Vitreous haemorrhage in tuberous sclerosis

Report of two cases

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Tuberous sclerosis is a well-defined clinical entity characterized by a triad of epilepsy, mental retardation, and adenoma sebaceum, with excellent clinical descriptions elsewhere (Critchley and Earl, 1932; Lagos and Gomez, 1967). The principal ocular manifestations comprise retinal tumours of two morphological types (van der Hoeve, 1920, 1921). Elevated mulberry-like tumours are found characteristically in the posterior pole where they may resemble drusen of the disc. Each tumour appears as a whitish-grey glistening mass, studded with nodules which may become cystic. A second type occurs in the retinal periphery which is flat, white or grey, circular or oval, and frequently multiple, ranging up to half the size of the optic disc (Koch and Walsh, 1939).

The condition is inherited as an autosomal dominant, so that early recognition is of paramount importance for genetic counselling. A large proportion of new cases, however, occur as mutations (Bundey, 1971).

The present report describes retinal phakomata in two cases of tuberous sclerosis. Fluorescein angiographic studies in one patient demonstrated for the first time an associated angiomatous anomaly in a disc tumour. Previous reports have neglected the vascular anomaly with its haemorrhagic potential.

Case reports

Case 1, a 15-year-old schoolboy, was found, during a routine examination to have reduced vision in the right eye with a visual field defect. An ophthalmologist confirmed these findings, and noted in addition an angiomatous lesion of the right disc. The patient was admitted to hospital for investigation. He had had infantile spasms at 4 months, and at 6 months developed a birthmark on the left cheek. At 12 years a radiologist was consulted regarding x-ray therapy to the facial lesion; skull films showed areas of intracerebral calcification. There was no relevant family history.

Physical examination

He was a well-developed youth of average intelligence with no abnormality of the cardiovascular, respiratory, or nervous system. There was a pink elevated naevus on the left cheek, and numerous pink spots on both sides of the face in the distribution of the second and third divisions of the trigeminal nerve. A dermatologist confirmed adenoma sebaceum and a cavernous haemangioma of the left side of the face.

Received for publication July 24, 1972.

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Ophthalmological examination

The visual acuity was 6/6 in the left eye, and 6/60 in the right eye with an upper altitudinal defect. Slit-lamp examination of the right eye showed a small posterior subcapsular cataract with haemorrhage adherent to the posterior lens surface. The anterior segment was normal in the left eye and the intraocular pressure was normal in both eyes.

The right fundus (Fig. 1) showed a pre-retinal haemorrhage extending into the vitreous, and condensing below. A white mulberry-like tumour was present arising from the optic disc, with numerous fine vascular channels throughout the tumour and on its surface. Scattered around the fundus were several small flat white lesions, with a smooth surface and apparently avascular. The macula was detached.

FIG. 1 Case 1. Right fundus, showing vitreous haemorrhage, and elevated mulberry tumour of the disc, and several flat peripheral retinal phakomata

The left fundus showed two small flat lesions in the upper nasal quadrant anterior to the equator, but was otherwise normal.

Radiology

The skull showed three areas of intracerebral calcification. The two largest were defined by pneumo-encephalography forming papillary projections from the inferior surface of the right and left ventricles respectively, while the third lay in the brain substance. Bilateral carotid angiograms showed normal arterio-venous patterns.

Case 2, a 23-year-old man, was referred to Mr. K. Wybar at Moorfields Eye Hospital in May, 1961, with an abnormality of the right eye observed during a routine examination. The patient complained of headaches for several years, but had no ocular symptoms. There was no relevant family history.

Ophthalmological examination

The visual acuity was 6/6 in each eye. The anterior segments and media were normal. Projecting into the vitreous from the lower part of the right optic disc (Fig. 2) was an extensive white mass with seedling-like nodules on its surface and an irregular border. The appearance of the left fundus was normal. A tentative diagnosis of drusen of the right disc was made.

FIG. 2 Case 2. Right fundus, showing nodular tumour arising from infero-nasal part of optic disc

Course

In September, 1961, the patient attended with mistiness of vision in the right eye. The visual acuity remained 6/6 but fundus examination showed a small vitreous haemorrhage situated three disc diameters below the projecting disc tumour (Fig. 3). At this time sebaceous adenomata were noted on the left side of the nose and the diagnosis of tuberous sclerosis was made. Skull x-ray showed no evidence of intracerebral calcification. The haemorrhage gradually cleared. On two further

FIG. 3 Case 2. Right fundus, showing vitreous haemorrhage both inferior and nasal to disc tumour

occasions during the next 3 years the patient presented with floaters in the right eye due to recurrent vitreous haemorrhages. In 1966 the patient was seen at the National Hospital where skull films demonstrated several areas of intracerebral calcification and an electroencephalogram showed changes compatible with a diagnosis of tuberous sclerosis.

The patient was last examined in March, 1971, when he was symptom free. The visual acuity was 6/6 in each eye, and fundus examination showed the mulberry tumour of the right disc to be unchanged in size and configuration, and the vitreous to be clear. Central field examination showed enlargement of the blind spot, corresponding with the area of retina obscured by tumour. The left fundus was normal.

FIG. 4 Case 2. Fluorescein angiograms of right fundus

- (a) Pre-injection, showing auto-fluorescence of disc phakoma
- (b) Arterial phase: abnormal vessels on tumour surface are seen to be filling from retinal arteries
- (c) Venous phase: numerous abnormal dilated capillary loops visible throughout tumour
- (d) Residual photograph, showing hyperfluorescence due to leakage of dye into retina around phakoma

A general examination showed the following positive features. Adenoma sebaceum of the face appeared in a typical butterfly distribution, with involvement of the chin. A shagreen patch was present over the lower lumbar spine, and an "aspen leaf" area of hypopigmentation over the right 6th intercostal space anteriorly. Subungual fibromata were noted on several digits of both hands.

