OCULAR COMPLICATIONS IN THALASSAEMIA MINOR*

BY

C. RUDD, P. JAMESON EVANS, AND A. L. P. PEENEY

Birmingham

MEDITERRANEAN anaemia is a disease which was originally found in persons native to the shores of that sea, but more recently it has been reported from the Caucasus region. It is a hereditary trait showing a dominant character and occurs in two main forms:

(a) the homozygous form, in which both parents are affected, is by far the more severe, and in the majority of instances the affected children die in infancy;

(b) the heterozygous form, in which a gradation of lesser severity is found, so that a number of patients are in fact symptom free, yet show the characteristic blood picture on examination.

The homozygous form often goes by the name thalassaemia major, while the heterozygous receives the name of thalassaemia minor. In the latter condition the most severe cases have been distinguished by the term Coolley's anaemia, after the physician in America who carried out work on these cases (Coolley and Lee, 1925).

The outstanding feature of the blood picture in these cases is the presence of large numbers of "target" cells in the red blood cells, these cells being excessively thin, especially in the midperiphery, and each showing on microscopy as three concentric rings. The other possible causes of target cell formation are absent in this case. The total red count may not be diminished, and some cases even show a polycythaemia, but the haemoglobin is usually reduced and the corpuscular volume in like proportion. The fragility to haemolysis is greatly reduced. Sick cells are not found in the blood. It has been stated that sickle-cell anaemia in Negroes is the equivalent of target-cell anaemia in Europeans, but it is not clear on what grounds this view is held, and the case here reported in no way supports it. American writers have reported a number of cases whose ancestry in the great majority is definitely or probably Mediterranean, but Schieber (1945) reports two cases in brothers of Caucasian origin. More recently Schwartz and Mason (1949) have reported four instances from the U.S.A. in Negroes and members of their families, but were not able to exclude definitely all possibility of Mediterranean admixture in the previous three generations.

In addition to the changes in the blood picture, this haemoblastic anaemia produces changes in the bone-marrow as seen by biopsy of the sternal marrow, and x rays reveal a curious radial striation in the calvarium. Splenomegaly is common in the severer forms; in the present case the spleen

* Received for publication January 16, 1953.

is only just palpable and its size is consistent with the history of malaria infection.

Two curious features strike one on initial review of the reported cases of this disease. First, the causes of death, where known, seem to be very ordinary (pneumonia, etc.) rather than related to the lesions one might expect in a blood dyscrasia. Secondly, there is an almost total absence of visual symptoms, and only two references to an ophthalmic examination: in one of these central retinal vein thrombosis is recorded and in the other a second stage hypertensive retinopathy.

The case recorded below presents therefore a number of interesting features. First, the patient is, as far as we have been able to discover, a pure West African Negro. The condition is the heterozygous thalassaemia minor, since his mother shows a very similar blood picture while that of his father is normal, and the degree of severity is Stage III according to the classification of Damashek (1940; 1943) who recognizes seven progressive stages (Table).

TABLE
TYPES OF MEDITERRANEAN ANAEMIA (after Damashek)

Type	Haemoglobin	Target oval or stippled cells	Splenomegaly	Jaundice	Bone changes	Nucleated red cells
(1) Congenital lepto- or elliptocytosis	% 80+	+	0	0	—	—
(2) Hypochromic erythrocytosis	80+	++	0	0	—	—
(3) Hypochromic anaemia ...	65—80	++	0	0	—	—
(4) Hypochromic erythrocytosis with splenomegaly ...	65—80	++++	+	+	—	—
(5) Congenital haemolytic target oval cell jaundice ...	50—65	++	++	+	+	—
(6) Adult anerythroblastic type of Cooley's anaemia ...	Less than 50	+	+++	++	++	—
(7) Cooley's erythroblastic anaemia	Less than 40	+	++++	+++	++++	+++

The common denominators of all the above types are decreased hypotonic fragility, presence of target and oval cells, and lack of response to iron therapy.

The presenting symptom was loss of vision. Examination revealed a quite exceptional series of fundus changes which are presumably part of the disease. It is our purpose to describe these changes in particular, and their progress during 12 months observation and treatment.

Case Report

A male West African Negro aged 22 years, first presented himself on October 17 1950, complaining of blurred vision in the right eye of 24 hrs' duration. A university student with acute observation, he gave the following history:

In February, 1949, he had noticed slight mistiness of the right vision and was treated by drops. The vision had returned to normal by May, 1949. Subsequently he passed two medical examinations with ophthalmoscopic tests without adverse comment. He arrived in England in August, 1950, and on entrance to the university on October 5, 1950, his vision was 6/6 in both eyes without glasses.

Past History.—Malaria in January, 1950.

Family History.—Father and mother Gold Coast natives: no consanguinity (Fig. 1). The patient is the second child of the second wife, whose offspring were as follows:

- 1st child (female) died very young, cause unknown.
- 2nd child (male) the patient.
- 3rd child (male) twin, alive and well—the other twin died in infancy.
- 5th child (male) alive and well.

Immediate History.—On October 16, 1950, red-brown fingers of mist spread across the vision of the right eye, with first nasal and then superior loss of visual field.

FIG. 1.—Patient's parents and siblings.

Examination on Admission to Hospital (October 17, 1950).—

Right Eye.—Vision reduced to perception of hand-movements at 2 ft, with loss of upper and nasal field to confrontation test. No changes seen in anterior segment. Vitreous partially opaque with moving streaks. Fundus poorly seen; a large darkish mass appeared in the lower and outer mid-periphery but no details were visible. Transillumination impaired.

