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Seizures as the presenting symptom of brain tumours in children

KHALID IBRAHIM & RICHARD APPLETON

The Roald Dahl EEG Unit, Department of Neurology, Royal Liverpool Children's NHS Trust (Alder Hey), Liverpool, UK

Correspondence to: Dr Richard E. Appleton, F.R.C.P.C.H., Consultant Paediatric Neurologist, The Roald Dahl EEG Unit, Department of Neurology, Royal Liverpool Children's NHS Trust (Alder Hey), Liverpool L12 2AP, UK.
E-mail: Richard.Appleton@RLCH-TR.NWEST.NHS.UK

Seizures were the presenting clinical symptom in 10 (12%) of 81 consecutive children with a primary brain tumour treated in a tertiary paediatric oncology unit over 5 years. Nine patients experienced partial seizures, and in seven a waking electroencephalogram showed focal or lateralising abnormalities. Astrocytoma was the most common tumour histology. The delay in tumour diagnosis from the onset of seizures ranged from 2 weeks to 2 years with a mean of 6 months. Complete resection of the tumour was the only treatment in three patients and four underwent resection followed by radiotherapy and/or chemotherapy. Two patients died. Three patients became seizure free receiving no antiepileptic medication and the remaining five showed a 50–80% reduction in seizures between 2 and almost 5 years following treatment.

Key words: children; brain tumours; seizures; outcome.

INTRODUCTION

Brain tumours are one of the most common solid tumours in children, with an incidence of approximately 1–5 per 100 000[1]. In the UK, the annual incidence in children under 15 years is 3 per 100 000 (350 cases annually)[2]. Presentation is usually with symptoms and signs of raised intracranial pressure with or without evidence of cranial nerve dysfunction, reflecting the fact that most brain tumours in children over 4 years of age are sited infratentorially and specifically within the posterior fossa or brainstem[2–5]. Supratentorial tumours are more common in children under 4 years of age and in adults. Although cognitive or behavioural difficulties may also be presenting features of brain tumours that are located supratentorially (typically within the frontal or temporal lobes), seizures are a relatively uncommon presentation of brain tumours. Previous studies have primarily focused on specific epilepsy populations and the proportion of epilepsy being caused by brain tumours, where the reported frequency is 0.2–6%, depending on the type of seizure[6, 7]. Studies that have examined the frequency of epilepsy as the initial presentation of a brain tumour in children have reported a wide range of rates, from 7–16%[4, 5, 8–11] to as high as 40%[12].

The purpose of this retrospective study is to review the detailed seizure history of a population of children with brain tumours.

METHODS

The case notes were reviewed retrospectively of all children aged 1 month to 15 years presenting with a primary brain tumour to a regional paediatric oncology unit in a tertiary care Children's Hospital over 5 years. Children with secondary (metastatic) brain disease and with a haematological malignancy were excluded from this review. The paediatric oncology unit serves a total population of 2.8 million and is the only paediatric unit in the region that manages and co-ordinates the care of children with brain tumours.

Information was collected on the following: sex, age at onset of seizures, age at diagnosis of brain tumour,

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type or types of seizures, additional neurological, cognitive or behavioural symptoms or signs at time of seizure onset, electroencephalographic (EEG) findings, magnetic resonance imaging (MRI) findings, histology of the tumour, treatment of the tumour, years of follow-up and seizure outcome (seizure frequency at latest follow-up compared to seizure frequency at time of tumour diagnosis).

Surface (scalp) EEG was undertaken in either the waking or drowsy (following sleep deprivation) state with a Micromed 'Brain Quick' 32 System 98 using the international 10–20 electrode placement with referential and bipolar montages and reported by one paediatric neurologist/neurophysiologist. In-depth EEG monitoring and intra-operative electrocorticography (ECOG) were not undertaken in any patient.

MRI was undertaken using a Philips 0.5T Gyroscan NT 5 scanner, with axial and coronal views employing T1, T2 and FLAIR sequences with and without gadolinium and interpreted by two paediatric neuroradiologists.

