AN UNUSUAL CASE OF HEMOGLOBIN BART'S HYDROPS FETALIS

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A baby with alpha-chain thalassemia hydrops fetalis was born to an Iraqian Jewish couple of Iraqi-Kurdish extraction. Hemoglobin Bart's constituted only 40% of the total hemoglobin, much less than usually found in alpha-thalassemia hydrops fetalis.
That this is a particular expression of hemoglobin H disease is considered. The likelihood of two alpha-chain loci, rather than one alpha-chain locus, in this family, is also discussed.

INTRODUCTION

Many cases of nonimmunological hydrops fetalis associated with alpha-chain thalassemia have been described (Lie-Injo and Jo Bwan Hie 1960, Lie-Injo and Lie Hong Gie 1961, Lie-Injo 1962, Lie-Injo et al. 1962, Banwell and Strickland 1964, Diamond et al. 1965, Pearson et al. 1965, Kan et al. 1967).

The clinical and laboratory findings in these cases are generally the same. Most of them occur in Southeast Asian families; a case has also been found among Greek Cypriots (Diamond et al. 1965).

We examined a baby suffering from alpha-thalassemia hydrops fetalis, born to an Iraqian Jewish couple. This is the first case reported in this ethnic group. The occurrence of alpha-thalassemia hydrops fetalis might be expected in this community in view of the high incidence of Hb Bart's found in Iraqian Jewish newborns (Halbrecht and Ben-Porat 1967, Zaizov and Matoth 1972). This case is thought to be of particular interest because it presents all the features of the typical nonimmunological hydrops fetalis, except that the proportion of Hb Bart's, instead of being 75%-100% of the total hemoglobin as in all the previously reported cases, is only 38.2%.

CASE REPORT

A baby girl with the typical clinical features of hydrops fetalis was born to an Iraqian Jewish couple of Iraqi-Kurdish extraction after an uncomplicated pregnancy of 34 weeks, during which the mother, aged 21 years, was healthy.

This was the second child born to this couple. Their first child is a healthy boy born 2½ years earlier. The wife and husband are related; the husband's mother and wife's father are first cousins. The delivery was spontaneous and hydramnion was present. The weight of the hydropic infant was 2770 g, its length 49 cm. The placenta was large, pale, and friable. The baby was pale, respiration was difficult, and it died 30 minutes after birth.

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At autopsy, marked hepatomegaly was evident; the liver weighed 250 g. The spleen weighed 15 g. No ascites was found. The heart was normal. There were no glomerular lesions, and pancreatic islets were normal. All blood vessels were normal. The brain was edematous, 280 g weight, and an intracranial hemorrhage was present.

Blood samples were obtained from the umbilical cord at the time of the delivery. Routine hematological and chemical investigations were carried out by standard methods used at our hospital. The blood was somewhat hemolytic.

RESULTS

Total serum bilirubin was 3 mg%, direct 0.6 mg%, indirect 2.4 mg%. The direct Coomb's test was negative. Total protein, cholesterol, total lipids, alkali phosphatase, cholinesterase, transaminase (GPT), creatinephosphokinase, and isocitricdehydrogenase, were in the normal range. Transaminase (GOT), aldolase, and lactic dehydrogenase (LDH) were elevated. Agar gel electrophoresis for LDH isoenzymes showed LDH_4 and LDH_5 to be significantly increased. The blood group was A, Rh positive. The blood smear showed macrocytosis, anisocytosis, poichilocytosis, hypochromia, polychromasia, target cells, and a large number of erythroblasts at all stages of maturation (Fig. 1). Reticulocyte count was 4%. Hemoglobin H inclusion bodies appeared in a very few red blood cells after incubation with Brilliant cresyl blue. On electrophoresis, hemoglobin was separated into three components: Hb A, Hb F, and Hb Bart's, recognizable on cellulose acetate in barbiturate buffer pH 8.6, in Tris buffer pH 8.9, and in phosphate buffer pH 6.5. Quantification of Hb Bart's was made eluting fractions after electrophoresis on cellulose acetate in barbiturate buffer, and by reading the optical density of each fraction at 405 mu. The percentage of Hb Bart's in the hydropic baby was 38.2%.

