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COMMUNICATIONS

GLIOMA RETINAE*

A Statistical Survey of New Cases at the Royal London
Ophthalmic Hospital (Moorfields Eye Hospital)

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A STUDY of all cases of glioma retinae treated at Moorfields Eye Hospital since 1871 was initiated by Lawford and Collins (1890) and subsequently maintained by Marshall (1897), Owen (1905), Berrisford (1916), and Davenport (1926). A further review of 76 patients who attended the Hospital between January, 1925, and December, 1947, is presented here. Certain new facts regarding the aetiology, histopathology, and treatment of this condition have come to light.

Aetiology

Although several authors have experimentally obtained the formation of rosettes, nothing definite is yet known in relation to

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the immediate or remote causes of glioma. There are two instances in the present series with a history of trauma and six cases had a definite history of previous exanthemata. The exact role of trauma and exanthemata in the causation of glioma, however, is still very uncertain.

The possibility of some type of disease in the expectant mother as an exciting factor, *e.g.*, rubella, must be borne in mind.

Incidence

Of all the admissions to the hospital during the past 22 years cases of glioma retinae formed only 0.0063 per cent.

Age.—The exact date of onset of glioma is difficult to ascertain, but the following observations may be made:

Year					Percentage
1st	...	...	...	...	46 (Including 8 per cent. noted at birth)
2nd	...	...	...	...	25
3rd	...	...	...	...	16
Later	...	...	...	...	12

These findings are in accordance with all the previous reports at the hospital. The oldest case recorded was that of a patient who came at the age of 7 years and six weeks, which is in fact the oldest case recorded since 1871. Seven years can, as a rule, safely be taken as the limit for the occurrence of glioma, although several older cases appear in the literature.

In the bilateral cases again the maximum incidence was in the first year and next in the second year. It is interesting to note that none of the bilateral cases showed the first incidence after the age of three years, a fact strongly pointing to the congenital basis of glioma and more so of the bilateral ones. There were four examples in which both eyes were affected at birth, and the most interesting feature is that of the six cases in which glioma was noted at birth, four were bilateral.

Eye Affected. —Right	...	...	...	...	33 per cent.
Left	...	...	...	...	29 per cent.
Bilateral	...	...	...	...	37 per cent.

The bilateral incidence in this series is rather higher than in some others. A careful previous history and follow-up over a sufficiently long period perhaps accounts for this.

The longest interval in the occurrence of the growth in the two eyes has been three and a half years, as against the three years suggested by Collins (1892, 1895).

Heredity.—Whereas a number of cases of familial and hereditary influence on the occurrence of glioma are recorded by different authors, the present series has failed to bring to light any marked influence of this nature. Of the only two instances, one is an example of vertical transmission and the other of horizontal transmission. Since 1871 there have been only three instances at the Moorfields Eye Hospital out of 286 cases (*i.e.*, about 1 per cent.), who gave a positive history of familial glioma, a conclusion quite contrary to the reports of other authors.

Sex.—This seems to have little effect on the occurrence of glioma. There were 41 male and 35 female children.

Symptomatology

The clinical features come under notice only when the condition becomes sufficiently advanced. About 60 per cent. of cases came with “amaurotic cat’s eye”, and the remainder with squint,

nystagmus, inflammation of varying degree, altered size of the eyeball, or general symptoms.

On examination, a dilated and inactive pupil was present in 50 per cent., raised intra-ocular tension in 31.5 per cent., and abnormal anterior chamber (absent, shallow, or irregular) in 30 per cent.

Histo-Pathology

Some interesting facts have emerged from the study of the histology :

(1) *Nature of Glioma*.—Retinoblastoma was present in 35 per cent., neuro-epithelioma in 16 per cent., and a mixed content in 36 per cent. of these cases. Thirteen per cent. remained undetermined.

(2) *Retinal Growth and Retina*.—In its earliest stages even the histological examination of the excised eye cannot, with any degree of certainty, reveal the clinical type of glioma and most of the neoplastic infiltration appears to occur in the plane of the retina, thus virtually increasing the incidence of glioma planum. Glioma endophytum was present in 21 per cent. of cases, glioma exophytum in 46 per cent. (i.e., it was twice as common as glioma endophytum), and 15 per cent. showed a mixed nature. In the remaining eyes this detail could not be ascertained.

In 60 per cent. there was a retinal detachment, half of them total.

(3) *Choroidal Infiltration* (Fig. 1).—In this series the choroid was found infiltrated in eight eyes (10.5 per cent.) with some doubt as to its involvement in another case. Seedlings were present on its surface in two instances, probably indicating a stage prior to its involvement. There is no specified time in the

FIG. 1.—Choroidal infiltration (pigment epithelium eaten up).

process of spread when the choroid becomes involved, and in almost all these cases the retinal growth was not particularly extensive. On the other hand, in eighteen eyes the retina was found to be totally or very extensively destroyed by glioma without any choroidal invasion. That the extent of the retinal neoplasm is not the determining factor in the secondary invasion of the choroid is certain from this observation. Further, in each of the eyes showing choroidal infiltration or its threatened invasion, glioma was of the exophytum type, except in one case where it was of a mixed nature. This points to implantation through the sub-retinal fluid as the commonest mode of spread to the choroid. Glioma cells lying upon the pigment epithelium seem to eat their way through it and affect the choroid.

