

Hypothalamic gliomas in children

CLIFFORD ROBERSON¹ AND KENNETH TILL

*From the Department of Neurosurgery, The Hospital for Sick Children,
Great Ormond Street, London*

SYNOPSIS Twenty children with gliomas of the hypothalamus were studied. Management was by radiotherapy alone, or operative treatment with or without radiotherapy, and in some cases treatment was withheld entirely. One half of the children died within one year of presentation, whereas the remainder are alive and well after many years. An attempt is made by analysis of the results to determine when surgery or radiotherapy or a combination of the two may appropriately be employed in the management of this condition.

In most publications concerning optic nerve gliomas (a general term for gliomas involving the optic nerve, chiasm, optic tracts, and hypothalamus) lesions confined to the hypothalamus are usually mentioned only incidentally. In this paper, gliomas involving only the optic nerves or chiasm are excluded. In all the children, the primary lesion involves the hypothalamus, or hypothalamus and optic chiasm.

Martin and Cushing (1923) first noted the difficulty of determining the site of origin of optic nerve gliomas, since these tend to extend up and down the optic pathways, often making it impossible to decide even at postmortem examination whether the growth originated in the chiasm and extended to the hypothalamus, or *vice versa*.

GENERAL CHARACTERISTICS Martin and Cushing (1923) found 0.84% of 823 tumours in all age groups to be gliomas of the optic pathways. In the Vienna series of Koos and Miller (1971) 3% of 700 brain tumours in children and adolescents were gliomas of the optic pathways, these being 8% of the total glioma group. Taveras *et al.* (1956) found 1.7% of 2,000 gliomas of all age groups to involve the optic pathways. It is generally agreed that about 75% of all optic nerve gliomas occur in patients less than 12 years old (Matson, 1969; Koos and Miller, 1971). The

ages of the 20 patients here reported are shown in Table 2. There is no predilection for either sex, 11 being female and nine male. In most reports of children with optic nerve gliomas (Udvarhelyi *et al.*, 1965; Matson, 1969) 30 to 50% have stigmata of von Recklinghausen's disease, but in this more restricted series of hypothalamic gliomas only one of the 20 had neurofibromatosis. Matson (1969) found 22% of optic nerve gliomas were intraorbital; 65% involved intracranial portions of the optic nerves, and 13% involved both. Different proportions were reported by Hoyt and Baghdassarian (1969): of 36 patients only 11% were confined to the orbit, the remainder involved intracranial portions of the nerves. Twelve of the 36 had signs of hypothalamic involvement. Approximately 50% of all optic nerve gliomas at this hospital appeared to be hypothalamic in origin.

Fowler and Matson (1957) considered optic nerve gliomas to be a form of astrocytoma, whereas other authors (Koos and Miller, 1971) consider them to be spongioblastomas. The histology of the purely hypothalamic gliomas is the same as those confined to the optic nerves. However, Matson (1969) stressed that primary gliomas of the hypothalamus and chiasm sometimes demonstrate a higher degree of malignancy microscopically when compared with those originating in the optic nerve. Of our 20 patients, the 14 with positive biopsies all had astrocytomas of grades 1 or 2. In three of the remaining six

¹ Present address: Orange County Medical Center, Department of Neurosurgery, 101 City Drive South, Orange, California, 92680 USA.

children, craniotomy was performed but either the biopsy specimen was inadequate or no biopsy was attempted for fear of needlessly inducing symptoms; however, the appearance at surgery in these three cases left no doubt that the tumour was a glioma of low grade malignancy. One child received radiotherapy without previous biopsy because the neuroradiological studies left little doubt as to the site and histology of the tumour, which was considered inoperable due to extension into the thalamus. Another child not biopsied presented with the sole finding of precocious puberty at age 6 years. The mass demonstrated by pneumoencephalography was so small that it was decided not to institute any treatment but to follow up with repeated pneumoencephalography. The final child not biopsied was already in terminal illness at the time of diagnosis.