The other members of the family: mother, father, and first child were also examined. Findings on two different occasions, one after the birth of the hydropic baby, the other a few years later, are summarized in Table 1. All tests for diabetes mellitus in the mother were negative. She did not receive any transfusion.

Since Hb H inclusion bodies were present in both the father and mother of the hydropic baby and in their first son, it is reasonable to conclude that mother, father, and first son, present alpha-thalassemia. In addition, the father had a Hb A_2 level in the lower limit of normalcy and a decreased osmotic fragility.

In the mother, blood changes were not very significant, while the blood picture in both father and son was very suggestive of thalassemia, even though in the son insufficient blood was available and only a few tests were performed. The count of cells with Hb H inclusion bodies was only one out of every four to five thousand red blood cells in the mother. In the father only a little higher count was found. Diagnosis of the " classical " alpha-thalassemia trait is generally accepted even with Hb H inclusion bodies in only a few red blood cells and only minor morphological changes of the red cells. Both parents, therefore, exhibit the " classical " alpha-thalassemia trait.

DISCUSSION

There may be many causes for hydrops fetalis (Driscoll 1966): maternal sentitization by a fetal erythrocyte antigen (immunological hydrops), thalassemia homozygous, twin transfusion syndrome (for the recipient twin), cystic adenomatoid malformation of the lung, achondro-

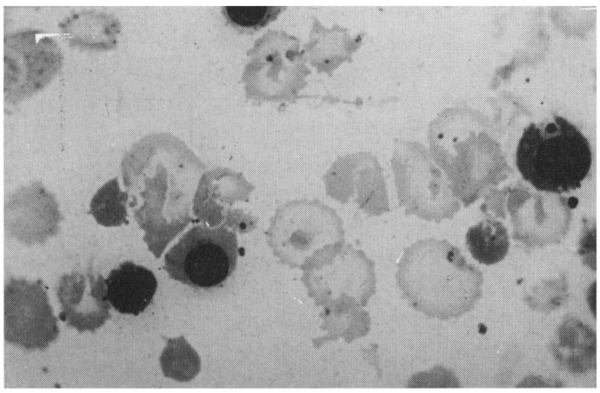

Fig. 1. Blood smear of the hydropic baby.

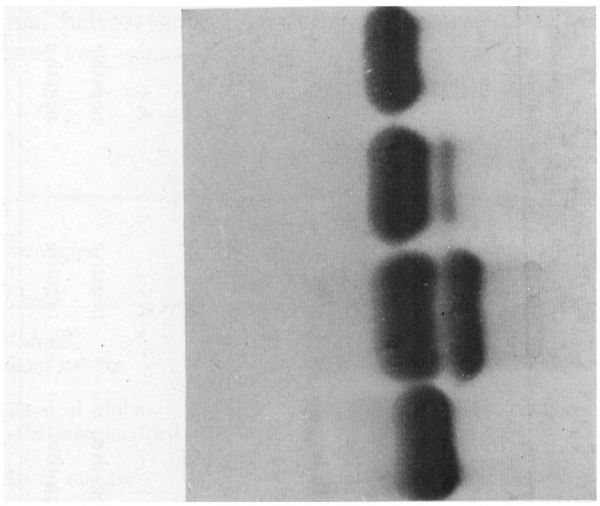

Fig. 2. Cellulose acetate electrophoresis in barbiturate buffer. *From top to bottom*: Normal newborn; Newborn with 9% Hb Bart's; The hydropic baby; Normal adult.

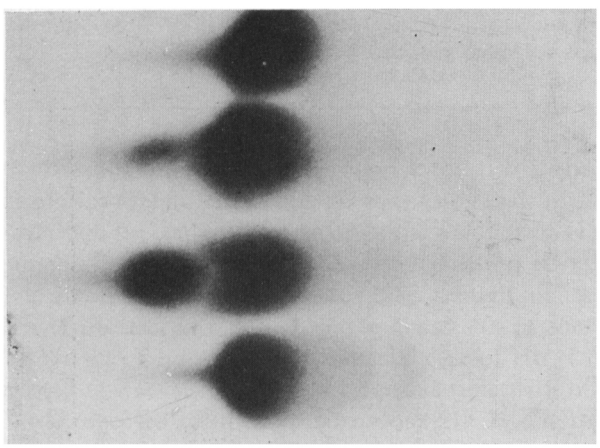

Fig. 3. Paper electrophoresis in barbiturate buffer. *From top to bottom*: Normal newborn; Newborn with 9% Hb Bart's; The hydropic baby; Normal adult.

