Ectopic intracranial retinoblastoma in childhood

JUDITH E KINGSTON,¹ P N PLOWMAN,² AND J L HUNGERFORD³

From the Departments of ¹Paediatric Oncology and ²Radiotherapy, St Bartholomew's Hospital, West Smithfield, London, and the ³Department of Ophthalmology, St Bartholomew's Hospital, West Smithfield and Moorfields Eye Hospital, City Road, London

SUMMARY Twelve out of a series of 630 children with retinoblastoma, treated in the ocular oncology units at St Bartholomew's and Moorfields Eye Hospitals during the past 30 years, have developed ectopic intracranial retinoblastoma. The ectopic tumour occurred in the pineal region in eight children and in the suprasellar region in four. Ten patients had bilateral retinoblastoma, one unilateral disease, and one child presented with an isolated suprasellar tumour but no evidence of retinal disease. The interval from the initial diagnosis of retinoblastoma to the development of ectopic intracranial disease ranged from 4 to 70 months, median 34 months. Methods of treatment for the ectopic tumour varied, but all 12 children died with a median survival of only 8 months following the diagnosis of ectopic retinoblastoma. Subsequent spread of tumour to other sites within the central nervous system proved to be the most frequent cause of death. Ectopic intracranial retinoblastoma is a potentially curable neoplasm, but it requires adequate therapy to the whole neuraxis as well as high dose equivalent radiotherapy to the primary tumour.

The problem of ectopic non-metastatic retinoblastoma was first recognised by Jacobiec *et al.* in 1977.¹ Three years later Bader and colleagues,² used the term 'trilateral' retinoblastoma to describe the clinical syndrome of bilateral retinoblastoma with an ectopic midline intracranial tumour. These authors subsequently reported on 11 children with features characteristic of trilateral retinoblastoma and also included details of three children with either parasellar or suprasellar retinoblastoma.³ They suggested that the development of an ectopic midline neuroblastic tumour in a patient with bilateral retinoblastoma represented an additional focus of multicentric retinoblastoma rather than a second primary tumour and drew attention to the ontogenesis of the pineal gland, likening the human pineal to a 'third eye'. They postulated that the retinoblastoma gene confers an increased susceptibility to the development of neuroblastic tumours which, although usually presenting in the retina, can occur in other intracranial sites, particularly in cells of photoreceptor origin. Photoreceptor morphology has certainly been identified in cases of pineoblastoma occurring without retinoblastoma,⁴ and the suprasellar or IIIrd ventricular region is a well recognised site of origin for primary 'ectopic' pineoblastomas.⁵

In this report we describe the clinical presentation, treatment, and outcome of 12 children with ectopic intracranial retinoblastoma seen at St Bartholomew's and Moorfields Eye Hospitals during a period of 30 years. Three of the 12 cases summarised in Table 1 have been cited in previous reports—cases 4 and 5³ and case 11.⁶ We also discuss ways in which treatment might be modified in an attempt to improve the current dismal prognosis.

Material and methods

PATIENTS

Six hundred and thirty children with retinoblastoma presenting to St Bartholomew's and Moorfields Eye Hospitals during the period 1954 to 1983 have been followed up. There were 360 males and 270 females, a male to female ratio of 1.4:1. Four hundred and thirty two (69%) of the children had bilateral disease, reflecting selection in the referral pattern. Twelve of these 630 children developed ectopic intracranial retinoblastoma. The clinical presentation and treatment given for the initial retinoblastoma of these twelve children is set out in Table 1. There were eight girls and four boys. One child (patient 7), a younger sibling of patient 3, presented with an isolated suprasellar tumour but no evidence of retinal disease. The mother of the two siblings had bilateral retino-

Correspondence to Dr Judith Kingston, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