PRESENTATION The presenting signs and symptoms of hypothalamic gliomas depend mainly upon the location and extent of the tumour. Chiasmatal involvement is often heralded by bi-temporal visual field defect, progressive loss of visual acuity, or occasionally by signs of hypopituitarism if the growth disturbs the pituitary stalk. Hypothalamic involvement may present as diabetes insipidus, obesity, emaciation, underdevelopment of external genitalia, or precocious puberty. The tumour may extend along the base of the brain to reach the interpeduncular region. Frequently the children present with signs of increased intracranial pressure due to occlusion of the foramina of Monro by tumour filling the third ventricle anteriorly. Only five of our patients did not present with signs and symptoms of increased intracranial pressure.

Two patients presented with diabetes insipidus; both were easily controlled with pitressin. None of the children developed diabetes insipidus after the initial admission. On the other hand, two of the four children who developed sexual precocity did not do so until two years after treatment (conventional radiotherapy in one and implantation of radioactive gold seed in the other). Precocious puberty is probably the result of involvement of the median eminence and may be produced by lesions other than gliomas such as ectopic pinealomas, teratomas, and hamartomas (Matson, 1969). Two of our four patients

with precocious puberty were among those whose diagnosis was not verified by biopsy.

Of the 20 children with hypothalamic gliomas, four presented with the diencephalic syndrome which Russell (1951) originally described as a paradox of skin pallor and extreme body wasting in spite of good appetite and food intake, a sense of well-being sometimes bordering on euphoria, hyperactivity, and normal haemoglobin levels. Our four cases were atypical in that all had histories of poor feeding and apathy. The wasting is usually the only physical abnormality in the diencephalic syndrome; other indicators of hypothalamic involvement such as diabetes insipidus and electrolyte disturbances are uncommon. The wasting is so severe that radiographs show a complete absence of subcutaneous fat, a finding first described by Poznanski and Manson (1963), which differentiates it from other causes of emaciation. The diencephalic syndrome has been reported in children with primary malignant tumours of the posterior fossa which extended upwards into the hypothalamic region, but the usual cause is an infiltrating glioma of the anterior hypothalamus and floor of the third ventricle as in the cases reported here. The lesion may range from an extremely slow growing glioma resembling a hamartoma to an astrocytoma of grade 4 malignancy. The commonest type reported have been astrocytomas grades 1 and 2 (Smiih *et al.*, 1965), as were three of the four cases in our series. The fourth was not verified histologically. The syndrome occurs most frequently in children less than 1 year old, although it has been reported in children up to 4 years. Our patients were aged 7 months, 2 years, 2 years, and 5 years on admission with lengths of history three months, one year, four months, and four months respectively.

DIAGNOSTIC PROCEDURES The diagnosis can usually be made by plain radiography of the skull followed by lumbar pneumoencephalography, without the use of angiography. If angiography is used, the internal carotid arteries, proximal portions of the posterior communicating and anterior choroidal vessels may show lateral displacement. Large hypothalamic masses can elevate and straighten the anterior cerebral vessels and the internal cerebral vein. Angiography was performed on only two of our 20

patients and in one of these the vessels were regarded as normal, the diagnosis being made afterwards by pneumoencephalography.

Plain radiographs of the skull aided by special views of the optic foramina may reveal enlargement of the optic canals in those children in whom there is forward extension of the growth. Often, however, the pre-chiasmatic areas are not involved due to the tendency of hypothalamic gliomas to extend more posteriorly than anteriorly (Taveras and Wood, 1964). The size of normal optic foramina is not known with certainty, although Fowler and Matson (1957) considered the normal range to be from 4.1 to 4.65 mm. Hence, asymmetry of the two foramina is often a better indication of optic nerve involvement in the optic canals than the actual size of these canals.

