Neurofibromatosis type 1 and sporadic optic gliomas

S Singhal, J M Birch, B Kerr, L Lashford, D G R Evans

Aims: To compare the natural history of sporadic optic glioma with those associated with neurofibromatosis type 1 (NF1).

Methods: Optic glioma cases were identified using both the Manchester Children’s Tumour Registry (CTR) and the North West Regional NF1 Database (NF1DB), with detailed information on natural history available from the former (in 34 of 36 cases identified).

Results: A total of 52 cases over a period of 41 years were identified. From the 34 whose natural history was known, almost all (n = 31) were symptomatic, with mean ages of presentation of 4.5 and 5.1 years for NF1 and sporadic cases respectively. The majority (n = 22) presented with visual impairment, seven of whom were blind in at least one eye. Sporadic cases were over twice as likely as NF1 to have visual impairment. Recurrence occurred in 12 patients. Fewer NF1 patients died as a direct result of their optic glioma, but overall mortality and 5 and 10 year survival rates between the two groups were similar. All five primary (non-metastatic) second central nervous system (CNS) tumours occurred in NF1 cases, two of these following radiotherapy.

Conclusions: Symptomatic sporadic optic gliomas presented with impaired vision more frequently and were more aggressive than NF1 optic gliomas. Only optic glioma cases with NF1 were at risk of developing a second CNS tumour. Aggressive treatment of sporadic optic gliomas and early surveillance of NF1 optic gliomas may be required. The use of radiotherapy in these children requires further clarification.

Neurofibromatosis type 1 (NF1) makes up 90% of the genetic disorders known clinically as the neurofibromatoses. It has a prevalence of about 1 in 3000, making it one of the most common genetic disorders. NF1 is inherited in an autosomal dominant manner and gene penetrance is such that almost all cases show sufficient evidence of the disorder to allow diagnosis in childhood. Complications of NF1 provide a more sinister slant to this otherwise relatively benign condition. One of the most notorious complications is that of the central nervous system (CNS) tumour. Optic nerve gliomas were initially reported in less than 5% of NF1 cases, but this was before the advent of computed tomography and magnetic resonance imaging. More recent estimates from longitudinal studies using modern neuroimaging techniques have put the prevalence between 11% and 19% of NF1 cases, although higher estimates have come from retrospective analyses of referral clinics. As the occurrence of other CNS tumours is thought to be well below 5%, this makes optic glioma the most common CNS tumour to complicate NF1. The natural history of optic gliomas has been increasingly studied in recent years, but it is not clear if these tumours produce significant morbidity or are relatively indolent. Some studies have found the former, but the majority have found the latter and do not see a case for screening or monitoring. However, this may depend on adequacy of treatment, and treatment itself is not without risk. The discrepancy in natural history may relate to differences in study design, with prospective studies picking up more non-progressive asymptomatic tumours. Some have found that the presence of NF1 in children with optic glioma confers a protective benefit. Therefore, we have therefore used retrospective data to establish the natural history of optic gliomas and whether NF1 related cases require a different clinical approach to sporadic ones. This also enabled assessment of the overall prevalence of mainly symptomatic optic gliomas in a large population based register of NF1 patients.

Abbreviations: CNS, central nervous system; CT, computed tomography; CTR, Children’s Tumour Registry; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NF1DB, North West Regional NF1 Database.
months. The mean and median ages of diagnosis were 5.0 and 4.0 years respectively. Diagnosis was based on either radiological (9/17) or histological (8/17) evidence.

Treatment
A total of 11 children received specific treatment for their glioma: either surgical excision of part or all of the glioma (7/17) or radiotherapy (4/17). In one of the children treated with radiation, there was a period of abnormally excessive growth during the following year. He went on to develop an asymptomatic recurrence and a cerebellopontine angle schwannoma 17 years later. Another case had a recurrence at the age of 12, six years after radiotherapy; he died of multiple intracranial tumours, aged 21. The other two appeared not to have had any untoward complications of cerebral irradiation. One of the children initially treated surgically developed a cerebellar astrocytoma at age 10, which was irradiated. Two years after this, his vision began to deteriorate and a recurrent optic glioma was diagnosed at age 17. Follow up information is lacking for one treated and one untreated case. For those on whom we have such data, five of the 10 treated were dead by study day compared with two of five untreated.