RESULTS

Eighty-one patients were diagnosed with a primary brain tumour between January 1996 and December 2000. Ten of the 81 patients (12.3%) presented with epilepsy. The tumour was sited supratentorially in all 10 patients. Demographic, treatment and seizure outcome details are demonstrated in Table 1. Neurological examination was normal in 7 of the 10 patients; 1 patient had a slight hemiparesis and another patient demonstrated behavioural changes (impulsivity and disinhibition) that had ante-dated the seizures by a number of months. One patient had precocious puberty and one patient each had tuberous sclerosis (TS) and neurofibromatosis (NF). The patient with TS (Patient 3) demonstrated developmental delay at the time infantile spasms and partial seizures were diagnosed at 13 months of age; the patient with NF (Patient 10) already showed global developmental delay and abnormal visual behaviour when infantile spasms were diagnosed at 6 months of age. Patient 3 became seizure free on vigabatrin and re-presented at 8.5 years with complex partial and secondarily generalised tonic–clonic seizures. Repeat MRI showed a subependymal giant cell astrocytoma (SEGA). Patient 10 presented at 6 months of age with infantile spasms and MRI showed an optic nerve glioma involving the optic chiasm and an enlarged, dysplastic-looking left temporal lobe. Complex partial and secondarily generalised seizures developed and were resistant to all antiepileptic drugs (AEDs). Sequential MRI revealed progressive expansion of the left temporal lobe and a subsequent temporal lobectomy revealed a low-grade glioma.

The mean age at onset of seizures was 5.7 years and the mean age at diagnosis of the tumour was 6.1 years. The duration of epilepsy prior to the diagnosis of the tumour ranged from 1 to 2 weeks (Patients 4 and 7, respectively) to 2 years with a mean of 0.5 years in the remaining eight patients. The longest period of active epilepsy prior to the diagnosis of a tumour was 2 years (Patient 6) whose initial (computerised tomography [CT]) brain scan performed 3 months after seizure onset was reported to be normal.

Seizures were occurring at least weekly in all 10 patients prior to the diagnosis of the tumour; in 7 the seizures were occurring at least once daily, including in Patient 6, where seizures had been occurring for 2 years prior to the diagnosis of the tumour.

Six patients were receiving one, and three patients, two drugs at the time the tumour was diagnosed. Monotherapy included carbamazepine (three patients), vigabatrin (two patients) and lamotrigine (one patient). Dual therapy included one patient with each of the following combinations: carbamazepine+ phenytoin, carbamazepine + vigabatrin and vigabatrin + clobazam. One family declined any medication after the first AED proved ineffective and prior to treatment of the tumour (Patient 7).

No patient had developed any new neurological deficit following surgery. Pre- and post-operative visual field examination was not performed routinely and it is therefore not possible to comment on whether surgery may have caused any new or additional visual field defects.

Resection of the tumour was undertaken in seven patients, in whom it was radical in five (Patients 3, 5, 7, 9 and 10). Patients 2 and 4 required additional resections because of persistent clinical seizures rather than because of tumour recurrence. The diagnosis was made by high resolution MRI without histological diagnosis in Patient 1; in Patient 6, histology was confirmed by biopsy with no resection due to tumour location. Resection was considered inappropriate in Patient 8 in view of the biopsy-proven histological diagnosis of a high-grade and malignant tumour.

At the time of the latest follow-up, three patients had remained seizure free and receiving no AED between 2 and 3.5 years after treatment of the tumour. Two patients died, both with persisting seizures at the time of death. The remaining five children continue to experience seizures but in all there has been a 50 to 80% reduction in seizure frequency, particularly secondarily generalised tonic–clonic seizures. Three of these five patients are receiving one, and the remaining two patients, two AEDs.