The classical radiological sign of chiasmal, and therefore frequently hypothalamic, gliomas is the J-shaped sella turcica first described by Martin and Cushing (1923). The anterior aspect of the sella turcica is flattened, and enlargement of the chiasmatic groove leads to a flattened tuberculum. The J-shaped sella (more accurately described as pear-shaped), although highly suggestive of chiasmal or hypothalamic glioma, is also seen in congenital hydrocephalus and gargoylism (Koos and Miller, 1971). It is seen in only about half the children with confirmed diffuse chiasmal gliomas (Schuster and Westberg, 1967). Nine of the present patients had no sellar changes.

Suprasellar calcification is very uncommon in primary tumours of the hypothalamus, in contrast with an incidence of over 90% in children with craniopharyngioma. Several of the present patients were subjected to craniotomy in the hope that the suprasellar mass was a craniopharyngioma, although no calcification had been seen on skull radiographs. One patient with suprasellar calcification was found at exploration to have a hypothalamic glioma instead of a craniopharyngioma.

Hypothalamic gliomas are usually best demonstrated by air contrast radiography. Pneumoencephalography shows the third ventricle to be displaced posteriorly, usually with a bulge into its anterior portion. The margin of a tumour growing downwards may be outlined where it projects into the cisterna interpeduncularis.

Infiltrating gliomas usually have an irregular surface on air study, unlike non-infiltrating masses. Efforts should be made to visualize the surface of the tumour adequately, since a non-infiltrating lesion obstructing the foramen of Monro may be operable (Koos and Miller, 1971).

TREATMENT AND RESULTS

Since hypothalamic gliomas cannot be removed, they are clinically malignant although histologically benign. However, the prognosis is often unpredictable because the astrocytoma may grow extremely slowly. There may be very long-term survival, the quality of life in the interim ranging from a vegetative existence to a complete lack of symptoms. The proper management of the patient will therefore depend upon an assessment of the signs and symptoms and of the tumour's probable rate of growth. In some, simple observation may be best, while in others combinations of radiotherapy, craniotomy or burr hole biopsy, sub-total removal, and shunts will be required. The management of all types of optic nerve gliomas is still controversial because no large series are available for study and because the commonly long-term natural history has made statistically valid conclusions difficult.

Since hypothalamic gliomas are of low grade malignancy, they are theoretically unlikely to respond to radiotherapy. However, many publications (Taveras and Wood, 1964; MacCarty *et al.*, 1970) have concluded that radiotherapy is often of considerable benefit. Others conclude that no improvement in clinical condition or decrease in the size of the mass can be attributed to radiotherapy (Fowler and Matson, 1957; Matson, 1969; Stein *et al.*, 1971). Matson (1969) concluded that, after establishing the inoperability of the optic nerve glioma by surgical exploration, radiotherapy was warranted in the hope that it might benefit the patient. Hoyt and Baghdassarian (1969) analysed 36 patients with optic nerve gliomas, 12 of whom had hypothalamic symptoms. They concluded that optic nerve gliomas are non-neoplastic, self-limiting, have a good prognosis, and that even chiasmatic and hypothalamic involvement is compatible with long survival and good vision. They felt that life could never be prolonged by either radiotherapy or transcranial procedures, and there-

fore neither radiotherapy nor excision (except when there is proptosis) is ever justified.

Matson (1969) recommended exploration in children with the diencephalic syndrome only if a finding such as calcification suggested the possibility of an extracerebral lesion, since he feels no treatment can do more than temporarily arrest the syndrome. However, there are reports (Bain *et al.*, 1966; Girdwood and Ross, 1969) that even gliomas responsible for the diencephalic syndrome are sufficiently responsive to radiotherapy to be compatible with long-term, high-quality survival. In the series of Bain *et al.* (1966) remissions were reported in which three patients were clinically well after four-and-a-half, three, and two years with a return of subcutaneous fat beginning about five weeks after completion of radiotherapy. The diagnosis of hypothalamic glioma was confirmed by craniotomy in two of these three patients. But the conclusion that radiotherapy was responsible for these remissions is clouded by Russell's experience, which he communicated to these authors. Of his 16 patients with the diencephalic syndrome, one lived four years after radiotherapy, two others were alive and well four and two years after irradiating, but three others who did not receive radiotherapy were alive 12, 11, and eight years after diagnosis. Bain *et al.* (1966) have speculated that the gradual transition to obesity in several of Russell's untreated patients may be due to extension of the glioma into adjacent areas of the hypothalamus.

