THALASSAEMIA MINOR IN AN ENGLISHWOMAN

BY

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[WITH SPECIAL PLATE]

Thalassaemia is a hereditary hypochromic microcytic anaemia for which there exist a number of synonyms—microcythaemia; hereditary leptocytosis; Mediterranean, Cooley's, and target-cell anaemia. In Europe it has hitherto been regarded as the prerogative of the Mediterranean races, although there have been reports of cases from Germany. The purpose of the present paper is to record an example in a woman of pure English stock.

The underlying defect in the disease is an interference with the synthesis of normal adult haemoglobin (Rich, 1952). Homozygous and heterozygous forms occur, but the first is commonly severe, while the second is often without symptoms. In consequence their relationship was not appreciated until it was established that the parents of children with Cooley's anaemia, or thalassaemia major, themselves exhibited a mild form of the disease, or thalassaemia minor (Gatto, 1941; Wintrobe, 1942; Dameshek, 1943).

Haematological Features

The peripheral blood is marked by microcytosis due to reduction in the thickness of the red blood cells, which confers upon them the characteristic "target" appearance. The hypochromia depends rather upon a low haemoglobin content of the cells than upon a low saturation. The red blood cell count may not be reduced and, indeed, may exceed normal. In the film anisocytosis, poikilocytosis, and punctate basophilia are to be noted as well as the target-cell deformity; normoblasts are common when anaemia is profound. The flattened red cells have an increased resistance to hypotonic solutions, consequently their osmotic fragility is reduced, although mechanical fragility is increased and their span of life shortened. The haemoglobin content of the red blood cells is so low that the increased rate of their destruction may not lead to a significant rise in serum bilirubin level or increase in stercobilinogen excretion. The bone marrow undergoes a normoblastic hyperplasia.

Foetal haemoglobin (Hb-F) has normally disappeared from the red blood cells by the age of 6 months; but the ability to form this pigment may be retained in any anaemia which develops in early infancy, and it is present in increased amounts in thalassaemia. Haemoglobin A₂ (Hb-A₂), a fraction of normal adult haemoglobin (Hb-A) resembling haemoglobin E in its electrophoretic properties (Kunkel and Wallenius, 1955), is normally present in quantities not exceeding 3%. In thalassaemia this proportion may rise to 15%.

Although the hypochromic microcytic anaemia of thalassaemia resembles that of iron deficiency, the level of iron in the serum is normal or high and there is no response to iron medication.

Study of the patient's relatives is essential before a diagnosis of thalassaemia can be established. The clear-cut genetic differences between the homozygous and heterozy-

gous forms do not extend to the clinical features because of the variable penetrance of the thalassaemia gene. Although the heterozygous state is usually asymptomatic, it may occasionally be associated with profound anaemia, splenomegaly, and skeletal changes.

In thalassaemia minor the low mean corpuscular haemoglobin is often combined with an increase in the red blood cell count which maintains the circulating haemoglobin concentration at a normal level. The patient is thus preserved from significant anaemia unless an additional load is imposed by haemorrhage or haemolysis. In these circumstances a minor loss of blood may result in severe anaemia which the already extended bone marrow cannot repair. Such circumstances led to the discovery of thalassaemia minor in the present instance.

Case Report

The patient, a housewife aged 48 years, was of pure English stock. Her family had been farmers in East Anglia for many generations and there had been no known intermarriage with foreigners in the past. Her mother was said to have been anaemic, although she lived to an advanced age.

The patient was referred to St. Bartholomew's Hospital in March, 1957, for investigation of a hypochromic anaemia which had proved refractory to treatment with iron. Three years previously she had been admitted to another hospital with a haematemesis; after a second haemorrhage on the day following admission the haemoglobin had fallen to 6.9 g. per 100 ml. She had made a satisfactory recovery, but even after intensive treatment with iron by mouth and by intravenous injection the haemoglobin level had not risen above 10.0 g. per 100 ml. A year later the figure had been 9.4 g. per 100 ml., and after further treatment with iron for a month, 9.8 g. per 100 ml. At this time physical examination had been normal. The serum bilirubin had been raised to 1.4 mg. per 100 ml., but liver function had been intact and there had been no radiological evidence of gastrointestinal disease. Three months later the haemoglobin reading was still only 10.4 g. per 100 ml.

On admission to St. Bartholomew's Hospital 10 months later she was pale but well nourished. The spleen and liver were impalpable and there were no physical signs of disease apart from slight cardiac enlargement. The details of her blood count are set out in the Table. The white cells

Haematological Findings in the Patient, Her Son, and Three Siblings

	Patient	Patient's Son	Brother of Patient	Brother of Patient	Sister of Patient
Haemoglobin (g. per 100 ml.)	11.2	13.9	12.7	12.4	14.5
Red cells (millions per c.mm.)	5.12	4.42	4.80	5.08	5.08
Cell volume (%)	35	43	37	40	45
M.C.V. (cubic μ)	68	97	77	79	89
M.C.H. (μ g.)	21.9	31.5	26.6	24.4	28.5
M.C.H.C. (%)	32.0	32.3	34.3	31.0	32.2
M.C.D. (μ)	7.6	8.0	7.6	8.1	7.8
M.C.A.T. (μ)	1.5	1.9	1.7	1.5	1.9
Reticulocytes (%)	3.4	0.4	0.7	0.6	0.4
Target cells	+	—	++	++	—
Stippling	+	—	+	+	—
Osmotic fragility (range in % NaCl)	0.48-0	0.45-0.35	0.40-0.10	0.40-0.15	0.45-0.30
Foetal haemoglobin (%)	3.1	Nil	6.1	5.4	Nil
Haemoglobin A ₂ (% of A)	5.1	2.1	8.5	5.8	1.9
Serum iron (μ g. per 100 ml.)	120	204	124	150	140

numbered 8,100 per c.mm. (neutrophils 62%, eosinophils 1%, basophils 1%, lymphocytes 34%, monocytes 2%), and platelets 260,000 per c.mm. Films of the bone marrow showed intense normoblastic hyperplasia. The serum bilirubin level was 0.7 mg. per 100 ml., and the mean daily faecal urobilinogen excretion 100 mg. Estimation of the serum iron gave a figure of 120 μ g. per 100 ml. Osmotic resistance of the red blood cells was increased (see Chart); the Wassermann reaction and the direct and indirect Coombs tests were

negative. Results of liver function tests were normal. There was no radiological evidence of oesophageal varices or of gastro-duodenal disease.