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TABLE 1

HEMATOLOGICAL AND CHEMICAL INVESTIGATIONS ON THE PATIENTS' RELATIVES AT THE TIME OF THE PATIENT'S BIRTH (I) AND FEW YEARS LATER (II)

	Mother		Father		Sibling (Brother)	
	I	II	I	II	I	II
Indirect Coomb's test	Negative	—	—	—	—	—
Hemoglobin g% ml	11.7	11.5	13.2	13.5	11.0	11.1
Hematocrit (Hmtc) %	38	41	45	46	41	42
RBC/mm²	4,800,000	4,900,000	5,600,000	5,800,000	5,200,000	5,300,000
Reticulocytes count %	1.0	0.8	1.5	0.7	0.7	0.1
Peripheral blood smear	very slight anisopoichilocytosis	slight hypochromia, some macrocytes	anisocytosis microcytosis spherocytosis	microcytosis, slight anisopoichilocytosis, some spherocytes	microcytosis, slight hypochromia, slight poichilocytosis	microanisocytosis, hypochromia, some target cells
Red cells Hb H inclusion bodies	very rare	very rare	rare	very rare	rare	rare
Hb A_2% (normal 1.8-3.4)	2.8	2.9	1.9	1.9		
Alkali resistant Hb%	1.4	1.3	1.8	1.2		
Abnormal Hb	not found	not found	not found	not found	not found	—
Osmotic fragility	slightly decreased	slightly decreased	decreased	decreased	—	—
Iron	normal	normal	normal	normal	normal	normal
Blood group	B+	B+	A+	A+	AB+	AB+
Kahn	negative	negative	negative	negative	—	—
VDRL	negative	negative	negative	negative	—	—

plasia, multiple congenital anomalies (particularly cardiac); maternal diabetes mellitus, fetal infection (Citomegalovirus-Toxoplasma, Treponema Pallidus), congenital nephrosis, renal vein thrombosis, chorionic vein thrombosis, umbilical vein thrombosis, prenatal closure of foramen ovale.

In our case isoimmunization was excluded because the direct Coomb's test was negative, jaundice was not severe (bilirubin did not exceed 3 mg/100 ml), and hepatomegaly was much more pronounced than splenomegaly. The autopsy of the baby and the large quantity of Hb Bart's in its blood, in addition to the laboratory findings in the family, lead us to think that only alpha-chain thalassemia could be the causative factor.

Two basic models have been proposed to explain the genetics of alpha-thalassemia diseases. A one-locus model requires the assumption of one normal and two different mutant alleles, severe (alpha-thalassemia$_1$), and mild (alpha-thalassemia$_2$). A two-loci model suggests that normal and mutant alleles are possible at each locus.

According to the one locus theory (Na-Nakorn et al. 1969) the parents are alpha-thalassemia$_1$ heterozygous. According to the two-loci theory (Kattamis and Lehmann 1970) they have two genes for alpha-thalassemia (see Table 2).

TABLE 2

ONE- AND TWO-LOCI MODELS

Phenotype	Hb Bart's at birth (%)	Hematological findings	Genotype	
			One-locus	Two loci
Normal	0	Normal	N/N	No gene affected
Silent carrier	~2	No or mild red-blood cell abnormalities	α-thal$_2$/N	1α-thal gene
Classical alpha--thalassemia trait	~5	Rare Hb H inclusion bodies, mild red-blood cell abnormalities	α-thal$_1$/N	2α-thal genes
Hb H disease	~25	Many Hb H inclusion bodies, striking red-blood cell abnormalities	α-thal$_1$/α-thal$_2$	3α-thal genes
Hydrops fetalis	~100	Lethal condition, Hb Bart's and Hb H present, no Hb A, striking red-blood cell abnormalities	α-thal$_1$/α-thal$_1$	4α-thal genes

The possibilities, respectively for the two theories, of alpha-thalassemia$_1$ homozygosity, or of four alpha-thalassemia genes causing hydrops fetalis syndrome, exist for their offspring. Although this baby was hydropic, the amount of Hb Bart's in its blood did not fit with these possibilities because alpha-chain production should have been almost totally depressed. The amount of Hb Bart's in our case, though higher than usually found in newborns carrying Hb H disease, is much closer to that than to the amount found in lethal hydrops fetalis.

