CONGENITAL HAEMOLYTIC ANAEMIA WITH NORMAL FRAGILITY OF THE RED BLOOD CELLS

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Case history

The patient is one year and eight months old. The father is healthy ; the mother had a septic infection after the delivery of the second child, which is one month old ; she is still under hospital care. There is no venereal disease or tuberculosis in the family and the Wassermann reaction of both parents is negative. The patient was born at full time with a normal delivery. A few days after birth the parents noticed that the child was extremely pale. They therefore transferred her to a hospital. Blood examination showed a haemoglobin content of only 32 per cent. and 1,900,000 red blood cells per c.mm. The liver and spleen were at that time already enlarged. There had been no disease to account for the anaemia and the white cell count revealed nothing pathological ; a diagnosis was made of congenital anaemia. The child was kept in the hospital for six months and treated with iron, ascorbic acid, ultra-violet radiation and liver preparations. As all these procedures failed to give a therapeutic result, blood transfusions were performed. Altogether, the child received 575 c.cm. of blood in twelve transfusions. The child was discharged from the hospital improved, with a haemoglobin content of 85 per cent. and a red blood count of 4,500,000 per c.mm. The enlargement of the liver and spleen remained unchanged. The child was then sent to an infants' home, where she stayed for four months. After two weeks, it was noticed that the anaemia increased again and a blood count showed a diminution of the red blood cells. For this reason, the parents brought the strikingly pale child to another children's hospital. On admission the child had 41 per cent. haemoglobin and 2,700,000 red blood cells per c.mm. The blood smear, as in former instances, showed only a few normoblasts. The liver was two finger breadths below the costal margin and a firm spleen reached almost to the level of the umbilicus. The child remained in this hospital for four months. She received liver injections without improvement of the anaemia ; only after blood transfusions the child became better. On discharge, the haemoglobin content was 74 per cent., and the red blood cells were three millions. After another four months, on July 7, 1937, the child was admitted under the author's care, again for the reason of her extreme pallor.

On admission, she was fairly well nourished ; she was somewhat small and underweight for her age (8,950 gm.). The skin and mucous membranes were extremely pale. On the lower limbs there were scars of healed impetigo contagiosa. There were no petechiae or other haemorrhages in the skin. The

tonsils were enlarged, but there was no glandular swelling. The liver and spleen were enlarged, being three finger breadths below the costal margin. The spleen was firm. The nervous system was normal; the static functions were developed according to the child's age.

Blood examination showed 45 per cent. haemoglobin and four million red blood cells. The colour index was 0.5; thrombocytes 249,000; reticulocytes, 124 per thousand red cells. There was a marked polychromasia, and anisocytosis and microcytosis. The leucocytes was 18,500 per c.mm.; sedimentation rate, 15 mm. in one hour, 22 mm. in two hours. The bleeding time, coagulation time and the retraction of the blood clot were normal.

The bilirubin of the blood serum was 2.6 mgm. per cent., the serum bilirubin giving only the indirect van den Bergh reaction. Serum protein was 8.12 per cent., non-protein nitrogen 33 mgm. per cent., and blood cholesterol, 120 mgm. per cent. The fragility test of the red blood cells showed haemolysis beginning at 0.47 per cent. sodium chloride solution, which is normal.

Urobilin and urobilinogen were present in the urine, which was otherwise normal. The faeces were of dark-brown colour and normal consistency. The Wassermann reaction was negative. X-ray examination of chest and bones revealed nothing abnormal. The child remained in the ward for two-and-a-half months, feeling well, and taking her food well; she gained 2,500 gm. in weight during that time.

The fragility of the red blood cells was repeatedly checked. As it is evident from table 1, the author, like the other physicians, never found this increased. The bilirubin content of the blood serum, on the other hand, was constantly increased, the level in several investigations ranging from 2.6 to 3.2 mgm. per cent. The blood cholesterol was never increased, repeated examinations showing values between 120 and 160 mgm. per cent. A differential blood count was done almost every second day. A few instances are shown in table 2.