Study of the patient's haemoglobin revealed 3.1% alkali-resistant pigment (Hb-F). On electrophoresis an increase in Hb-A₂ was noted in the unstained paper strip (reproduced herewith). On staining with a protein dye and subsequent elution, colorimetry showed the proportion of Hb-A₂ to be significantly raised to 5.1% of the total Hb-A.

Chart showing osmotic resistance of red blood cells.

resistant hypochromic microcytic anaemia with target cells, basophilic stippling, and reticulocytosis; increased osmotic resistance of the red blood cells; the presence of Hb-F and an increase in the Hb-A₂ fraction; and a normal level of serum iron. These results provided evidence that the patient had thalassaemia minor, and the diagnosis was conclusively

Paper electrophoresis of haemoglobin of patient and of a normal control. The strip has not been stained, but even so a band of haemoglobin is visible in the position of Hb-A₂ in the case of the patient but not in that of the control.

established by the demonstration of similar changes in the blood of two out of three siblings, neither of whom had any symptoms or was conscious of being anaemic (see Special Plate). The patient's only son was normal and thus afforded proof of her heterozygous state (see Table).

Discussion

Reports of thalassaemia in persons of English descent are few. An example was recorded by Bywaters as long ago as 1938. The patient died during the war, but, by the courtesy of Professor Bywaters, we have been in touch with her parents and the blood of neither has the features of thalassaemia. It seems unlikely, therefore, that the case would have met present-day diagnostic requirements. Thalassaemia was noted in a family of Scottish immigrants in Canada (Israels, Suderman, and Hoogstraten, 1955), but there was evidence of illegitimacy in one of the propositus children, and, as they came from a Scottish port, it is probable that the gene was of recent and irregular acquisition. Israels and Turner (1955) have reported "target-cell anaemia" in two young Englishwomen without Mediterranean ancestry. In both cases the essential criteria required for the diagnosis of thalassaemia were present, and family studies provided supporting evidence.

It seems probable that this disorder is less rare in persons of English stock than these scanty reports would suggest. The discovery of another affected family underlines the importance of considering the possibility of thalassaemia when confronted by a patient with refractory hypochromic anaemia.

Summary

The case is reported of a middle-aged woman of East Anglian farming stock in whom a refractory hypochromic anaemia was shown to be due to thalassaemia minor. Evidence of this disorder was also found in her two brothers, but not in her sister or her son.

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OIL GRANULOMA OF THE LUNG

REPORT OF THREE CASES

BY

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[WITH SPECIAL PLATE]

The condition of lipid granuloma of the lung was first described in 1925 by Laughlen. The large numbers of reports in the American literature on the subject have recently been reviewed by Buechner and Strug (1956) and also by Steinberg and Finby (1956). Most of the cases reported have been due to collections of liquid paraffin in patients taking this substance by mouth or as nasal drops or sprays. However, mineral oils are not the only source of the trouble, vegetable and animal oils and various fats having also been indicted. In addition there is a special group of cases due to poppy-seed oil used for bronchography.

These exogenous oil and fat granulomas must be distinguished from lesions containing endogenous fatty substances occurring in association with bronchial obstruction and generalized disturbances of fat metabolism. In this paper are reported three cases of lipid granuloma believed to be of exogenous origin and forming localized tumour masses clinically resembling carcinoma of the bronchus.

Incidence

From the few reports of such granulomas which have appeared in the literature in this country (Paterson, 1938; Rewell, 1947; Belcher, 1949; Nelson, 1954) it might be concluded that the condition is a great rarity, but the three cases here described occurred in the author's practice in just over one year, suggesting that the condition must be fairly common. The cases reported in the literature show that, though the disease may occur at any age, it is fairly common in babies with feeding disturbances, when milk may reach the lungs, where its fat content tends to remain, as it is much more slowly removed than the other constituents. At the other extreme of life it becomes more common again, so that in a hospital treating the aged with such conditions as neurological disorders (especially Parkinsonism), cerebrovascular conditions, and rheumatoid arthritis it has been reported in as many as 14.6% of inmates (Volk *et al.*, 1951). This high incidence is presumably associated with disturbance of swallowing; the

C. W. H. HAVARD *ET AL.*: THALASSAEMIA MINOR

Appearance of red cells of patient (A), her son (B), her two thalassaemic brothers (C and D), and her normal sister (E). ($\times 500$)

A. H. M. SIDDONS: OIL GRANULOMA OF LUNG

FIG. 1.—Case 1. Radiograph showing lesion in postero-basilar segment of left lower lobe.

FIG. 2a, b.—Case 3. Radiographs showing mass in right upper and middle lobes.

F. OSMOND-CLARKE AND M. MURRAY: VAGINAL SMEARS

FIG. 1.—Vaginal smear from patient with secondary amenorrhoea, showing marked degree of atrophy of epithelium. ($\times 240$.)

FIG. 2.—Vaginal smear from patient with ovarian agenesis, showing marked oestrogenic activity six months after implantation of 300 mg. stilboestrol. ($\times 240$.)