Ectopic intracranial retinoblastoma in childhood

Table 1 Characteristics of patients with ectopic intracranial retinoblastoma

Patient no.	Sex	Age at diagnosis of RB	Year of diagnosis of RB	Initial treatment of retinoblastoma	Interval between diagnosis of RB + ectopic tumour
1	M	2/12	1954	Enucleation L eye + RT 16 Gy to L orbit, Co plaque to R eye	5 yr 8/12
2	M	8/12	1956	Enucleation L eye, Co plaque to R eye	2 yr 5/12
3	F	2/12	1969	PC L eye, PC R eye	4/12
4	F	2/12	1973	Enucleation R eye, PC + Cryo + RT 35 Gy to L eye	6 yr 8/12
5	F	1/12	1973	35 Gy to both eyes	6 yr 5/12
6	M	5/12	1974	Enucleation R eye, PC + Cryo L eye	3 yr 3/12
7*	F	5/12	1976	NA	NA
8	F	9/12	1977	Enucleation L eye, RT 36 Gy R eye	4 yr 7/12
9	F	2/12	1978	Enucleation R eye, RT 35 Gy L eye	2 yr 10/12
10†	F	14/12	1981	Enucleation R eye	1 yr 7/12
11	M	12/12	1982	Enucleation R eye	1 yr 2/12
12	F	3/12	1982	Enucleation L eye, RT 36 Gy R eye	1 yr 3/12

*Child with isolated suprasellar retinoblastoma and sib of patient 3.

†Child with unilateral retinoblastoma.

Co plaque = ⁶⁰ cobalt plaque. RT = external beam irradiation. PC = xenon photocoagulation. Cryo = cryotherapy. NA = not applicable.

blastoma and developed a malignant melanoma as a second primary tumour at the age of 31 years. The father of the child with unilateral disease also had unilateral retinoblastoma.

Results

Ten of the 11 children with retinal involvement had bilateral disease diagnosed between the age of 1 and 12 months, median 2 months. Enucleation of the worst affected eye was carried out in eight children. The remaining eye was treated with a cobalt plaque in two children, external beam irradiation in four children, external beam with cryosurgery and xenon photocoagulation in one child, and xenon photocoagulation and cryosurgery alone in the remaining child. Of the two children who did not undergo primary enucleation one was treated with external beam irradiation to both eyes while the other received bilateral xenon photocoagulation. The child with unilateral disease (patient 10) was treated by enucleation alone. No child received chemotherapy.

There was no evidence of tumour involving the cut end of the optic nerve in any of the enucleated eyes, although two eyes did show invasion of the optic nerve head. In neither case did the infiltration extend beyond the lamina cribrosa. In two children there was evidence of choroidal invasion, which was minimal in both cases. Details of the histology of the enucleated eyes are shown in Table 2. The interval from diagnosis of retinoblastoma to development of the ectopic intracranial tumour ranged from 4 to 70 months, median 34 months. The diagnostic investigations and site of the ectopic tumour are listed in Table 3. In all cases the diagnosis was initially made on radiological evidence, confirmed by histology in the four children who underwent surgery. No patient in this series had myelography at the initial diagnosis of intracranial disease. Chromosome studies were carried out on two children, and both were normal, though high resolution banding studies were not done.

Table 2 Histology of enucleated eyes

Patient no.	Differentiation	Choroidal invasion	Optic nerve invasion
1	Well differentiated	None	None
2	"	"	"
4	"	"	"
6	"	Yes	Nerve head only
8	"	Yes	None
9	"	None	"
10	Poorly differentiated	"	Nerve head only
11	"	"	None
12	Well differentiated	"	"

Table 3 Proof of diagnosis of ectopic intracranial retinoblastoma

Patient no.	Site of ectopic retinoblastoma	Radiology	Histology
1	Pineal region	Ventriculogram	None
2	"	"	None
3	Suprasellar region	Carotid angiogram	Yes
4	Pineal region	CT scan	None
5	"	"	Yes
6	"	"	Yes
7	Suprasellar region	Carotid angiogram	Yes
8	Pineal region	CT scan	None
9	"	"	None
10	Suprasellar region	"	None
11	"	"	None
12	Pineal region	"	None

Table 4 Treatment of ectopic intracranial retinoblastoma

Patient no.	Treatment of ectopic tumour	Response	Subsequent outcome	Interval from diagnosis of ectopic tumour to death
1	RT 30 Gy to cranium + cyclo	NE	Spinal metastases at 7/12	13/12
2	RT 54 Gy to cranium + chl	NE	NK	8/12
3	RT 25 Gy to cranium	Partial	Spinal metastases at 8/12	9/12
4	None	—	Progressive disease	1/12
5	Surgical resection RT 46 Gy to midbrain + chemo	Complete	Spinal metastases at 5/12	17/12
6	RT 50 Gy to midbrain + 30 Gy to spine	Complete	Spinal metastases at 6/12	8/12
7	None	—	Progressive disease	4/12
8	RT 20 Gy to midbrain	None	Spinal metastases at 1/12	5/12
9	None	—	Progressive disease	2/12
10	RT 38 Gy to cranium	Complete	Spinal metastases at 2/12	4/12
11	RT 24 Gy to cranium + CVA × 1	Partial	Relapse at primary site at 3/12 + meningeal dissemination at 6/12	9/12
12	None	—	Progressive disease	1/12

RT = external beam irradiation. Cyclo = cyclophosphamide.