Left Eye.—Negroid fundus. No abnormalities discovered.

Diagnosis.—A provisional diagnosis of tuberculous choroiditis.

Treatment.—Tuberculin injections.

Laboratory Findings.—

Mantoux test : positive	Hb, 120 per cent.
Eosinophilia : not increased	Colour index, 0.96
Red blood cells, 6,180,000	White blood cells, 5,200; differential white cell count not exceptional
Wasserman reaction : negative	

Radiological Examination.—X rays of chest and skull normal.

Progress.—The condition of the right eye deteriorated and the dark grey mass spread round the periphery, but little detail could be made out because of vitreous haze. There seemed to be a large area of detached retina in the lower temporal periphery which was partly dull on transillumination. The condition improved slowly and, through fundus examination was difficult, vision improved so much that by February, 1951, vision in the right eye was 6/9 partly. The detached retina in the periphery was less opaque on transillumination. The patient continued under observation as an out-patient. Tuberculin was continued to the end of April.

Later Developments.—Onset of mistiness of vision in the left eye, July, 1951. Treatment was commenced with subconjunctival injections of cortisone (2.5 mg.) to each eye.

Further Tests.—*

Van der Bergh : Indirect slightly positive; direct positive

Blood film: many target cell red cells.

Sternal marrow biopsy: normoblastic hyperplasia, hyperplasia, megaloblasts not seen, sickling not seen.

Vitamin C saturation test: normal.

Fat analysis of stools: normal.

Liver function tests: normal.

Faeces: no excess of fatty acid crystals.

Bile salts and pigments: Urobilin and urobilinogen slightly positive;
Bilirubin and bile salts negative.

Haematology:

Red blood cells, 5,940,000

Hb, 118 per cent.

Colour index, 0.99

Reticulocytes, 1.6 per cent.

Cell volume, 48.5 ml.

Mean corpuscular volume, 81.6

Mean corpuscular Hb concentration, 33.6

Ultra-violet spectrophotometry of haemoglobin: no abnormality in absorption curve.

Blood fragility: corpuscular fragility very much diminished.

Radiological Examination.—Skull, pelvis, femur, and humerus: no abnormality.

Diagnosis.—The diagnosis of thalassaemia minor was made on the blood films of the patient and his mother (Fig. 2*a*, *b*, *c*), together with the lowered corpuscular fragility (Fig. 3).

Progress.—The condition of the left eye remained indeterminate in July and August, 1951. In September, 1951, there was a further recurrence of activity in the left eye in which the following fundus changes were observed:

The first change seemed to be the appearance of a flat, evenly red area in the fundus. This seemed to be a deep retinal haemorrhage. In the course of a few days an exudative reaction appeared in and superficial to the red area which presented a yellow-grey mass coming forward towards the vitreous. A haze of cells was seen in the adjoining vitreous. This grey exudate was evidently the source of the "detached retina" in the eye first observed (right eye). As

FIG. 2 (*a*).—Patient's father (I, 2).

FIG. 2 (*b*).—Patient's mother (I, 3).

* For these we are indebted, as also for the diagnosis, to Dr. Peeney.

FIG. 2 (c).—Patient (II, 2).

FIG. 3.—Blood corpuscular fragility curve (II, 2).

the reaction increased, the vitreous was invaded by very heavy exudates, and at a later stage the retinal exudates acquired superficial glistening specks, possibly from cholesterol deposition. At a later stage pigmentation of choroidal hyperaemic reaction was seen at the edge of the fundus lesion (Fig. 4, overleaf).

Therapy.—Further retinal lesions being seen in the left eye, the patient was re-admitted to hospital and given cortisone, both locally by drops, and systemically by injection, together with ascorbic acid by mouth. Drops of atropine, cocaine, dionine, and adrenaline were given locally thrice daily. The patient improved more rapidly on this occasion and was again able to return to his studies.

Result.—On October 23, 1951, visual acuity was 6/5 partly in the right eye. The right fundus was clear above but still obscured in the lower half by vitreous opacities. Some exudate was seen along the course of the vessels, and several white opacities below. The left fundus showed haemorrhages in the lower half and some vitreous opacities.

Recent developments.—A more recent examination of the patient's blood revealed definite latent sickling in addition to the findings reported above. This raises the possibility that the haematological condition is a combination of the traits of sickling and thalassaemia. Such a combination was reported in a family of Sicilian ancestry by Powell, Rodarte, and Neel (1950).

The inaccessibility of all this patient's relatives in West Africa has unfortunately precluded a complete study, but it is intended to publish more definite haematological data elsewhere.

Summary

A case of thalassaemia minor is described which shows several unusual features. First, there are no previous records of ocular signs in thalassaemia minor. Secondly, the patient and his mother have no connexion with the Mediterranean littoral. Thirdly, the mother, although also affected by the

FIG. 4.

disease, seems to have had no major symptoms, and has produced five children, three of whom are alive and well.

REFERENCES

- COOLLEY, T. B., and LEE, P. (1925). *Trans. Amer. pediat. Soc.* **37**, 29.
 DAMASHEK, W. (1940). *Amer. J. med. Sci.*, **200**, 445.
 ——— (1943). *Ibid.*, **205**, 643.
 POWELL, W. N., RODARTE, J. G., and NEEL, J. V. (1950). *Blood*, **5**, 887.
 SCHIEBER, J. (1945). *Lancet*, **2**, 851.
 SCHWARTZ, S. O., and MASON, J. (1949). *Blood*, **4**, 706.