PATHOLOGICAL EXAMINATION OF NINE CASES OF RETROLENTAL FIBROPLASIA

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Retrolental fibroplasia is an apparently new disease affecting the eyes of premature babies of low birth weight, commonly occurring bilaterally, and developing during the first six months of life in eyes which were normal at birth. The possibility that the increased survival rate of premature babies might account for the increased incidence of the disease has been considered. In the United States the statistics of Kinsey and Zacharias (1949) and of Gilger (1949) show that the increased survival rate cannot be accepted as a complete explanation. Terry (1942, 1943, 1945) was the first man to appreciate this disease as an entity, and his work has stimulated a great interest in the condition in the United States, where a large number of publications have appeared. In the United Kingdom, an extensive review of the literature is given by Cross (1950), but the only pathological study so far is that of Wolff (1950).

The fully developed disease is characterized by a total retinal detachment, the development of a fibro-vascular membrane behind the lens, and, later, by signs of a low-grade inflammation in the anterior half of the eye. The clinical and pathological interest of the disease is that eyes may be removed on the basis of a diagnosis of retinoblastoma. Retrolental fibroplasia constitutes one variety of pseudoglioma, the combination of the history with the characteristic histological appearance enabling it to be separated from the other members of the group.

Present Series

We have examined nine eyes in which we made the histological diagnosis of retrolental fibroplasia, and we describe below the various features which these eyes show in differing degrees and on which we based our opinion. Bad fixation of one of the eyes made the histological details difficult to interpret, but it is included in the series because a diagnosis was possible when the histology was considered together with the clinical history. The Table gives brief details of the cases.

Case No.	Birth Weight		Gestation	Eyes Affected	Age at Enucleation
	lb. oz.	kg.			
1	2 3	0.99	28 wk.	Both	24 months
2	2 9	1.16	32 "	"	5 "
3	2 10	1.19	Uncertain	"	6 "
4	2 13	1.27	32 wk.	"	4 "
5	3 3	1.45	27 "	"	9 "
6	3 4½	1.49	33 "	R. only*	6 "
7	3 9	1.62	30 "	Both	8 "
8	3 10	1.64	33 "	"	16 "
9	4 14	2.21	36 "	"	5 "

* Early signs of the disease were present in the left eye, but have since regressed.

The retrolental membrane is formed of vascular connective tissue (Fig. 1). In all our cases this membrane was attached to the epithelium of the anterior part of the pars plana, or as far forward as the ciliary processes.

FIG. 1.—The fibro-vascular retrolental membrane (Case 2.)

This connexion is occasionally very clear, and the non-pigmented cells of the ciliary epithelium invade the connective tissue for some distance (Fig. 2). The fibroblasts and newly formed capillaries give the appearance of an inflammatory reaction, although inflammatory cells are not an outstanding feature of the membrane.

The retina in every case was completely detached and greatly folded, lying immediately behind and attached to the membrane which separated it from the lens. In each case the detached retina extended peripherally to the pars plana, or even further forward, a separation between the inner clear cells and the pigment cells anterior to the ora serrata having occurred. Fig. 3 shows

FIG. 2.—Ciliary epithelium invading the membrane (Case 7).

FIG. 3.—Retinal detachment extending up to the ciliary body. Proliferation of clear cells of ciliary epithelium (Case 2).

the retinal detachment extending up to the ciliary body, and another section (Fig. 4) shows the separation occurring in the pars plana between the clear cells and the proliferating pigment cells. Retroretinal inflammatory changes may occur, however, and obscure this relationship between the pigment layer and the clear cells of the ciliary region.

All the cases showed a separation in some degree, but they also showed a partial reunion of the other retinal layers with proliferating pigment cells, and a formation of strands of connective tissue in the angle between these cells and the detached retina. In two cases there was a distinct separation to one side of the section, but to the other side a reunion had occurred as the result

FIG. 4.—Separation between the clear cells and the proliferating pigment cells (Case 5).

of proliferative changes. The considerable folding of the retina made it difficult to decide whether it was fully differentiated before detachment occurred.

Rosettes (Fig. 5) were fairly common, but there were areas in which all layers of the retina could be made out. It is possible that the finding of rosettes in the thickened, detached retina might give the impression that we were dealing with a retinoblastoma, especially if retinal differentiation was poor. We saw, however, nothing suggestive of the characteristic areas of degeneration found in retinoblastoma. Haemorrhages and exudates were present in the folded retina in six of the cases, and in two of these the haemorrhages were particularly large. Blood vessels of the retina may connect with the membrane (Fig. 6), and, in addition to this vascular connexion, glial fingers may penetrate the membrane from a glial hyperplasia on the front of the retina (Fig. 7).

Every case showed an exudate between the retinal pigment epithelium and the other retinal layers. In this exudate a common feature was the presence of numerous "ghost" cells (Fig. 8), which in one case invaded the retina itself. The origin of these cells is uncertain, but they are probably derived from the retinal pigment epithelium (Lamb, 1938), which shows a tendency to proliferate. These "ghost" cells are, of course,

FIG. 5.—Rosette in the detached retina (Case 1).