Chl = chlorambucil. CVA = cyclo + vincristine + adriamycin. NE = not evaluated. NK = not known.

TREATMENT OF THE ECTOPIC INTRACRANIAL RETINOBLASTOMA

Details of the treatment given to the children and their subsequent outcome are shown in Table 4. Four children received no specific treatment for the ectopic tumour, and all died within four months. Six children received radiation to the midbrain and cranium. Five of these developed spinal metastases within six months. The sixth child (patient 2) died 8 months following radiotherapy but the nature of his relapse is not known. Three of these six children also

received chemotherapy. One child received whole neuraxis radiation with 50 Gy to the midbrain and 30 Gy to the spine but developed spinal metastases six months following radiotherapy. In the remaining child surgical resection of the pineal tumour was possible and was followed by radiation (46 Gy) to the midbrain. No spinal radiation was given, and this child developed spinal metastases five months after diagnosis, though there was no clinical or radiological evidence of recurrence at the primary site.

The three children who received between 24 and 25

Fig. 1 CT head scan of patient 8 showing discrete calcified mass in the pineal region with hydrocephalus of the IIIrd and lateral ventricles.

Fig. 2 CT scan of patient no 11 showing mass in suprasellar region.

Gy to the pineal region showed only partial resolution of the primary lesion on radiological criteria, whereas one child given 50 Gy to the midbrain had complete resolution of the primary lesion on CT scan with no evidence of recurrence at the primary site at necropsy. Unfortunately spinal irradiation in a dose of 30 Gy did not prevent the development of spinal metastases in this child. The child treated with 54 Gy to the primary lesion went abroad after completion of treatment, and so it was impossible to assess the response of the primary lesion to radiotherapy.

Discussion

Retinoblastoma is an eminently curable cancer of childhood, with an overall 5-year survival rate in excess of 85% in the United Kingdom.⁷ It is a highly radiosensitive tumour, and large tumours are effectively treated by external beam radiation conventionally fractionated to 40 Gy. Smaller tumours are treated by photocoagulation or cryotherapy alone. In most cases metastatic disease is initially responsive to vincristine and cyclophosphamide, but the relapse rate is high and there are no published reports of long-term survival.

The child with an ectopic intracranial tumour presents with symptoms and signs of raised intracranial pressure, and on CT scanning a calcified mass is seen in either the pineal or parasellar regions (Figs. 1 and 2). The histology of the ectopic tumour is

indistinguishable from a primary retinoblastoma arising in the eye (Figs. 3 and 4). It has been argued that ectopic intracranial retinoblastomas merely represent metastatic spread from the eye. Features which militate against this have been discussed by Bader *et al.*³ and include the absence of pathological features usually associated with the development of metastases, namely invasion of the optic nerve posterior to the lamina cribrosa, massive choroidal invasion, and intraorbital extension. In addition the discrete nature of the solitary intracranial tumour, in contrast to the typical diffuse leptomeningeal spread or multiple cerebral lesions which usually characterise metastatic retinoblastoma, and also the relatively long latent interval from the diagnosis of retinoblastoma to the development of an ectopic tumour are uncharacteristic of metastatic spread from an embryonic tumour.

Ectopic intracranial tumours occur exclusively in children with bilateral or the genetic form of retinoblastoma. The one child in this series who had unilateral disease (patient 10) is presumed to have had the familial form of retinoblastoma, as her father also had unilateral retinoblastoma. We found a predominance of females developing trilateral retinoblastoma (M:F 1:2) in contrast to the overall excess of males with retinoblastoma (M:F 1.4:1) in the whole series.

In our experience ectopic intracranial retinoblastoma is not common, though in patients with

Fig. 3 Histology of a poorly differentiated ectopic retinoblastoma from patient 3. (Haematoxylin and eosin, $\times 470$).