TABLE 1
FRAGILITY OF THE RED BLOOD CELLS

	HAEMOLYSIS BEGINNING AT :			
	0.47 per cent. NaCl solution.			
November 26, 1936	0.44	"	"	"
February 8, 1937	0.45	"	"	"
July 9, 1937	0.42	"	"	"
July 15, 1937	0.47	"	"	"
July 28, 1937	0.40	"	"	"
August 27, 1937	0.37	"	"	"
September 14, 1937				

Beside the hypochromic anaemia, there was a striking and constant increase of the number of the reticulocytes and comparatively high values of leucocytes. Almost every blood examination revealed occasional erythroblasts. The counting of the eosinophils gave peculiar results; whereas the number of the eosinophils during the first two weeks of the child's stay in the ward varied between 1 and 3 per cent., reaching only exceptionally 6 per cent., there occurred a sudden rise during the third week. For the last two months the eosinophils ranged between 17 and 21 per cent.

Repeated stool examinations for ova were always negative. There were no signs of allergy, so that there was no obvious reason for the high eosinophil count.

As far as the clinical course is concerned, the fever occurring four times during the two-and-one-half months was the most remarkable phenomenon. Within two days the temperature reached 39° to 40.6° C.; after two to three

days, it fell spontaneously. These febrile attacks are emphasized as in no instance could any pathological cause be found to explain them. It is noticeable that during the fever period the blood examination did not show essential changes, nor acceleration of the sedimentation rate. The latter varied from 15–16 mm. in one hour and 22–37 mm. in two hours with normal temperature and was 14–33 mm. during the attacks of fever.

TABLE 2
BLOOD COUNTS

	1935 NOV. 26	1936 OCT. 4	1937 JAN. 24	1937 JULY 4	1937 JULY 14	1937 AUG. 14	1937 SEPT. 7
	3 WEEKS OLD	11 MONTHS OLD	14 MONTHS OLD	20 MONTHS OLD	—	—	22 MONTHS OLD
Haemoglobin, per cent.	32	35	41	45	47	50	52
Red blood cells, millions per c.mm.	1.9	2.4	2.1	4	3.4	3.56	3.89
Colour-index	0.84	0.72	0.97	0.56	0.69	0.71	0.68
Reticulocytes	—	590	—	—	124	126	219
Normoblasts	1	4	5	—	1	1	2
White blood cells, per c.mm.	15,800	14,000	14,000	18,500	13,500	19,800	22,100
Lymphocytes, per cent.	58	61	—	55	52	41	49
Monocytes, per cent. . .	—	3	—	—	1	—	—
Juvenile cells, per cent. .	1	—	—	1	1	1	—
Rodlike cells, per cent. .	15	2	—	2	3	—	—
Polymorphonuclears, per cent.	23	33	—	38	40	40	30
Eosinophils, per cent. . .	3	—	—	3	3	19	21
Basophils, per cent. . . .	—	1	—	1	—	—	—
Plasma cells,	—	—	—	—	—	—	—
Thrombocytes	—	—	—	146,280	249,000	195,000	248,000

TABLE 3

	JULY 8, 1937 TEMPERATURE 36.6° C.		JULY 15, 1937 TEMPERATURE 38.9° C.	
Haemoglobin, per cent.	..	..	45	47
Erythrocytes, millions per c.mm.	..	..	4	3.4
Leucocytes, per c.mm.	..	..	18,500	13,500
Lymphocytes, per cent.	..	..	55	52
Juvenile cells, per cent.	..	..	1	—
Rodlike cells, per cent.	..	..	2	3
Polymorphonuclears, per cent.	..	..	38	40
Eosinophils, per cent.	..	..	3	3
Basophils, per cent.	..	..	1	—
Monocytes, per cent.	..	..	—	1
Reticulocytes, per 1,000 white cells	..	..	—	124
Thrombocytes	..	..	249,000	195,000
Sedimentation time	..	..	16/37 mm.	14/33 mm.

Comment

In the first days of life, the infant already showed a severe hypochromic anaemia with swelling of the liver and spleen. In the blood serum the bilirubin

content was increased, the bilirubin giving only the indirect van den Bergh reaction. No bilirubin was found in the urine, which, however, contained abundant urobilin and urobilinogen. The stools were dark brown. The reticulocytes were markedly increased in number. In vital-stained smears a large number of microcytes were found. The fragility test of the erythrocytes against sodium chloride solution was found constantly normal. Finally, there occurred periodically marked sudden rises of the temperature without changes of the white blood cells or increase of the sedimentation rate.