FIG. 6.—Vascular connexion between retina and retrolental membrane (Case 6).

FIG. 7.—Glial hyperplasia on the surface of the retina (Case 6).

not peculiar to the condition of retrolental fibroplasia but occur in many retinal inflammatory and degenerative diseases. The signs of irritation in the anterior part of the eye are also not specific, and occur late in the disease. Irritative inflammation of the iris leads to adhesion between iris and lens, and the periphery of the anterior chamber is often obliterated, apparently owing to the lens and the iris being pushed forward by the mass of tissue behind them. In one case Descemet's membrane showed a split where the iris had been adherent to the cornea; only two cases had no pathological changes in the anterior chamber.

Aetiology

It has only been possible to examine eyes excised in the late stage of the disease, and in our series of cases no single pathological sign demonstrated how the disease may start. Wolff (1950) believes that a failure of coaptation of the two layers of the optic cup at about the

FIG. 8.—"Ghost" cells in subretinal exudate (Case 6).

third month of intrauterine life leads to a quiet cyclitis and the development of a retrolental cyclitic membrane. Examination of these eyes would support Wolff's contention that the retinal detachment extends beyond the ora serrata, our evidence being the frequent separation between the pigmented and clear cells of the ciliary epithelium. We think, however, that retroretinal inflammatory changes are not so rare as Wolff suggests. Klien (1949) thinks that angioblastic tissue may invade the retina and prevent its proper development, or that a normally developed retina may be detached owing to traction by such angiomatous tissue within remains of the vitreous. What constitutes angiomatous tissue is difficult to define, but we found no new vessel formation which could not be explained as a simple reaction to some irritation. None of the patients had naevus formation elsewhere in the body.

Reese and Blodi (1951) also concluded that retrolental fibroplasia represents the eye manifestation of a generalized congenital angioplastic process. Their pathological material is particularly interesting, because the eyes show the early stage of the disease. One patient was one of twins, weighed 2 lb. 14 oz. (1.3 kg.) at birth, and died when 11 weeks old. Retrolental fibroplasia had been diagnosed at 8 weeks. The other twin lived and developed the disease in both eyes. The sections Reese and Blodi described showed vascular budding from the inner surface of the retina and much new vessel formation in the vitreous. There were also haemangiomas of the right orbit, the choroid plexus of the fourth ventricle, the carotid body, and the cervical region of the pharynx. From their examination of the material they concluded that an angioplastic process of the vitreous is the characteristic feature of the disease. It seems equally possible, however, that a haemorrhage from the retina or exudation into the vitreous could lead to new vessel formation of this kind, in the same way as occurs in the development of retinitis proliferans.

Minton and Cole (1951) reported two cases of retrolental fibroplasia with pathological details of one of these, that of a full-term infant in which the eye disease was accompanied by multiple congenital deformities—congenital encephalo-ophthalmic dysplasia (Krause, 1946). Previous authors (Reese and Blodi, 1950, 1951; Parker Heath, 1950) have tended to separate this syndrome from the retrolental fibroplasia of prematurity, and on the clinical and pathological evidence available we consider it hardly justifiable to regard Minton and Cole's first case as one of retrolental fibroplasia.

A congenital condition with which retrolental fibroplasia should not be confused is a persistent posterior vascular sheath of the lens, which is usually unilateral, present at birth, and not accompanied by a detachment of the retina. Terry (1942, 1943, 1945) thought that a fibroplastic overgrowth of a vascular sheath of the lens persisting in premature infants was the cause of retrolental fibroplasia.

Conclusion

We believe that an exudative process occurring in the retina or choroid could produce a serous detachment of the retina and vitreous opacity, with the subsequent development of a cyclitic membrane and total retinal detachment. This view is advanced only after considering the histological evidence in conjunction with clinical observations, and histological examination of eyes in an early stage of the condition is necessary before the aetiology can be determined. We are examining the

eyes of stillborn infants and of those dying in the early weeks of life, and hope that this will throw some light on the problem.

Summary

Histological appearances of nine eyes enucleated in the late stage of retrolental fibroplasia are described.

It is considered that the condition is inflammatory in origin, but the cause of the irritation cannot be deduced from the histology.

We are grateful to the surgeons of the Oxford Eye Hospital for permission to use the histories of cases under their charge.

REFERENCES

- Cross, A. G. (1950). *Ophthalm. Lit., Lond.*, **4**, 80.
 Gilger, A. P. (1949). *Amer. J. Ophthalm.*, **32**, 917.
 Heath, P. (1950). *J. Amer. med. Ass.*, **144**, 1148.
 Kinsey, V. E., and Zacharias, L. (1949). *Ibid.*, **139**, 572.
 Klien, B. A. (1949). *Arch. Ophthalm., Chicago*, **41**, 553.
 Krause, A. C. (1946). *Ibid.*, **36**, 387.
 Lamb, H. D. (1938). *Amer. J. Ophthalm.*, **21**, 618.
 Minton, J., and Cole, P. (1951). *British Medical Journal*, **1**, 450.
 Reese, A. B., and Blodi, F. C. (1950). *Amer. J. Ophthalm.*, **33**, 23.
 — (1951). *Ibid.*, **34**, 1.
 Terry, T. L. (1942). *Ibid.*, **25**, 203, 1409.
 — (1943). *Arch. Ophthalm., Chicago*, **29**, 36.
 — (1945). *Ibid.*, **33**, 203.
 Wolff, E. (1950). *Proc. roy. Soc. Med.*, **43**, 227.