MANAGEMENT OF PRESENT SERIES This is summarized in Table 1. The child who did not

TABLE 1

SUMMARY OF MANAGEMENT AND SURVIVAL IN 20 CASES OF HYPOTHALMIC GLIOMA IN CHILDREN

Cases (no.)	Treatment	Survival (yr)
1	None	1
1	Radiotherapy only	2
1	Burr-hole biopsy with radiotherapy	12
2	Burr-hole biopsy without radiotherapy	< ½* (2)
3	Craniotomy biopsy with radiotherapy	1*, 2, 4
1	Craniotomy biopsy without radiotherapy	2†
2	Craniotomy biopsy, shunt, radiotherapy	4½, 13
3	Subtotal excision with radiotherapy	½*, 4†, 6
2	Subtotal excision without radiotherapy	< ½* (2)
4	Emergency burr-hole decompression	< ½* (4)

* Dead.

† Unsatisfactory condition.

receive treatment had a small lesion with little evidence of progression of symptoms and remains the same after one year. With one exception, all patients who survived the admission period or who were not in a terminal state on admission received radiotherapy. The boy who received radiotherapy without previous biopsy was not surgically explored because pneumoencephalography had shown extensive thalamic involvement. In one case radiotherapy was given after burr-hole biopsy rather than after craniotomy because the tumour was known to be large, clearly inoperable, and not producing increased intracranial pressure. The diagnosis was confirmed by burr-hole biopsy in two other children both aged 4 months, who did not then receive radiotherapy because of their young age, their poor neurological status, and the size of the growth. Three others deteriorated so rapidly after diagnosis that radiotherapy could not be given. A 2 year old girl with the diencephalic syndrome was admitted comatose with extensor rigidity and was initially decompressed with marked improvement in her condition, but when the nature of the lesion had been ascertained, was decided not to intervene further. Two of the three children who had biopsy at the time of craniotomy without any attempt at removal of the tumour were thought possibly to have craniopharyngiomas (since they did not have pear-shaped sellas). Two of these children are clinically well two and four years after radiotherapy, one with objective improvement of visual acuity and the other without signs or symptoms of increased intracranial pressure. The third presented with the diencephalic syndrome. Her weight increased 50% in the three months after radiotherapy before her excellent health deteriorated, culminating in death after one year. A male baby aged 7 months with a large porencephalic cyst and hypothalamic glioma who presented with retardation did not receive radiotherapy after craniotomy because it was felt at the time that such gliomas were radio-resistant. Two years later he was alive but debilitated with several seizures a day. One patient without changes of the sella turcica was treated by biopsy through craniotomy, ventriculocisternostomy (Torkildsen's procedure), and radiotherapy. He is alive with normal health four-and-a-half years later. Another child re-

ceived a craniotomy for gold seed implantation and remained well for 13 years apart from precocity until recently requiring a shunt for progressive obstructive hydrocephalus. This was followed by radiotherapy. His vision improved but it is not clear whether this is the result of the shunt or the irradiation. Two patients were treated by subtotal removal of the tumours without radiotherapy. The first was rapidly deteriorating at the time of diagnosis, the mass protruding through the foramen of Monro. It was hoped that a satisfactory decompression could be achieved by partial removal, but the child died in the postoperative period. The other patient, who had the diencephalic syndrome, had a midline tumour filling the pituitary fossa which resembled a large craniopharyngioma. At craniotomy a partial removal was achieved, but death occurred in the postoperative period. Another diencephalic patient had partial removal and radiotherapy but led a vegetative existence till death occurred five months later. Surgery was undertaken in another patient because the tumour was considered to be partially accessible since the optic foramina were enlarged. She is well four years later apart from mental retardation, making it impossible to assess her visual acuity. The final patient presented with decreasing visual acuity and raised intracranial pressure. His huge tumour, extending from the optic canals to the cerebral peduncles and blocking the foramen of Monro, was partially excised. Six years after radiotherapy he is in good health with restoration of normal vision to his right eye.