We may be dealing with a special case of Hb H disease where Hb Bart's, for some reason, existed at a level too high to be compatible with life. In 1964 Swedish authors (Sjölin et al. 1964) reported on a baby born with Hb H disease. This baby also had many features in common with typical cases of hydrops fetalis (edema, ascites, enlargement of liver and spleen,

and erythroblastosis without isoimmunization), though Hb Bart's constituted only one fifth of the total hemoglobin. In their case, the boy survived the neonatal period.

According to the one-locus theory, both parents in our case are alpha-thalassemia$_1$ heterozygous. Therefore, their offspring may be normal, have an alpha-thalassemia$_1$ trait, or suffer from hydrops fetalis with more than 75% Hb Bart's. The offspring couldn't have Hb H disease because they would have to be double heterozygotes possessing both the severe and the mild gene. The possibility that " classical " alpha-thalassemia trait is the homozygous state for the mild gene has been mentioned, but the findings in the first son are incompatible with the possibility of one of the parents being alpha-thalassemia$_2$ homozygous.

If both parents have two alpha-thalassemia genes and two normal genes, as in the two-loci theory, then their offspring, who may inherit from none to four alpha-thalassemia genes, may be normal, or have a silent, or a " classical " alpha-thalassemia trait, or suffer from either Hb H disease, or hydrops fetalis.

There are reports demonstrating the presence of only one alpha-chain gene in certain populations (Abramson et al. 1969); other reports present genetic and chemical evidence for two unlinked genes (Brimhall et al 1970). It is possible that there are genetic differences in different populations. The possibility also exists that the two genes may be linked (Lehmann 1970).

In our case duplication of the alpha-chain gene should be assumed. Presuming that each locus has its own potential mutation, mild or severe, a rare combination of the affected genes may have been responsible for the significant deficiency of alpha-chains. This caused the 40% Hb Bart's in the baby's blood, and the consequent hydropic state which was incompatible with life.

It should be noted here that one more hydropic baby was born to this couple in another hospital. Unfortunately we were unable to examine it.

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RIASSUNTO

Un Insolito Caso di Idropisia Fetale con Emoglobina Bart

Una coppia ebrea di estrazione curdo-irachena ha concepito un bambino affetto da idropisia fetale con talassemia alfa. L'emoglobina Bart è risultata costituire solo il 40% dell'emoglobina totale, molto meno di quanto si trovi di solito nell'idropisia fetale con talassemia alfa.
Questo caso viene considerato come una particolare espressione della malattia da emoglobina H e viene anche discussa la possibilità che in questa famiglia vi siano due loci della catena alfa, piuttosto che uno solo.

RÉSUMÉ

Un Cas Insolite d'Hydropisie Foetale avec Hémoglobine Bart

Un couple juif d'extraction kurdo-irakienne a conçu un enfant atteint d'hydropisie foetale avec thalassémie alfa. L'hémoglobine Bart ne constituait que le 40% de l'hémoglobine totale, beaucoup moins que la quantité généralement perçue dans l'hydropisie foetale avec thalassémie alfa.
Ce cas est considéré comme une expression particulière de la maladie d'hémoglobine H et l'on discute la possibilité qu'il y ait dans cette famille deux loci de la chaine alpha plutôt qu'un seul.

ZUSAMMENFASSUNG

Ungewöhnlicher Fall von Fötalhydrops mit Hb-Bart

Ein jüdisches Ehepaar kurdisch irakischer Abstammung hatte ein Kind (männl.), das an Fötalhydrops mit alpha-Thalassämie litt, wobei das Hb-Bart nur 40% des Gesamt-Hb betrug, viel weniger also als sonst bei dieser Krankheit.
Der Fall wird als besondere Ausdrucksform der Hb-H-Krankheit angesehen, und man vermutet, dass die alpha-Kette in dieser Familie zwei Loci anstelle von nur einem hat.

Prof. I. Halbrecht, Hasharon Hospital, Petah Tikva, Israel.