A CASE OF POLYARTERITIS NODOSA TREATED WITH CORTISONE

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The following case of polyarteritis nodosa is reported in order to demonstrate that cortisone can heal the characteristic lesions, and to show that the use of the drug in the later stages of the disease may have undesired sequelae.

Case Report

A male shop assistant aged 47 was referred to Professor Henry Moore in November, 1950, by Dr. Michael Kelleher, for investigation of persistent leg pain. The family history was no help, but the previous personal history was one of sporadic illnesses since 1945.

In 1945 his right maxillary antrum was drained, and two weeks later he developed joint stiffness, which was diagnosed as "rheumatic fever." These joint symptoms persisted for several weeks. Some weeks later he developed a chest complaint which was diagnosed as "pneumonia."

No information regarding treatment during this period could be obtained. Special attention was directed to the question of sulphonamide therapy because of the possibility that there may be some connexion between polyarteritis nodosa and the sulphonamides. It seems probable that the patient did receive these drugs, but we have been unable to obtain definite information on this point.

From the end of 1945 he had no definite ailments, but there was a gradual loss of weight until July, 1950, when he began to suffer from loss of energy, night sweats, and a productive cough. Later he developed pain in a small area of

the right calf, which gradually became more severe and spread over the entire calf. A similar pain then began in the left calf.

On admission clinical examination was unrewarding; observation showed an evening pyrexia. The latter, together with the loss of energy and of weight and the occurrence of night sweats, suggested a diagnosis of phthisis. This was not substantiated by a radiograph.

The blood pressure was normal. The urine contained a moderate quantity of albumin, a few granular casts, and a few red cells. The urinary findings were constant on repeated examination. The blood urea was 51 mg. per 100 ml. Total and differential white cell counts were normal. The Widal reaction and blood culture were negative.

Renal tuberculosis was then considered, but no tubercle bacilli were demonstrated on repeated examination of the urine, and excretion urography was normal.

Over a period of seven days the leg pains became more intense; the upper limbs also became painful and the patient complained of marked weakness. The following abnormal nervous signs were noted: (1) In the upper limbs there was generalized wasting and weakness consistent with the poor physical health. (2) In the right hand there was paralysis of the thenar muscles with complete loss of power in the opponens pollicis and the abductor pollicis brevis. Perception of pin-prick and light touch was lost over the entire volar surface of the thumb and first two fingers and over the distal third of the dorsal surface. (3) On the left forearm along the medial border was an oval area extending from elbow to wrist where pin-prick and light touch were not appreciated. The patient complained of numbness in this area. (4) The deep reflexes were present and equal in both upper limbs. (5) The superficial abdominal reflexes were absent on the right side but present on the left. (6) Both lower limbs were markedly wasted, and weakness was considerable. Pin-prick and light touch were lost over the lateral aspect of the right calf and dorsum of the foot. Postural sense was absent in the right great toe and was impaired in the left. All deep reflexes were absent, and the right plantar response was doubtfully extensor.

The overall picture was that of an asymmetrical polyneuritis involving the lower limbs, with median neuritis of the right hand and a lesion of the left medial cutaneous nerve of the forearm.

The picture of widespread nervous disorder associated with pyrexia and abnormal urinary findings suggested the possibility of polyarteritis nodosa. Eosinophil counts were carried out every four or five days, and a daily search was made for peripheral arterial nodes. The earlier eosinophil counts were below 300 per c.mm., but on the 18th day in hospital the count rose to 3,450 per c.mm. This was regarded as strong collateral evidence in favour of the suspected diagnosis. On the 28th day subcutaneous nodes were found in the left upper arm. One node was removed from a superficial branch of the left brachial artery (by Mr. P. Carey). The pathological report confirmed the diagnosis.

On the same day the patient developed a subarachnoid haemorrhage (presumably due to rupture of an intracranial node) and had multiple epileptiform attacks. At this stage cortisone treatment was under active consideration, but was rejected because of shortage of supplies. Later the relatives procured some "cortone" from America and treatment was begun on the 50th day, when the patient's condition was grave. The drug was administered by deep intramuscular injection in single daily doses of 200 mg. for four days followed by 100 mg. for six days—a total of 1.4 g. in 10 days. At the end of this period, 60 days after his admission to hospital, the patient died.

In the terminal stages full neurological examination was repeated and more widespread nervous damage was noted as follows. The patient complained of severe continuous paraesthesia in his hands and feet. The cranial nerves were still normal. The upper limbs were markedly wasted, and