Fig. 4 Cytospin preparation of CSF from patient 6 at time of relapse, showing clumps of retinoblastoma cells. (Haematoxylin and eosin, $\times 600$, oil immersion).

bilateral disease it is the most frequent cause of death during the first decade following diagnosis. Among 432 children with bilateral retinoblastoma the prevalence of 'trilateral retinoblastoma' was 2.3%. However, we believe that a more realistic estimate of the prevalence, calculated from the number of cases diagnosed since CT scanning has been available, is about 4%. It has recently been suggested the CT scanning should be part of the routine assessment of all patients with bilateral retinoblastoma,⁶ but we consider that the prevalence of the problem is probably too low to justify serial CT scanning of all such patients. However, we accept that a prospective trial is indicated in an attempt to define the role of serial CT scanning in children with bilateral retinoblastoma.

Children who develop ectopic intracranial retinoblastoma appear to have a particularly poor prognosis. This may be due to inadequate treatment of the primary lesion and also to a failure to appreciate the potential of these tumours to metastasise within the central nervous system. From this retrospective review it is apparent that doses of radiation less than 30 Gy are insufficient to eradicate the primary tumour. It is also clear that the major cause of death in these children is the development of spinal metastases.

Consideration of the behaviour and optimal therapy of primary pineal tumours is pertinent to this problem. Primary pineal tumours are highly radiosensitive and radiocurable, with a 66–80% survival in large series.^{8,9} Our own experience at St

Bartholomew's Hospital agrees with this. It is well recognised that there are different categories of primary pineal tumours and that the pineal parenchymal tumours most relevant to the present discussion, pineocytomas and pineoblastomas, constitute only 12–15% of the total.⁴ Recent reports emphasise the propensity of pineal germinomas and pineoblastomas to seed via cerebrospinal fluid (CSF) pathways and therefore the necessity for and efficacy of neuraxis radiotherapy.⁸

Specific reports of patients with pineoblastoma and the results of therapy are sparse, but all are informative. In an analysis by the Children's Cancer Study Group of 57 children with biopsy proved pineal and suprasellar tumours there were seven with pineal parenchymal tumours. Of these seven patients six died of their disease, two with spinal metastases, neither of whom had received neuraxis radiotherapy. The dose of radiation to the primary tumour was 50 Gy conventionally fractionated, and the authors imply that local control of the primary was not a significant problem.⁸ Of eight patients (five adults and three children) with pineoblastoma reported on by Borit *et al.*¹⁰ seven died with recurrent tumour within two years of diagnosis and one after an interval of seven years. Leptomeningeal spread, usually extensive, was present in five, but no metastases were encountered outside the central nervous system (CNS). These authors do not state whether the patients received neuraxis radiotherapy. Rubinstein¹¹ reported a clinico-pathological study of 28 patients with pineal parenchymal tumours of

whom 11 had pineoblastomas. Widespread metastases within cerebrospinal pathways were present in all these 11 patients. The author concluded that the entire neuraxis should receive radiotherapy. In contrast to these dismal results of therapy Sung *et al.*⁸ reported on two of three patients with pineoblastoma alive and free of disease at three and six years after neuraxis radiotherapy with a total dose of 50 Gy to the primary.

The literature cited suggests that these tumours are radiosensitive, have a propensity to disseminate within CSF pathways, and that with adequate therapy limited to the primary site metastases develop in other CNS sites and are usually fatal within two years.

These conclusions initiate two other discussion points: a child with retinoblastoma who subsequently develops ectopic intracranial disease may have already been treated with radiation. Following a lateral orbital radiation portal the cerebral contribution will be low, but following an anterior megavoltage photon portal to the eye a portion of the underlying brain, including the region of the IIIrd ventricle, will have already received a radiation dose to partial tolerance. Where possible, therefore, we recommend that radiotherapy for familial retinoblastoma should be delivered through a lateral portal.

With regard to relapse at other sites within the CNS, particularly the spine, the analogy with medulloblastoma may be appropriate. Deutsch and Reigel¹² described unsuspected spinal deposits in seven of 16 newly diagnosed children with medulloblastoma, and this high incidence has persuaded many workers, including ourselves, to include myelography in the assessment of patients with medulloblastoma. In cases with positive myelograms the abnormal area is boosted with radiotherapy to a higher dose than the routine 'prophylactic' dose administered to the whole neuraxis. This widely accepted treatment of medulloblastoma may well provide an object lesson for the management of children with ectopic intracranial retinoblastoma.

From our experience it is evident that a more aggressive approach is required for the treatment of children with ectopic intracranial retinoblastoma. We would suggest that combined modes of treatment are most likely to produce a prolonged remission and possible cure. We therefore recommend surgical excision of the ectopic tumour whenever possible, followed by whole neuraxis irradiation 30 Gy, boosting the primary lesion to 50 Gy, or 45 Gy in the very young child. Intrathecal therapy with methotrexate should also be considered.