Complications
Four gliomas recurred with new symptoms, three following radiotherapy (two, six, and 17 years later), and the other nine years after surgery. A further child who actually died from an axillary neurofibrosarcoma was found to have an incidental chiasmal glioma 17 years after his initial glioma was irradiated. Two children developed endocrinological disorders following glioma diagnosis. One underwent excessive growth from the age of 8, a year after he had received radiotherapy. The other child, who was female, had had radiotherapy for an optic glioma at the age of 7, and was then diagnosed with glioma recurrence at the age of 14 following investigation of primary amenorrhoea. She later developed epilepsy, which by the time she was 36 was described as “uncontrolled”. A further child, whose glioma was initially excised when she was aged 1, developed aqueduct stenosis, a recognised complication of NF1, at the age of 7. This was complicated by hydrocephalus, and despite shunt insertion she died a few days later. Complications were not inevitable and seven children had no further serious problems. Of these, two had been treated surgically, two with radiotherapy, and three had not had specific therapy.

Second tumours
Five children (29%) with NF1 went on to develop second primary CNS tumours, all of which were intracranial and occurred between seven and 32 years from initial treatment. Two of these five occurred in cases treated with initial radiotherapy. One of these was the aforementioned boy who died aged 24 from an axillary neurofibrosarcoma and was found to have, in addition, both a cerebellopontine neurilemoma (schwannoma) and a chiasmal glioma. He had received radiotherapy at the age of 7. Two of the five also suffered with recurrent optic gliomas. Only one of the five appeared to survive his second tumour (a cerebellar astrocytoma), through a combination of radiotherapy and surgery which he received in 1977 at the age of 10. It may be of note that two years after this treatment his vision began to deteriorate and he went on to have further radiotherapy for a recurrent optic glioma in 1984.

Mortality
Overall there was a 47% mortality rate among the 15 of 17 NF1 patients with an optic glioma whose survival was recorded. However, of these seven deaths only two were directly attributable to the optic gliomas. The remaining causes of death were intracranial neoplasia (n = 3), the neurofibrosarcoma (n = 1), and the girl with aqueduct stenosis who had a shunt inserted to drain her hydrocephalus and who died from bilateral subdural haemorrhaging following a fit postoperatively.
Survival
The 5 and 10 year survival rates from first presentation probably give the most realistic idea of the severity of an individual child's condition. These are 77% and 67% respectively, with two outcomes unknown and three cases not applicable (being diagnosed within 10 years of study day).

Location
Further subanalysis using site of glioma was conducted. Using the categories intraorbital (that is, chiasm spared) and chiasmatic (that is, chiasm with or without one or both optic nerves involved), 10 children had chiasmatic gliomas. In addition, two had “bilateral gliomas”, but no reference to the chiasm was made. Four chiasmatic and both bilateral cases presented with visual symptoms, five chiasmatic and one bilateral had endocrine abnormalities, and both asymptomatic patients were chiasmatic. Only one recurrent glioma appeared to have involved new territory, initially affecting the left optic nerve. Nine years after glioma excision and two years following radiotherapy (for a cerebellar tumour), the optic glioma recurred in the chiasm. Of the 10 with definite and initial chiasm involvement, three received radiotherapy, three were excised, and four were left untreated. Information regarding survival in these cases is complete for only five, two of whom died within 10 years of diagnosis (giving a 10 year survival rate of 60%).

Sporadic optic gliomas
Distribution
Of the 17 cases without a diagnosis of NF1, eight were male and all were white Europeans. Three children presented over the age of 10, being 11, 12, and 13. The youngest presented at 3 months with apparent visual symptoms and hypercalcaemia, but was not diagnosed until 12 months old.

