Glial hamartoma of the retina in generalized neurofibromatosis

von Recklinghausen's disease

L. J. MARTYN AND D. L. KNOX

From the Wilmer Institute, the Johns Hopkins Hospital, Baltimore, Maryland, U.S.A.

Retinal tumour is one of the less frequent manifestations of von Recklinghausen's neurofibromatosis, and the histology of the retinal lesions is rarely reported. It is the purpose of this paper to present a case of extensive glial hamartoma of the retina associated with glaucoma and advanced proliferative changes of the uvea in an adolescent girl with generalized neurofibromatosis. The case is reported to describe the histopathology of the tumour and of uveal changes, to emphasize the importance of the iris manifestations of the disease, and to stimulate further thought about pathogenesis of the ectropion uveae and of the late onset glaucoma in von Recklinghausen's disease.

Case report

A 12-year-old white girl was seen by her ophthalmologist on September 13, 1967, with a 3-week history of mild discomfort and redness in the right eye, and recent awareness of loss of vision.

Initial examination of the right eye revealed light perception, a dilated and unreactive pupil, severe glaucoma, engorgement of the iris vessels, heavy aqueous flare and vitreous clouding, haemorrhage on the disc, and dilatation of the retinal vessels. She was treated with miotics, acetazolamide, and systemic steroids. The unexplained glaucoma persisted and the patient was referred to the Wilmer Institute for further evaluation and treatment.

Examination

On October 9, 1967, the visual acuity of the right eye was hand movements in the inferotemporal field with poor light projection in the other quadrants. The bulbar conjunctiva was diffusely hyperaemic. The cornea was oedematous and there was moderately heavy aqueous flare. The pupil was irregularly dilated and unreactive to direct and indirect light. There were multiple discrete pigmented iris nodules of various sizes, advanced neovascularization of the iris, widespread peripheral anterior synechiae, and ectropion uveae (Fig. 1). Relative stromal atrophy was present in the upper temporal iris; the atrophy was not of sufficient degree to explain the ectropion. Vitreous haze hampered the ophthalmoscopic examination, but yellowish elevations of the retina were seen around the disc, and a smooth yellow retinal elevation several disc diameters in size was noted in the superotemporal periphery. The nature of the fundus lesions could not be determined ophthalmoscopically. The retinal vessels were engorged, particularly those going to the upper temporal lesion. The ocular tension was 55 mm.Hg (Schiotz).

In the left eye the visual acuity was 20/15 with a full field, and the left eye was normal in all respects except for the presence of pigmented iris nodules similar to, but less numerous and less prominent than, those of the right iris.

FIG. 1 Iris, right eye (medical illustrator, Diane Abelloff)

There were irregular *café-au-lait* patches on the trunk and extremities, many small rubbery subcutaneous nodules, and a subcutaneous plexiform mass of the left brow. The skin pigmentation and subcutaneous masses had been present since infancy and had not increased noticeably in size or number with age.

The family history was negative for manifestations of phakomatosis.

Therapy

Medical treatment failed to control the glaucoma. Paracentesis and cyclodiathermy, performed in the inferonasal quadrant October 16, 1967, caused vitreous haemorrhage which prevented further examination of the fundus. The blind painful right eye was enucleated in December, 1967, 4 months after the onset of symptoms.

Pathology

GROSS

The enucleated right globe measured 25.5 mm. (AP) by 27.5 mm. (H) by 27 mm. (V) (Fig. 2). The specimen was sectioned obliquely through the 11 to 5 o'clock meridian because of the upper temporal lesion. The vitreous cavity was filled with blood and a large haemorrhagic mass.

MICROSCOPICAL

The basal cells of the corneal epithelium were oedematous and the corneal stroma had mild lymphocytic infiltration. The sclera was normal except for dilated vessels at the corneo-scleral junction. The iris was bound to the cornea by peripheral anterior synechiae and the angle and trabecular meshwork were filled with haemorrhage. The iris (Fig. 3) was thickened by diffuse hypercellularity of the stroma. Aggregates of pigmented cells produced nodularity of the stroma and of the anterior border layer. The inferonasal iris leaf was thicker and more nodular than the superotemporal leaf. The iris vessels were dilated, especially at the base, and newly formed thin-walled vessels were present in the

FIG. 3 Cornea—iris angles, nasal side. $\times 15$

FIG. 2 Whole right eye, sectioned from 10 to 4 o'clock.
 $\times 3$

stroma and on the anterior surface. There was migration of the pigment epithelium around the pupil margin.

The upper temporal choroid was generally thickened and hypercellular, and the ciliary body contained a few foci of acute inflammatory cells.

The retina was extensively detached by subretinal haemorrhage posteriorly and superotemporally, and artefactually detached inferonasally. The peripapillary and temporal retina were markedly thickened by glial proliferation, hypercellularity, vascular engorgement, and neovascularization. Posteriorly there was marked thickening of the nerve fibre layer and inner plexiform layer, disruption of the ganglion cell layer, and infiltration of these layers by cells with small round nuclei; the architecture of the outer retinal layers was fairly normal. Further peripherally, the superotemporal retina expanded into a tumour mass of fine fibres and cells. Most of the nuclei were round or oval and deeply stained, and some were arranged in swirl-like formations. Cells with spindle-shaped nuclei and cells with large pale nuclei were dispersed through the mass. Holzer stain demonstrated stellate cytoplasmic processes of some cells. There were several foci of calcification in the tumour (Figs 4 and 5, overleaf).