According to these findings, a so-called primary anaemia of the new-born, as described by Ecklin, E. Bonar-Barnet, R. Canina, E. W. Ehrmann, J. A. Foot, F. Gelston, and E. Sappington, McClelland, E. Stransky, and others, can be ruled out. All the results rather speak in favour of an increased haemolysis causing the anaemia, so that the case appears to be one of congenital haemolytic anaemia in an infant. In this connexion the above-mentioned periodical attacks of fever are remarkable. Stress is laid on them because Grob (1934) has described unexplained high temperatures as occasionally the sole symptom of a crisis in haemolytic jaundice. As in this case, Grob found that during these rises of temperature leucocytosis did not occur and the sedimentation time remained unaltered. He also found no shift in the albumin-globulin ratio of the blood plasma. It is, therefore, justifiable to exclude an infectious origin of the fever. Grob claims that it might possibly be a reaction similar to that observed with resorption of haemorrhages.

Haemolytic anaemia in new-born children has been seen repeatedly and described. However, this case is different from all the others on account of the absence of one of the main symptoms of haemolytic anaemia, namely, of the increased fragility of the erythrocytes. I have had the opportunity of observing in my ward of the Children's Hospital of the Berlin University two similar cases in infants. In these infants also I found all the symptoms of haemolytic anaemia except for the increased fragility. I have not been able to trace similar observations in the paediatric literature; whereas, A. Adler (1927) has described three adolescents of fifteen, sixteen and nineteen years respectively and a forty-years-old woman, all of whom showed anaemia with enlarged spleen, bilirubinaemia, with an indirect van den Bergh reaction, urobilinuria as well as a marked increase of the reticulocytes. Thus all the symptoms of haemolytic anaemia were present, while the fragility test of the erythrocytes against salt solutions was constantly normal. Hereditary influence could not be proved in any of these cases nor was it possible in the present case. At any rate, physical and blood examination of the parents did not reveal any essential point in favour of an existing haemolytic anaemia.

O. Naegeli already pointed out that even in typical cases of haemolytic jaundice in adults the diminishing of osmotic resistency (increased fragility of the erythrocytes) may, rarely, be lacking temporarily. In one of his cases, for instance, the abnormal fragility of the erythrocytes had only become manifest during a stay in the high mountains. It was also noticed in these rare cases that increased fragility of the erythrocytes may be elicited by means of certain artificial influences as, for instance, irradiation of the spleen with

ultra-violet rays. This method was tried in the case reported here, without success.

Though the increased fragility of the erythrocytes is lacking, all the other symptoms in the present case tell in favour of a congenital haemolytic anaemia. The observation points to the fact that no matter how much value is attached to the fragility test, a decisive significance in making the diagnosis cannot be attributed to it. In this connexion, an observation made by E. Lesné, R. Launey and I. Hurez (1935) is noticeable. These authors report the case of a woman suffering from typical haemolytic jaundice; her spleen was greatly enlarged and the fragility of the erythrocytes markedly increased. One of her eight-year-old twins also had a much enlarged spleen. The fragility of the erythrocytes, however, was almost normal. The twin sister's spleen was only slightly enlarged; the child was anaemic while the fragility test was normal. Unquestionably from this observation, it must be concluded, as the authors emphasize, that in haemolytic anaemia the symptoms of the disease may not all be present at the same time. This has long been known as regards the jaundice. Because this symptom is so often lacking, it is customary to-day not to use the term 'haemolytic jaundice,' as formerly, but plainly haemolytic anaemia (with or without jaundice). By the way of parenthesis, it may be mentioned that G. Frontali (1936) described typical haemolytic anaemias in children in whom the osmotic resistance of the erythrocytes was found to be even constantly increased.

Summary and conclusion

The history of a one-year-and-eight-months' old girl is reported in whom, in the first days of its life, a severe hypochromic anaemia together with enlargement of the liver and spleen was already present. Further examination showed all the typical symptoms of a congenital haemolytic anaemia; the fragility test of the erythrocytes, however, was normal throughout the observation period. During periodically occurring rises in temperature, no essential changes in the blood could be demonstrated, nor an acceleration of the sedimentation rate. These febrile attacks are considered as equivalents of haemolytic crises. The disease could not be proved to be inherited.

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