Presentation—age
The mean and median ages of presentation were 5.1 and 5.0 (range 0.25–13) years respectively. Only two patients had initial symptoms predating presentation by greater than a year. One had poor growth for probably two years prior to presentation, the other had various endocrine symptoms starting about 15 months earlier. A further five children had a 12 month history of symptoms at presentation, four of these being visual in nature and one having symptoms of raised intracranial pressure.

Presentation—symptoms
The most common presenting symptom was again visual disturbance (15/17 or 88%), with five of these having one blind eye. Proptosis (7/17), endocrine disturbance (5/17, of which two had precocious puberty), and raised intracranial pressure (5/17) were also common, with two cases having nystagmus. Only one case was asymptomatic and picked up via a routine eye check that revealed optic atrophy. Despite no presenting symptoms and receiving radiotherapy, he still went on to develop a blind eye.

Diagnosis
Time to diagnosis from first presentation was just under nine months, with mean and median ages of diagnosis being 5.8 and 5.0 years respectively. Most cases were diagnosed on biopsy (11/17), the remainder either seen on scan (4/17) or directly visualised at craniotomy (2/17).

Treatment
A large majority of these children (14/17) received specific treatment. Most underwent surgery alone (8/17), four had radiotherapy alone, and two children had both kinds of treatment. One of those surgically treated went on to have radiotherapy for recurrence 12 years later and had a second recurrence five years after that. Of the six who initially received radiotherapy, three went on to have a recurrent glioma (four, four, and 23 years later). Six of the 12 treated for whom we have follow up information were dead by study day, compared with two of the three who were untreated.

Complications
A minority (6/17) of sporadic gliomas failed to show disease progression, four having had their tumour excised, one having had radiotherapy, and one having been untreated. Four gliomas recurred. Of these, two may have had a second recurrence. The first was a girl treated initially at 16 months with radiotherapy who then developed bilateral nerve gliomas at age 7, for which she was treated surgically. She died at the age of 10 following an acute right middle cerebral artery infarct, and was found on postmortem examination to have a chiasmal glioma. It is not clear if this was remnant tumour from the previous surgery or true recurrence. The other child had his glioma excised at the age of 4, and was then treated with radiotherapy for its first recurrence at the age of 16. He had a second recurrence at the age of 21, which was untreated and from which he died. The same boy had required shunt insertion at the age of 11 to drain hydrocephalus. Endocrine dysfunction occurred in two cases, one with growth hormone deficiency and one with secondary amenorrhoea. Both had received radiotherapy, respectively, 9 and 14 years previously.

Second tumours
None of the sporadic gliomas appeared to develop another primary CNS tumour, although one boy who was diagnosed on biopsy at the age of 11 months died five months later and the cause of death given was “cerebral tumour”. Most likely this referred to the known glioma as there was no postmortem examination.

Mortality
Of seven deaths, five were definitely directly related to the optic glioma; one other had a fatal complication at the time of her second glioma recurrence in that she sustained a stroke at the age of 10. The final death was a result of a fall from a bike, but no further information is available. Hence, overall mortality was approximately 44%. The five year survival rate at study day was 80%, with one case discounted because of diagnosis after 1991. This fell to 57% for 10 year survival rate, with a further case discounted because of diagnosis within 10 years of study day.

Location
Six sporadic cases involved the chiasm. Four presented with visual symptoms, one had endocrine symptoms, and one was asymptomatic. Three received radiotherapy, and two were untreated, and one was excised. Ten year survival for these six cases was 67%.

Comparative analysis
Table 1 presents a comparative analysis of the patients. The gender and racial distributions in our study were similar for sporadic and NF1 optic gliomas. Mean and median ages at presentation, time from presentation to diagnosis, and age at diagnosis were not significantly different between the groups, although sporadic gliomas tended to occur later in all three categories. Two cases in each group recalled symptoms beginning over a year before they presented to the medical profession. Five further sporadic cases noted symptoms had started about a year previously, four of these visual in nature.