TABLE 2

RELATIONSHIP OF SURVIVAL TO AGE AT PRESENTATION

Cases (no.)	Age (yr)	Survival (yr)
3	$\frac{1}{2}$	< $\frac{1}{4}$ *, $\frac{1}{2}$ *, 2†
1	1	2
3	2	< $\frac{1}{4}$ * (2), 4†
1	3	13
2	4	< $\frac{1}{4}$ *
5	5	< $\frac{1}{4}$ * (2), 1*, 6, 12
1	7	1
1	9	4 $\frac{1}{2}$
2	11	< $\frac{1}{4}$ *, 4
1	13	2

* Dead. † Unsatisfactory.

DISCUSSION

Of the 20 patients, 10 did not receive radiotherapy either as a matter of deliberate policy or because they died before therapy could begin. One patient continued a downhill course in spite of radiotherapy. The remaining nine all demonstrated objective improvement and are still alive and well except one who showed initial response to irradiation before succumbing. The improvement in five of these nine can be directly attributed to radiotherapy since they had no other treatment.

TABLE 3

RELATIONSHIP OF PRESENTING CONDITION TO SURVIVAL

Cases (no.)	Presenting condition	Survival (yr)
4	Good	1, 2, 6, 12
7	Fair	< $\frac{1}{4}$ * (2), 2†, 4†, 4, 4 $\frac{1}{2}$, 13
7	Poor	< $\frac{1}{4}$ * (5), $\frac{1}{2}$ *, 1*
2	Critical	< $\frac{1}{4}$ * (2)

* Dead. † Unsatisfactory condition.

Of the five patients with partial removal of the tumour, two died in the postoperative period and one five months later. The other two presented with hydrocephalus and are now long-term survivors without the problems plaguing children with shunts. There are not enough patients treated by subtotal excision and radiotherapy or controls with partial excision without such therapy to judge whether or not subtotal removal adds to the improvement achievable by radiotherapy alone. However, most children presenting with hydrocephalus need more immediate relief from their symptoms than radiotherapy can provide, and therefore require either a shunt or partial excision in addition to radiotherapy. Because the natural history of hypothalamic glioma is so variable and frequently favourable, craniotomy should not be performed except to carry out partial removal of the growth in order to relieve increased intracranial pressure or to explore if there is some doubt about the diagnosis and the possibility exists that the mass may be either extracerebral or a non-gliomatous hypothalamic lesion.

Satisfactory long-term survival appears to be more related to the patient's presenting condition (Table 3) than to his age (Table 2). Criteria used in Table 3 are as follows:

Good: alert and oriented but with a mild decrease of visual acuity, mild symptoms of increased intracranial pressure, precocious puberty, etc.

Fair: alert, oriented but with severer symptoms.

Poor: debilitated, or disabled by severe neurological abnormality but conscious.

Critical: consciousness and general condition deteriorated to an extent requiring emergency decompression.

Table 3 thus suggests that (1) if the child presents in sufficiently good condition to survive six months, he can expect a good long-term survival, and (2) children presenting in either poor or critical condition should not be treated at all.

This second conclusion implies that no children with the diencephalic syndrome should be treated, but because of the encouraging results reported by Bain *et al.* (1966), this conclusion should probably be modified for the time being. Such children who present in an alert mental state should receive radiotherapy sometimes preceded by decompression and only those in critical condition left untreated.

