Angioid streaks in a case of beta thalassaemia major

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SUMMARY We report a case of beta thalassaemia major in which angioid streaks were present in both fundi with macular involvement in one eye. To our knowledge this is the first report of an association between angioid streaks and beta thalassaemia major. The possible theories of the pathogenesis of angioid streaks in patients with haemoglobinopathies are considered.

Angioid streaks were first described in 1889 by Doyne in a patient who had suffered ocular trauma.¹ Since then they have been described in association with numerous systemic diseases of which the most important are pseudoxanthoma elasticum,² Paget's disease of bone,³ and sickle cell disease.^{4,5} The appearance of angioid streaks on fundus examination is typical, since they consist of dark reddish-brown bands of irregular contour which irradiate from the optic disc. The angioid streaks represent cracks in Bruch's membrane, and fibrovascular ingrowth may occur.⁶

Case report

A 36-year-old Ugandan Asian woman was diagnosed as having homozygous beta thalassaemia in 1972 when she first came to the United Kingdom. She had presented to the medical department initially for investigation of anaemia and hepatosplenomegaly. Recurrent leg ulcers and serial blood transfusions necessitated several hospital admissions.

Both her parents were alive and well, but 2 brothers and one sister were known to have died in childhood from haematological diseases. In addition a niece living in Britain was said to be anaemic. The patient's surviving sister and one of her 3 surviving brothers resident in this country were examined and found to have normal haemoglobin electrophoretic patterns.

On examination the patient was of small stature and showed frontal bossing of the head with rather prominent malar bones. She was clinically anaemic and jaundiced. Her liver was enlarged to 3 finger-breadths beneath the costal margin, and her spleen

was palpable to her umbilicus. She had swelling of the distal end of her right tibia and a chronic ulcer on her right foot. There were no clinical signs of pseudoxanthoma elasticum, though a skin biopsy has not been performed.

She first presented to the eye department in February 1982 with a one-week history of blurring of vision in the left eye. On examination visual acuity was 6/9 right eye and 6/24 left eye. Anterior segment examinations were unremarkable and intraocular pressures were 19 and 20 mmHg right and left eye respectively. Fundus examination revealed angioid streaks radiating from the optic discs in both eyes, and in the left eye there was a large subretinal haemorrhage inferotemporal to the fovea (Fig. 1).

Fluorescein angiography showed the characteristic hyperfluorescence of angioid streaks with a subretinal neovascular membrane outside the foveal avascular zone in the left eye (Fig. 2). This membrane was subsequently treated with argon laser.

Laboratory investigations in February 1982 were as follows: Haemoglobin 7.2 g/dl, red cell count $3.14 \times 10^{12}/l$, MCV 75 fl, MCH 23.3 pg. Haemoglobin electrophoresis showed HbF 90%, HbA2 1.0%, and no HbA was detected. The red cell survival time was normal, serum iron was 38.6 $\mu\text{mol}/l$, and the total iron binding capacity was 38.0 mol/l .

Skull x-rays showed widening of diploe and the typical hair-on-end appearance of radial striations. Chest x-ray was unremarkable, but x-ray of the long bones showed deformity of the lower femora and upper tibiae, with loss of normal bone architecture.

Discussion

Beta thalassaemia is a dominantly inherited condition in which the patient has an inability to form beta globin chains in the haemoglobin molecule. Beta

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Fig. 1 Composite fundus photographs of the left eye showing angioid streaks radiating from the optic disc and subretinal haemorrhage at macula.

Fig. 2 Fluorescein angiogram in midvenous phase showing area of haemorrhage of leakage of dye from a subretinal neovascular membrane inferior to fovea of left eye.

thalassaemia major is the homozygous form, and almost all the haemoglobin is in the form of HbF, the small remainder being HbA₂. The patient usually becomes severely anaemic within the first year of life.

The disease is widespread throughout the Middle East and Asia, and most patients fail to survive beyond childhood. The major complications are severe anaemia, haemosiderosis, and recurrent infections. There is also a well recognised milder form of this condition in which survival into adulthood is well documented.⁷

Angioid streaks have been reported in a wide variety of diseases, of which many are probably coincidental findings. However, they have been reported in several different types of haemoglobinopathy, of which homozygous sickle cell disease (HbSS) is the best known.⁸ Sickle cell trait (HbAS),⁹ sickle cell haemoglobin C disease (HbSC),¹⁰ sickle cell thalassaemia (HbS-thalassaemia),¹¹ and haemoglobin H disease (HbH)¹² have all been reported in association with angioid streaks. It appears that the association between angioid streaks and haemoglobinopathies is therefore of significance and not a chance phenomenon.

The pathogenesis of angioid streaks in these haemoglobinopathies, however, remains unclear. Histopathological examination of cases of pseudoxanthoma elasticum has shown calcification of Bruch's membrane, which may render it brittle and liable to breaks.^{13,14} In Paget's disease of bone calcium can be deposited in Bruch's membrane, and this is undoubtedly contributory to angioid streak formation.¹⁵ Such calcification appears to be uncommon in cases of sickle cell disease. Paton has postulated that chronic haemolysis results in deposition of iron in Bruch's membrane.¹⁶ This theory is supported by the findings of Hagedoorn, who noted increased iron staining of Bruch's membrane in patients with angioid streaks.¹³

However, more recently stainable iron could not be demonstrated in biopsy specimens from patients with sickle cell disease and angioid streaks.¹⁷

The case that we report is unusual in 2 respects. Although the patient had severe anaemia, she appears to belong to the recognised group of patients with beta thalassaemia major who survive into adulthood. In common with other patients suffering from this disorder she had haemosiderosis from frequent blood transfusions, but unlike most patients with this condition she had refused treatment with chelating agents. It is possible that the reason angioid streaks have not been noted in this disorder before is either because of the poor survival of these patients, or because the attendant haemosiderosis is normally treated at an early stage. If this latter theory is correct, it would implicate iron deposition in Bruch's membrane in the pathogenesis of angioid streaks. Patients with haemosiderosis from other causes have not been reported to develop angioid streaks to our knowledge, although they have been observed in 2 patients with haemochromatosis.¹⁷

Another theory to explain the presence of angioid streaks in patients with haemoglobinopathies is that there is an inherent defect in Bruch's membrane similar to the defect in the haemoglobin molecule. This defect could lead to breaks in Bruch's membrane and the resultant picture of angioid streaks. It would be expected that, if this was a genetic defect, angioid streaks would be found at an early age. It is therefore interesting to note that with the exception of the study by Geeraets and Guerry,⁸ all patients with sickle cell haemoglobinopathy and associated angioid streaks have been over the age of 25 years.¹⁸ This would seem to favour the iron deposition theory as being more likely. Further histopathological examination of eyes with angioid streaks from patients with haemoglobinopathies will perhaps make this clear.

The finding of angioid streaks in this case adds a further type of haemoglobinopathy to those already described as being associated with angioid streaks. It

would therefore seem essential that all patients with haemoglobinopathies have a full ocular examination.

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