One sporadic and two NF1 gliomas were asymptomatic. Of the remaining 31 gliomas, significantly more sporadic (15/16 or 94%) than NF1 (7/15 or 47%) presented with visual symptoms (p = 0.01). A total of seven sporadic (41%) and four NF1 (24%) cases presented with proptosis. Fewer numbers
**TABLE 1** Comparisons of NF1 and sporadic gliomas for presentation, diagnosis, and complications

<table>
<thead>
<tr>
<th>Presentation and diagnosis</th>
<th>NF1 cases</th>
<th>Sporadic cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Visual: non-blind/blind</td>
<td>5/2</td>
<td>10/5</td>
</tr>
<tr>
<td>Proptosis</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Endocrine</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Space occupying symptoms</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Age at presentation in years—mean</td>
<td>4.47</td>
<td>5.11</td>
</tr>
<tr>
<td>Age at presentation in years—median</td>
<td>4 (1-14)</td>
<td>5 (0.25-13)</td>
</tr>
<tr>
<td>Age at presentation in years—mode</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Time from presentation to diagnosis in years—mean</td>
<td>0.53</td>
<td>0.72</td>
</tr>
<tr>
<td>Age at diagnosis in years—mean</td>
<td>5.00</td>
<td>5.83</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>NF1 cases</th>
<th>Sporadic cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Non-CNS tumour</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial neoplasm</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Endocrinological</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>None</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Optic gliomas account for less than 5% of childhood brain tumours. Their prevalence in the general population is thought to be around 1 in 100 000. The estimated prevalence of neurofibromatosis in patients with optic gliomas ranges from 10% to 70%. From our population, the most accurate estimate of prevalence looks at the number of NF1 related cases from the CTR alone, as using NF1DB cases would introduce selection bias. This gives a population based value of 18/36 or 50%.

In patients with NF1, the lifetime risk of developing an optic glioma has generally been found to be between about 10 and 20%, although estimates range from under 5% to as high as 28%. In our NF1 database, the prevalence was 5%. Although we lack sufficient data on the reasons for scanning the group of children with NF1 from which the 25 gliomas were identified, it is likely that the majority were symptomatic in order to merit special investigation. Indeed, only two cases were recorded as not having symptoms attributable to an optic glioma at diagnosis. Hence, our figures are likely to reflect prevalence of symptomatic rather than all gliomas.

Particular significance has traditionally been attached to chiasmal involvement of optic gliomas. In contrast to previous studies we found a preference towards chiasmal involvement in NF1 but not in sporadics, and identified cases of isolated nerve gliomas causing precocious puberty, suggesting compression of the hypothalamus might not be solely a manifestation of chiasmal involvement. There was no clear evidence that location affected either management or survival in either group. Nor was there evidence that treatment altered long term outcome, although this is bound to be affected by selection bias, the more aggressive tumours probably being more often treated but also probably having a worse prognosis. Although chemotherapy is a promising new addition to therapeutic options, the cases in our study predated the chemotherapy era.

Nine of our cases had a lag of a year or more between first symptoms and diagnosis, suggesting insidious growth. However, seven of these were sporadic cases where the index of suspicion would be expected to be low. Nonetheless, visual symptoms and mortality directly caused by the glioma were significantly more common among sporadic cases. This

**Table 2** Investigation on which diagnosis was based

<table>
<thead>
<tr>
<th>Diagnostic tool</th>
<th>NF1 cases</th>
<th>Sporadic cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Histological [+/- radiological]</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Macroscopic evaluation (surgically)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Radiological with macroscopic confirmation (surgically)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
suggests that sporadic gliomas are more aggressive than their NF1 counterparts. Despite this, absolute mortality figures and 5 and 10 year survival rates were very similar. The reason for this disparity is the high preponderance of fatal second primary CNS tumours in patients with NF1. Thus, five NF1 children with optic gliomas developed an intracranial neoplasm (aged 10–34 years). Conversely, no sporadic case was definitely diagnosed with a second CNS tumour. The propensity of second CNS tumour development in NF1 optic gliomas has been noted before, and the NF1 gene has been putatively considered tumour suppressant, although the only other direct comparative study of NF1 and sporadic optic gliomas did not identify any second malignancies. These findings go against the prevailing attitude that CNS tumours in NF1 regress or are indolent and hence do not require intervention.