CONCLUSIONS

Twenty children with hypothalamic gliomas from the Hospital for Sick Children, Great Ormond Street, were reviewed in an attempt to determine the appropriate management. If the child's condition at the time of diagnosis is such that survival for several months is likely, the long-term prognosis for good survival is excellent and is enhanced by treatment. It is concluded that radiotherapy has a definite beneficial effect and should be given to every child not presenting in poor or critical condition. These are best left untreated. An exception is a child with the diencephalic syndrome whose general condition is poor but there is little or no impairment of consciousness; such a child should be treated by radiotherapy sometimes preceded by a shunt operation.

If there is increased intracranial pressure with radiological evidence to suggest that the obstruc-

tion may be relieved by operation, then partial removal should be carried out. If it is judged that obstruction cannot be relieved, a shunting procedure is required. Craniotomy is also indicated if there is anything in the clinical or radiological examination to suggest that the lesion may be extracerebral. Otherwise, biopsy through a burr hole may be adequate for confirmation of the diagnosis.

REFERENCES

- Bain, H. W., Darte, J. M. M., Keith, W. S., and Kruff, E. (1966). The diencephalic syndrome of early infancy due to silent brain tumor: with special reference to treatment. *Pediatrics*, **38**, 473-482.
- Chutorian, A. M., Schwartz, J. F., Evans, R. A., and Carter, S. (1964). Optic gliomas in children. *Neurology (Minneapolis)*, **14**, 83-95.
- Fowler, F. D., and Matson, D. D. (1957). Gliomas of the optic pathways in childhood. *Journal of Neurosurgery*, **14**, 515-528.
- Girdwood, T. G., and Ross, E. M. (1969). The diencephalic syndrome of early infancy. *British Journal of Radiology*, **42**, 847-850.
- Hoyt, W. F., and Baghdassarian, S. A. (1969). Optic glioma of childhood. Natural history and rationale for conservative management. *British Journal of Ophthalmology*, **53**, 793-798.
- Koos, W. T., and Miller, M. H. (1971). *Intracranial Tumors of Infants and Children*, pp. 172-188. Churchill: London.
- MacCarty, C. S., Boyd, A. S., Jr, and Childs, D. S., Jr (1970). Tumors of the optic nerve and optic chiasm. *Journal of Neurosurgery*, **33**, 439-444.
- Martin, P., and Cushing, H. (1923). Primary gliomas of the chiasm and optic nerves in their intracranial portions. *Archives of Ophthalmology*, **52**, 209-241.
- Matson, D. D. (1969). *Neurosurgery of Infancy and Childhood*, 2nd edn. Thomas: Springfield, Ill.
- Poznanski, A. K., and Manson, G. (1963). Radiographic appearance of the soft tissues in the diencephalic syndrome of infancy. *Radiology*, **81**, 101-106.
- Russell, A. (1951). A diencephalic syndrome of emaciation in infancy and childhood. (Abstract.) *Archives of Diseases of Childhood*, **26**, 274.
- Schuster, G., and Westberg, G. (1967). Gliomas of the optic nerve and chiasm. *Acta Radiologica, Diagnosis*, **6**, 221-232.
- Smith, K. R., Jr, Weinburg, W. A., and McAlister, W. H. (1965). Failure to thrive: the diencephalic syndrome of infancy and childhood. A case report. *Journal of Neurosurgery*, **23**, 348-351.
- Stein, B. M., Fraser, R. A. R., and Tenner, M. S. (1971). Radiological characteristics and surgical management of third ventricular tumors in children. *Acta Neurologica Latinoamericana*, **17**, 131-140.
- Taveras, J. M., Mount, L. A., and Wood, E. H. (1956). The value of radiation therapy in the management of glioma of the optic nerves and chiasm. *Radiology*, **66**, 518-528.
- Taveras, J. M., and Wood, E. H. (1964). *Diagnostic Neuro-radiology*. Williams and Wilkins: Baltimore.
- Udvarhelyi, G. B., Khodadoust, A. A., and Walsh, F. B. (1965). Gliomas of the optic nerve and chiasm in children: an unusual series of cases. *Clinical Neurosurgery*, **13**, 204-237.