Table 1: Demographic features of the 10 patients

Patient no. (sex)	Age at onset of seizures (years)	Age at diagnosis of tumour (years)	Seizure types(s)	Neurological/physical signs at time of seizure onset	EEG findings	Tumour type	Tumour treatment	Years of follow-up	Current seizure status
1. (M)	7.9	8.0	CP; gelastic	Early precocious puberty	Left temporal spike	Hypothalamic hamartoma	Nil	3.2	Monthly[#]
2. (F)	12.7	13.0	Myoclonic	None	N	Astrocytoma (grade 1, left temporal lobe)	Resection (×2) chemotherapy (×2)	3.6	Every 2–3 months[#]
3. (F)	1.1 (9)[*]	10.0	Infantile spasms; (CP; SGTC)[*]	Tuberous sclerosis	Right frontal spike	SEGA	Resection	4.2	Weekly[#]
4. (F)	1.4	1.4	SP; CP; SGTC	Minimal right hemiparesis	Left frontal spike	Oligodendroglima (grade 2, left frontal lobe)	Resection (×3) chemotherapy (×2)	1.8	Seizure free (no anti-epileptic medication)
5. (M)	3.1	3.8	SP; SGTC	None	Right temporal spike	DNET (right temporal lobe)	Resection	2.2	Every 2–3 weeks[#]
6. (F)	5.7	7.7	CP	None	N	Astrocytoma (grade 2, right temporal lobe)	Chemotherapy	2.8	Seizure free (no anti-epileptic medication)
7. (F)	6.9	6.9	CP	None	ND	PNET (right parietal lobe)	Resection radiotherapy chemotherapy	3.4	Seizure free (no anti-epileptic medication)
8. (F)	8.5	8.6	SP; CP	Behaviour change	Left frontotemporal spike	Astrocytoma (anaplastic, left frontal lobe)	Nil	–	Died aged 9.5 yrs
9. (M)	1.1	1.3	SP; CP; SGTC	None	Left temporal sharp wave	Astrocytoma (grade 2, left temporal lobe)	Resection	4.7	Weekly[#]
10. (M)	0.6	0.7	Infantile spasms CP	Neurofibromatosis	Hyps; left temporal spike	Optic nerve glioma; left temporal glioma	Resection (temporal lobe chemotherapy)	–	Died aged 5 yrs

CP = complex partial; SGTC = secondarily generalised tonic-clonic; SP = simple partial; SEGA = subependymal giant cell astrocytoma; DNET = dysembryoblastic neuroepithelial tumour; PNET = primitive neuroectodermaltumour; N = normal; ND = not done; Hyps = hypsarrhythmia.

[*] presented at 13 months with infantile spasms; re-presented at 9 years with partial and secondarily generalised seizures.

[#] seizures persist but >50% reduction in seizure frequency of all seizure types compared to seizure frequency prior to tumour diagnosis.

DISCUSSION

Approximately one in nine (12%) of our patients presented with seizures as the first symptom of an underlying brain tumour. This is similar[5, 8–10] or almost identical[11] to previous paediatric studies, but almost one half of adult studies[9, 12]. The study by Low *et al*. reported a very high incidence of seizures (49 of 123 children, 40%) but it was unclear whether this related to the initial presenting symptom or to all patients who experienced a seizure at any time during their study[13]. The increased rate in adults is likely to reflect the fact that proportionately, most brain tumours in adults are supratentorial and sited in the cerebral hemispheres. Most of the tumours in our series were low-grade gliomas or astrocytomas, tumours that are commonly seen in children and which are recognised to cause seizures[2, 8, 14, 15]. One patient each had a dysembryoplastic neuroepithelial tumour (DNET), primitive neuroectodermal tumour (PNET) and oligodendroglioma, tumour types that are also known to cause epilepsy. Somewhat surprisingly, neither DNETs nor PNETs were found to be associated with epilepsy in an earlier and slightly larger paediatric series[15], in contrast to a very recent series of 23 patients with intractable epilepsy caused by brain tumours[11], in which DNETs accounted for 9 of 23 tumours. Tumour series reported prior to 1973/1974 would not have included PNETs, as this type was only introduced to tumour classifications after this time[16]; previously, these tumours were usually labelled ‘cerebral neuroblastomas’. Although there is some debate as to whether DNETs should be regarded as a tumour, the most recent World Health Organisation (WHO) classification includes them in the category of ‘neuronal and mixed neuroglial tumours’[17, 18].

The two children with a neurocutaneous syndrome (TS and NF) developed characteristic tumour types known to occur in these disorders. The presentation with seizures of the patient with TS who developed a SEGA was atypical; the more usual presentation of this tumour is with symptoms and signs of hydrocephalus. The course of the patient with NF was also atypical, firstly in terms of the initial presentation with infantile spasms and secondly with the subsequent development and rapid growth of the temporal glioma.