Whether the presence of an optic glioma in NF1 children is in itself a marker of tumour susceptibility was not specifically tested by this study. It would require for comparison a group of NF1 patients who developed any other type of tumour and who did not have evidence of an optic glioma. It has been suggested that CNS tumours are specific to those NF1 cases with, as opposed to without, optic glioma. In conjunction with our finding of CNS tumours being specific to optic glioma cases with, as opposed to without, NF1, it could be extrapolated that a dual diagnosis of NF1 and optic glioma is the critical factor for CNS tumour development.

One of the five NF1 children with a second CNS tumour was a boy who later died from an axillary sarcoma at the age of 24. He was found on postmortem examination to have an incidental chiasmal glioma and a cerebellar pontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma. This latter tumour may have been related to incidental chiasmal glioma and a cerebellopontine angle schwannoma.

In conclusion, these data suggest that NF1 related optic gliomas are less aggressive than their sporadic counterparts. They are less often aggressively treated, but still less likely to recur or shorten life expectancy. Nonetheless, they produce the same constellation of symptoms and are still responsible, from an early age, for much morbidity and mortality through both visual loss and in particular second CNS tumour development. The implications for management are twofold. Firstly, an aggressive management approach directed at sporadic optic gliomas should be considered in line with improvements in therapeutic efficacy given the higher mortality directly attributable to these tumours. Secondly, in young children with NF1, we agree with the North American consensus statement of 1997 that serial ophtalmological examinations should be carried out in NF1 from an early age if we wish to be able to detect and treat early optic gliomas. For practical reasons the target age group could be limited to those under 6 years old as most cases were diagnosed by this age in our and previous studies. However, follow up of identified cases with particular attention to second CNS tumour development should be mandatory. This expectant management strategy with recommendations for treatment is part of an international study under the auspices of the International Society for Paediatric Oncologists.

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**Table 3** Subsequent occurrence of second CNS tumours, recurrence of optic glioma, or both among all patients who ever received cranial irradiation

<table>
<thead>
<tr>
<th>Tumour event</th>
<th>Irradiated NF1 cases (n=5)</th>
<th>Irradiated sporadic cases (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second CNS tumour only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent and second CNS tumour</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent tumour only</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No recurrent or second tumour</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: second recurrences are excluded.

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**References**

Feeding infants of diabetic mothers

In general, breast feeding protects against later obesity and diabetes. Infants of diabetic mothers have an increased risk of later obesity and glucose intolerance. It might be thought, therefore, that breast feeding might protect the infants of diabetic mothers from these later developments but the milk of diabetic mothers contains more glucose, insulin, and energy than that of nondiabetic mothers, especially in the early neonatal period, and could be harmful. A study in Berlin (Andreas Plagemann and colleagues. Diabetes Care 2002;25:16–22) has suggested that early breastfeeding by diabetic mothers may have adverse consequences.

Between 1980 and 1989 112 infants of diabetic mothers (83 type 1 diabetes, 29 gestational diabetes) were followed up at a clinic in the then East Berlin. The mothers were encouraged to breastfeed and supplements of banked donor breast milk were given when deemed necessary. Infants who took more of their mother’s milk were more likely to be overweight at age 2 years (proportions overweight in first, second, and third centiles for weight of mother’s breast milk taken in the first week were 5/37, 11/38, and 14/37). The weight of mother’s milk taken in the first week correlated directly with relative body weight at age 2 years whereas the weight of banked donor breast milk taken correlated inversely with relative body weight at age 2 years. Similar associations were found between amounts of mother’s and donor milk taken in the first week and the 120 minute blood glucose concentration on oral glucose tolerance testing at 2 years. The risk of impaired glucose tolerance at age 2 years was inversely related to the amount of donor breast milk taken.

Breast feeding by diabetic mothers may increase the risks of later overweight and glucose intolerance in their infants. (The authors of this article are careful to point out that in their opinion the advantages of breastfeeding still outweigh the disadvantages even for diabetic mothers.)
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Arch Dis Child 2002 87: 65-70
doi: 10.1136/adc.87.1.65

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