Fundus photography showed autofluorescence of the retinal tumour before the intravenous injection of fluorescein (Fig. 4a). The arterial phase (Fig. 4b) showed normal flow with early filling of the dilated capillaries on the surface of the tumour. Gross dilatation of the peripapillary retinal plexus was observed with filling from the retinal arteries. Abnormal dilated capillary loops were visible in the venous phase (Fig. 4c) and some microaneurysms of the peripapillary plexus at the inferior and temporal disc margins. The residual photographs (Fig. 4d) taken 10 minutes after injection showed massive hyperfluorescence of the papillary region with leakage into the surrounding retina (Fig. 4e). Comparison with angiograms taken 4 years previously showed no change.

Discussion

Estimates of the incidence of phakomata in cases of tuberous sclerosis vary from 4 per cent. (Critchley and Earl, 1932) to 53 per cent. (Lagos and Gomez, 1967). When such lesions are present they do not usually cause visual disturbance. Large tumours of the disc may cause subtle changes in the visual field (Case 2), though severe visual loss from vitreous haemorrhage or macular detachment has not been reported.

The first description of vitreous haemorrhage as a feature of tuberous sclerosis was by van der Hoeve (1921). Cystic spaces in a mushroom-like tumour of the disc were noted to fill with blood on separate occasions, and on one occasion haemorrhage into the vitreous from a ruptured cyst was observed. Koch and Walsh (1939) reported a case with vitreous haemorrhage occurring in association with papilloedema secondary to raised intracranial pressure. A vascular retinopathy was described by Dyer, Hill, Rowan, and Taylor (1967) in a patient with tuberous sclerosis and megaloblastic anaemia, but this cleared with treatment of the anaemia.

The histological structure of ocular phakomata first received attention from van der Hoeve (1923). A tumour arising from the disc was described, consisting of fibre-like processes interspersed with large polymorphic cells having large nuclei and prominent nucleoli. The cytoplasm of adjacent cells fused in places to form a syncytium. Situated between the fibres and cells were areas of calcification, and large spaces filled with blood or serum. A disc tumour of similar structure has been described by Messinger and Clarke (1937).

Peripheral retinal tumours consisting of pleomorphic cells within a framework of fibre-like strands have also been described (Schob, 1925; Feriz, 1930; Kuchenmeister, 1934; Vogt, 1934). Areas of calcification or cystic degeneration appear to be rare in peripheral lesions. These tumours usually lie in the nerve fibre or ganglion cell layer, but may involve all layers of the retina. Fluorescein studies of the peripheral lesion demonstrated numerous abnormal vessels in association (Harley and Grover, 1970).

The fibrillar structure of phakomata and their apparent origin from the nerve fibre layer led van der Hoeve to postulate that nerve fibres contributed to tumour formation. Subsequent reports have emphasized the glial-like nature of the fibre network (Schob, 1925; Kuchenmeister, 1934), the tumours in cases of tuberous sclerosis described by Messinger and Clarke (1937) and McLean (1937) being classified as astrocytic in origin, probably hamartomata rather than true tumours.

Astrocytomas of the retina or optic disc occurring without clinical signs of neurofibromatosis or tuberous sclerosis have been reported by McLean (1937), Foos, Straatsma, and

Allen (1965), and Ganley and Streeten (1971). The similarity in appearance and structure to ocular phakomata and the rarity of such cases makes the search for other manifestations of phakomatosis of great importance if reliable genetic counselling is to be achieved.

Vitreous haemorrhage occurring in drusen of the disc has been described by Gifford (1895), Reese (1940), and Gaynes and Towle (1967). Haemorrhages on or around the disc have been reported by Brégeat (1956), Sanders and ffytche (1967), and Walsh and Hoyt (1969). Of particular interest is a recent report by Sanders, Gay, and Newman (1970) of seven cases of drusen of the disc with haemorrhagic complications. In two instances, the haemorrhage extended into the vitreous, while in the remainder the haemorrhage was either within the substance of the nerve head or subretinal.

The nature of the vascular supply of disc and retinal tumours has received little attention in pathological studies. Numerous fine vessels on the surface of the disc tumour were noted by van der Hoeve (1923), though Koch and Walsh (1939) emphasized the apparent avascularity of the flat peripheral tumours. The description of sebaceous adenomata by Pringle (1890) emphasized the vascular nature of the skin tumours, the sebaceous lesions showing concomitant capillary dilatation and telangiectasis. Histological studies of skin biopsies from 38 patients with tuberous sclerosis were presented by Nickel and Reed (1962). Dilatation of blood vessels and lymphatics was commonly observed, and the prominent vascular changes led these authors to regard the lesions of adenoma sebaceum as angiofibromata. The fluorescein angiograms presented here clearly demonstrate numerous dilated capillaries throughout the optic disc tumour, which are abnormal and highly permeable to fluorescein.

These findings provide an explanation for the recurrent vitreous haemorrhages but also suggest that the ocular lesions resemble the cutaneous lesions in containing a significant angiomatous element. Pathological verification of this has been recently reported (Barsky and Wolter, 1971).

Conclusion

Vitreous haemorrhages as a complication of tuberous sclerosis is reported in two cases with large peripapillary tumours. Fluorescein angiograms show an extensive vascular plexus on the surface of the lesions and it is suggested that the vascular anomaly may be part of the hamartomatous process.

We should like to thank Mr. K. Wybar for permission to publish case 2, Miss Sue Ford for the photographic prints, Miss Lace for secretarial assistance, and the Medical Research Council for financial support.

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