(4) *Infiltration of the Optic Nerve*.—The optic nerve has been suggested as being next to the choroid in frequency of involvement. In this series, however, the optic nerve was invaded in 24 eyes (31·5 per cent.), as against nine cases of choroidal involvement. In five cases both the choroid and the nerve were affected and it cannot be said which was the first to be involved. The rest of the nineteen eyes showed involvement of the nerve only. The optic nerve was affected in the following ways:

- (a) disk only, sixteen eyes;
- (b) up to the lamina cribrosa, five eyes (Fig. 2);
- (c) beyond the lamina cribrosa, three eyes (Fig. 3).

In four eyes a deposit of glioma cells was present on the surface of the disk without the nerve being actually affected, which perhaps indicated the first step in the process of dissemination.

(5) *Vitreous*.—In all eyes examined in this series except one, the vitreous was degenerated, and the fluid vitreous contained clumps of glioma cells.

(6) *Iris and Ciliary Body*.—Seedlings of glioma cells were present on the ciliary body in two instances (Fig. 4), and were found in the anterior chamber, on the

FIG. 2.—Infiltration of optic nerve up to lamina cribrosa.

FIG. 3.—Infiltration of optic nerve beyond lamina cribrosa.

FIG. 4.—Glioma clusters on ciliary body, in posterior chamber, in front of iris, and on back of cornea.

FIG. 5.—Glioma nodule on anterior surface of iris.

back of the cornea, in front of the iris (Fig. 5), and/or on the anterior lens capsule in twelve eyes (16 per cent.). Similarly, inflammatory reaction by way of keratic precipitates, cells or exudates in the anterior chamber, and/or cellular infiltration of the uvea or posterior synechiae were present in 54 eyes (71 per cent.).

(7) *Lens*.—Wintersteiner (1897) found only three cases out of 32 in which the lens was normal, flat anterior polar cataract having formed in one-fifth of his cases. In the present series the lens showed no particular damage. Complicated cataract was present in two eyes and undefined degenerative changes in one.

(8) *Sclera*.—This was involved in one case only near the disk.

(9) *Globe*.—There were two instances where the eye shrank after degeneration without perforation—one after radiation and the other spontaneously—both of which contained largely necrotic and calcareous gliomata (Figs 6 and 7). In two other instances there was a perforation and subsequent shrinking (Fig. 8), but since the eyes were removed immediately the sequelae could not be studied.

Difference between Unilateral and Bilateral Glioma

Cummings and Sorsby (1944), in ascribing to the site of origin of glioma the possible histological differences, said that the unilateral neoplasms appeared to arise rather from the outer nuclear layer, and bilateral ones from the inner layer only or from both.

In this series, a statement as to the exact sites of origin of the neoplasm was given by the pathologist in very few instances. A study of these slides showed that in the majority the tumour was so much advanced that it was not possible to determine the exact

FIG. 6.—Calcareous deposits in glioma retinae.

FIG. 7.—Spontaneous shrinking.

FIG. 8.—Shrinking after perforation.

site of origin. A definite opinion could be given in the cases set out in Table I (overleaf).

Whereas the single factor of a greater number of bilateral gliomata arise from the inner nuclear layer favours the opinion

of Cumings and Sørsby, the remaining three factors, being no less significant, are against it. The number under consideration is not large, but certainly opens a new line for investigation. It is necessary that several sections should be examined at the time of making the first report and a definite note should be made about the layer which appears to be the site of origin.

TABLE I
Site of Tumours

Tumours	Site of Origin		Total
	Inner nuclear layer	Outer nuclear layer	
Unilateral	3	1	4
Bilateral	6	3	9
Total	9	4	13

Treatment

Table II gives the line of treatment adopted for these cases and the results obtained.

TABLE II
Treatment and Results

Treatment	Results				
	No. treated	Permanent recovery	Alive but not cured	Not traced	Failure
Unilateral enucleation ...	46	21	1	24	0
Bilateral enucleation ...	11	3	—	8	0
Enucleation followed by exenteration on the same side... ..	1	1	—	—	0
Enucleation on one side and exenteration on the other side... ..	1	—	—	—	1 dead
Enucleation on one side and radiation on the other ... *of remaining nine enucleated ...	17	{ 5 5	1 —	1) 4)	10* (1 died on table)
Total	76	35	2	37	2 dead

It is clear from this study that enucleation offers the best chances for a permanent recovery and the results of radiation have not been particularly encouraging. The best results were obtained with radium treatment (about 36 per cent. cure) and deep x ray proved a complete failure. One case treated with a diathermy barrage around the tumour showed a good reaction, but could not be followed up.