Reintoblastoma cells have a similar morphology and some surface antigens indistinguishable from

those of other neuroectodermal tumours such as neuroblastoma and medulloblastoma. Children with disseminated neuroblastoma respond to intensive combination chemotherapy with vincristine, cyclophosphamide, cis-platinum, and etoposide, and we have observed a partial response to this drug combination in a girl with a primary cerebral neuroblastoma, implying 'access' of these drugs to the CNS. We have recently used this combination of drugs with some success in children with metastatic retinoblastoma. An argument could therefore be made for the administration of intensive systemic chemotherapy in addition to spinal irradiation and intrathecal drug therapy in an attempt to prevent the development of spinal metastases.

In conclusion, ectopic intracranial retinoblastoma is an uncommon condition. In this retrospective analysis of 630 children seen in the ocular oncology units at St Bartholomew's and Moorfields Eye Hospitals over the past 30 years we have identified 12 children with clinical and radiological evidence of this syndrome. It is possible that the condition has been underdiagnosed and that some children thought to have died from intracranial metastases may initially have had localised ectopic pineal tumours. Undoubtedly the advent of CT scanning during the past decade has facilitated diagnosis, and indeed eight of our 12 cases have been diagnosed since 1970. We would suggest that the diagnosis of ectopic intracranial retinoblastoma should be considered in all children with retinoblastoma who develop symptoms or signs of raised intracranial pressure or evidence of cerebral metastases.

A greater experience and understanding of the management of children with ectopic intracranial retinoblastoma is needed to improve the current dismal prognosis, and in view of the rarity of the condition we would suggest that such children should be referred to a centre with a special interest in the condition.

We thank Professor L E Zimmerman for his helpful comments and encouragement, Miss Chrysanthopolou at the Institute of Ophthalmology and members of the Childhood Cancer Research Group in Oxford for their assistance in the ascertainment of cases, and the numerous clinicians who provided follow-up information. We are grateful to Dr A G Stansfeld and Dr O M Curling for providing the photographs reproduced in Figs. 3 and 4 respectively.

References

- 1 Jacobiec FA, Tso MOM, Zimmerman LE, Danis P. Retinoblastoma and intracranial malignancy. *Cancer* 1977; **39**: 2048-58.
- 2 Bader JL, Miller RW, Meadows AT, Zimmerman LE, Champion LAA, Voute PA. Trilateral retinoblastoma. *Lancet* 1980; *ii*: 582-3.
- 3 Bader JL, Meadows AT, Zimmerman LE *et al.* Bilateral retinoblastoma with ectopic intracranial retinoblastoma:

- trilateral retinoblastoma. *Cancer Genet Cytogenet* 1982; **5**: 203—13.
- 4 Stefanko SZ, Manschot WA. Pinealoblastoma with retinoblastomatous differentiation. *Brain* 1979; **102**: 321—32.
- 5 Russell DS, Rubinstein LJ. Pineal neoplasms. *Pathology of tumours of the nervous system*. 4th Ed. London: Arnold, 1977: 283—94.
- 6 Dudgeon J, Lee WR. The trilateral retinoblastoma syndrome. *Trans Ophthalmol Soc UK* 1983; **103**: 523—9.
- 7 Draper GJ, Birch J, Bithell JF, *et al.* Childhood cancer in Britain—incidence, survival and mortality. London: HMSO, *Studies on medical and population subjects*. 1982: no.37.
- 8 Sung D, Harisiadis L, Chang CH. Midline pineal tumours and suprasellar germinomas: highly curable by irradiation. *Radiology* 1978; **128**: 745—51.
- 9 Wara WM, Jenkin RDT, Evans A, *et al.* Tumours of the pineal and suprasellar region: Children's Cancer Study Group treatment results 1960—1975. *Cancer* 1979; **43**: 698—701.
- 10 Borit A, Blackwood W, Mair WGP. The separation of pineocytoma from pineoblastoma. *Cancer* 1980; **45**: 1408—18.
- 11 Rubinstein LJ. Differentiating potential of the neoplastic cell in the tumours of the pineal parenchyma and its therapeutic implications (Abstr.) *Childs Brain* 1981; **8**: 52—3.
- 12 Deutsch M, Reigel DH. The value of myelography in the management of childhood medulloblastoma. *Cancer* 1980; **45**: 2194—7.