The optic nerve itself was normal. The tumour mass did not seem to arise directly from the papilla, but from the nerve fibre layer immediately around it.

Discussion

Glial hamartomas of the retina and/or optic disc in von Recklinghausen's neurofibromatosis are relatively rare and only sparse reports of the histology of such lesions have appeared in the literature since van der Hoeve's early descriptions. Retinal lesions have usually been discrete small masses, resembling the retinal hamartomata of tuberous sclerosis. Optic disc tumours of neurofibromatosis have rarely extended very far into the surrounding retina. The tumour in this case was massive and was composed of a dense network of glial fibres and cells, some of which could be identified as astrocytes; there were also areas of

FIG. 5 *Tumour cells.* $\times 275$

FIG. 4 *Temporal retinal mass.* $\times 20$

calcification and enlarged vascular channels. The structure of this large tumour was similar to that of the smaller retinal and optic nervehead tumours of neurofibromatosis recorded in the literature. It was felt that the tumour could justifiably be called an astrocytic hamartoma of the retina in a patient with generalized neurofibromatosis. The question of its differentiation from massive gliosis did arise, but the latter characteristically occurs in eyes altered by long-standing inflammation or degenerative changes; this young patient's symptoms were of relatively short duration and there had been no previous injury or inflammation of this eye.

Iris nodules have long been recognized as a manifestation of neurofibromatosis, and in this patient the iris lesions in fact provided the clue to diagnosis before the presence of *café-au-lait* spots and subcutaneous nodules was observed. Iris "tumours" are usually bilateral, and vary in size from microscopic to grossly visible ball-like formations situated on the iris or deep in the crypts. The nodules are usually pigmented but may be pale and rather flat or "soft" in appearance. Microscopically the lesions consist of aggregations of spindle-shaped cells. In general, the iris stroma, like the rest of the uveal tract in these cases is hypercellular.

Ectropion uveae in neurofibromatosis presents a particularly interesting entity and is probably a distinct expression of the disease process rather than a mere secondary ectropion due to iris atrophy, especially in such a case as this in which the ectropion was present early in the course of involvement and could not be attributed to any pronounced degree of iris atrophy. It has been proposed that ectropion uveae represents an active proliferation of the pigment epithelium around the pupil border or a disturbance in the growth rates of the mesodermal and ectodermal components of the iris, or to shrinkage of a newly-formed cell layer on the surface of the iris in neurofibromatosis.

The glaucoma of von Recklinghausen's disease is usually present at birth or becomes apparent early in life, and is often attributable to developmental anomalies of the filtration angle. In other cases, the glaucoma is associated with neurofibromatous involvement of the uvea. The mechanism of this glaucoma, whether of childhood or adult onset, is not understood; the direct cause of the angle closure which complicates these cases is also not known. The glaucoma in this adolescent patient was the presenting sign and initially obscured the diagnosis of intraocular tumour. The degree of neovascularization and peripheral anterior synechiae on initial examination was out of proportion to the amount of retinal pathology seen in the early stage, and it would seem, therefore, that the glaucoma was a distinct manifestation of the disease related more to the generalized uveal hypercellularity than to the presence of the retinal tumour itself. The angle closure and neovascularization may well be part of the total proliferative nature of this disease.

Summary

An adolescent girl with *café-au-lait* spots and subcutaneous nodules characteristic of neurofibromatosis presented with loss of vision and severe glaucoma in one eye. There was proliferation of the cellular and vascular components of the uveal tract and a massive glial tumour of the retina.

This study was supported in part by the Heed Ophthalmic Foundation.

The authors are indebted to Dr. Frederick L. Graff of Hagerstown, Maryland, who referred the patient.

Bibliography

- BLOCH, F. J. (1948) *Arch. Ophthalm. (Chicago)*, **40**, 433
 DAVIS, F. A. (1939) *Ibid.*, **22**, 761
 FRIEDENWALD, J. S. (1926) "Contributions to Ophthalmic Science", p. 23. George Banta Publishing Co., Menasha, Wisconsin
 GOLDSMITH, J. (1949) *Arch. Ophthalm. (Chicago)*, **41**, 718
 GOLDSTEIN, I., and WEXLER, D. (1930) *Ibid.*, **3**, 288
 HALES, R. H. (1963) *Ibid.*, **70**, 648
 LIEB, W. A., WIRTH, W. A., and GEERAETS, W. J. (1959) *Confin. neurol. (Basel)*, **19**, 230
 SARAN, N., and WINTER, F. C. (1967) *Amer. J. Ophthalm.*, **64**, 607
 STALLARD, H. B. (1938) *Brit. J. Ophthalm.*, **22**, 11
 TRUEMAN, R. H., and RUBIN, I. E. (1953) *A.M.A. Arch. Ophthalm.*, **50**, 468
 VAN DER HOEVE, J. (1932) *Trans. ophthalm. Soc. U.K.*, **52**, 380
 WIENER, A. (1925) *Arch. Ophthalm. (N.Y.)*, **54**, 481
 WOLTER, J. R., and BUTLER, R. G. (1963) *Amer. J. Ophthalm.*, **56**, 964