Where the choroid is involved it is suggested by certain authors that some orbital extension may have taken place even in the absence of apparent clinical evidence, and that exenteration or the less drastic treatment of radiation should be employed. In this series all the nine cases showing choroidal infiltration were treated by enucleation only; no post-operative radiation was given to any case and none is reported to have developed a recurrence. This shows that no matter what the involved tissues are, as long as the neoplasm is strictly intra-ocular, enucleation alone offers as good a chance of recovery as enucleation followed by radiation. If, on the other hand, there is definite clinical evidence at the time of enucleation, or histological evidence later, that secondaries are present outside the eye, nothing short of exenteration combined with radiation should be considered a complete treatment.

A combined intracranial and orbital operation for bilateral retinoblastoma has been suggested by Jean (1922). Ray and MacLean (1943) justify such a drastic course by arguing that the survival rate of the classic enucleation with resection of the maximum portion of the optic nerve is found as low as 35 per cent. and as high as 57 per cent., *i.e.*, in 65 per cent. of the first and 43 per cent. of the second, the operation was a failure. Reese (1931), however, is of the opinion that the intracranial operation is unnecessary.

Considering the 76 cases here, the drastic so-called foolproof treatment appears to be unnecessary. In 24 eyes only out of the 104 affected with glioma was there involvement of the optic nerve. Thus, if this operation had been undertaken as a routine in every instance, it would not have been worth while in eighty eyes (77 per cent.). Further, out of these 24 eyes with optic-nerve involvement, there was positive evidence of extension of the neoplastic infiltration beyond the point of section in one instance only, although there were orbital metastases in two others also. This shows that although the tumour is known to spread along the nerve quite early, yet if the longest possible piece of the optic nerve is excised along with the globe at the earliest opportunity one can be more or less certain of leaving no residual tumour behind. Thus in three instances only was there a justification

for undertaking the combined operation, and the necessity for it could not be established until the eye was removed and the stump of the nerve sectioned. Of these three cases, one was treated by exenteration and showed a permanent recovery, another died in spite of exenteration because of the delay in obtaining consent for a bilateral enucleation, and one case remains untraced. Clinically it is impossible to decide whether the optic nerve is involved or not, and if so how far. In view of the added risk of the intracranial operation and all its involved complications, it is worth considering to what extent the combined intracranial and orbital operation is justified.

III-Effects and Complications of Radiation

One or more of the following damaging effects were met with in our cases :

- Skin*.—Hyperaemia, oedema, destruction and falling of lashes—two cases.
- Conjunctiva*.—Acute conjunctivitis in one case, complete symblepharon in one, and degenerative changes in one. Transient oedema and hyperaemia are of frequent occurrence.
- Cornea*.—This first became hazy, then opaque, and sclerosed in one case. Infiltration, ulceration, and ultimate perforation occurred in two cases. The cornea is relatively radioresistant and the commonest occurrence therein is a temporary clouding only.
- Lens*.—Posterior lenticular opacities were present in three cases. In this series the maximum time was two years when the earliest opacities were first noticed in one case, and five years later a generalized sclerosis was present. In another case the earliest opacities were noted 17 months after radiation, and a more marked star-shaped opacity was found four and a half years afterwards in the posterior cortex. It is evident from this, that the changes giving rise to opacification start after a considerable length of time and progress slowly. The average time mentioned, however, is three years.
- Panophthalmitis*.—This was caused by radiation in two instances.

Prognosis

Prognosis depends upon the stage when the treatment is commenced, the type of treatment employed, and the completeness with which the entire neoplasm is eradicated. The survival rate reported by Hirschberg (1868) was 5 per cent., Wintersteiner (1897) 17 per cent., Parkhill and Benedict (1941) 35 per cent., Adam (1911) 57 per cent., and Reese (1931) 57 per cent. In the present series the results were as follows :

Results	Percentage
Known deaths	2.6
Known permanent recoveries	46.0
Spontaneous retrogression	2.6
Living, but treated less than three years ...	2.6
Untraced (but no record of death found) ...	48.7

In bilateral cases, the prognosis is supposed to be worse, but this was not so in the present series. Of 28 bilateral cases, twelve recovered permanently, one died, one is alive two and a half years after the treatment, and fourteen cases remain untraced.

After extra-ocular extension has occurred through the optic nerve or the sclera the outlook is reported to be very grave and recurrences are thought to be more common in them. In our cases, out of the 24 with nerve involvement twelve are known to have permanently recovered and twelve are untraced. The sclera was found to be affected in one instance which remained untraced. Recurrence was found in four instances—in one in the eye itself, and in three cases in the orbit. Only one case showed extension of the neoplastic infiltration beyond the point of section, and that case developed recurrence in the orbit but survived, and one case died of what was diagnosed as the sarcoma of the maxilla. It is evident that, no matter how far in the orbit the neoplasm may have extended, as long as the malignant infiltration is strictly confined to the orbit and the infiltrated areas can be removed completely, there is a good prognostic outlook. If, on the other hand, any infiltrated portion of the optic nerve or the orbital tissue is left behind at the time of excision, a fatal issue would be imminent.

In the absence of death certificates at the office of the Registrar-General, a high proportion may be presumed as survivors. With early surgery and with improved technique, the prognosis has unquestionably become much better.

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