Interlingua**

Es presentate reportos del casos de quatro patientes, omnes chinese, con morbo a hemoglobina Q-H, etiam designate como thalassemia a hemoglobina Q-\(\alpha\). Tres del patientes eseva fraternos. Symptomata de chronic anemia hemolytico con jalnessa e hepatosplenomegalia eseva presente in omne le quatro subjectos. Le erythrocytos eseva microcytic. Leve grados de hypochromia eseva presente in tres. Poikilocytosis e anisocytosis con cellulas “oculo de ave” e micre crystallos intraerythrocytic eseva trovate in le sanguine. Electrophorese a gel con amylo revelava le presentia de un grande quantitate de hemoglobina Q, de un micre quantitate de hemoglobina H, e de un minor componente hemoglobinico lente con un mobilitate inferior a illo de hemoglobina A\(_2\) al mesme grado al que le mobilitate de hemoglobina Q eseva inferior a illo de hemoglobina A. Un micre quantitate de hemoglobina “Bart’s” eseva probablemente etiam presente. Le lente componente minor eseva considerate como hemoglobina \(\alpha_2^6\delta_2\alpha\) o hemoglobina Q\(_2\). Eses seva trovate nulle tracia de hemoglobina A e hemoglobina A\(_2\) excepte post recente transfusiones de sanguine. Le studio de catenas de polypeptida hemoglobinico monstrava
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le presentia de normal catenas $\beta^A$ e anormal catenas $\alpha^q$, sin demonstrabile catenas $\alpha^A$ in le prime tres patientes. In le quarte patiente, normal catenas $\alpha^A$ esseva demonstrabile solmente post recente transfusiones de sanguine. Le matre del tres fraternos esseva heterozygotic pro hemoglobina $A$; le patre habeva un character genic de thalassemia $\alpha$.

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LIE-INJO LUAN ENG, R. P. PILLAY and V. THURAISINGHAM