Most of the patients were found to have a brain tumour within 3 or 4 months of the onset of seizures. This is considerably shorter than has been found in previous studies, where the lag time between seizure onset and tumour diagnosis has been as short as 3 weeks and as long as almost 10 years, but typically with a mean duration of 1–3 years[4, 5, 8, 9, 15]. Previous studies that have evaluated the relationship of epilepsy and brain tumours have reasonably suggested that the presence of focal neurological signs may contribute to an earlier diagnosis of the tumour. In our series, 6 of the 10 patients had neither focal neurological signs nor a history of either cognitive or behavioural difficulties. In children with supratentorial tumours and particularly in those with tumours of the temporal lobes, focal neurological abnormalities and fundoscopic signs of increased intracranial pressure usually develop late. Behavioural and cognitive difficulties, additional features of tumours within the cerebral hemispheres, may also be identified—and taken seriously—only after many months.

The EEG may clearly be useful in suggesting a structural abnormality, particularly in children with simple and complex partial seizures; however, the correlation between focal EEG findings and structural lesions is neither close nor consistent[19]. Previous reports have shown that focal or lateralising abnormalities occur in between 80[8], 82[15] and 92%[5] of children who have seizures and brain tumours within the cerebral hemispheres. At least one report has suggested that the initial EEG, as distinct from repeated EEGs, may be of no localising value in adult patients with chronic epilepsy due to slow growing brain tumours[20]. Seven of the patients (70%) in the present series had focal EEG changes, which together with the partial semiology of the seizures, would have resulted in early neuroimaging based on the local guidelines of when to undertake brain scans in children with epilepsy. These guidelines, in common with international guidelines[21], also recommend that MRI should be undertaken in all children with infantile spasms. Adherence to our local neuroimaging guidelines may be one explanation for the relatively early identification of the tumours in our patients.

Few previous reports have evaluated the long-term seizure outcome in children with brain tumours. Of the 15 patients reported by Patel *et al*.[15], 80% showed a ‘very significant’ improvement in seizure frequency, with 8 becoming seizure free and 4 experiencing only ‘rare’ seizures, based on the Engel classification[22]. In the earlier study of Sjors *et al*.[8], which did not state the duration of follow-up, 8 of the 10 patients who survived were seizure free, 5 on antiepileptic medication. Eight of our patients survived, of whom three became seizure free and receiving no antiepileptic medication and the remaining 5 showed a reduction in seizure frequency of between 50 and 80% at the time of the most recent follow-up (approximately 2–5 years after the diagnosis of the tumours). There may be a number of reasons for the relatively poor seizure outcome in our patients compared to earlier studies[8, 15], including tumour histology, the extent of surgical resection and late complications of chemotherapy and radiotherapy. The duration of seizures is unlikely to have been a

contributory factor as the delay in diagnosis of the tumour was considerably shorter in our patients than in earlier studies[8, 14]. It is likely that intra-operative EEG monitoring with ECOG may have allowed a more precise surgical resection that could have potentially influenced seizure outcome. It is also possible that lesionectomy (resecting only the macroscopically visible limits of the tumour) may not be as effective as a more radical resection that removes not only the tumour but also any additional epileptogenic tissue around the tumour[11]. Unfortunately, the numbers of patients in the present, and previous[8, 11, 15], studies are too small to try and correlate seizure outcome with tumour histology, delay in tumour diagnosis, extent of tumour resection or additional treatments (radiotherapy and chemotherapy). The influence on long-term seizure outcome of some of these factors could potentially only be clarified by national or even international collaborative studies.

CONCLUSION

Seizures are an uncommon presentation of brain tumours in children, occurring in approximately 10% of cases and are rarely accompanied by focal neurological signs, particularly in older children. The semiology of the seizures are typically partial and the presence of focal or lateralising EEG abnormalities which do not suggest one of the idiopathic partial epilepsy syndromes, should lead to early consideration of neuroimaging, specifically with MRI.

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