Seizure characteristics and the use of anti-epileptic drugs in children and young people with brain tumours and epileptic seizures: analysis of regional paediatric cancer service population

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HIGHLIGHTS

- Epileptic seizures are a neurological complications in children with brain tumour.
- Seizure treatments and their withdrawal are not codified.
- In our cohort we found a relationship between tumour site and seizure occurrence.
- Levetiracetam was used for its good tolerability and poor interaction with chemotherapy.
- Further studies are required to assess the time of AEDs withdrawal

Abstract

Purpose: Epileptic seizures complicate the management of childhood brain tumours. There are no published standards for clinical practice concerning risk factors, treatment selection or strategies to withdraw treatment with antiepileptic drugs (AED).

Method: we undertook a case note review of 120 patients with newly diagnosed brain tumours, referred to a regional paediatric cancer service.

Results: data was available on 117/120 (98%) children <18 years: median age at tumour presentation was 8.1 years (IQR $^{25°\text{-}75°}$: 3.6-12.7), median follow up was 33 months (IQR $^{25°\text{-}75°:}$ 24-56), and 35/117 (29%) experienced seizures.

A cortical tumour location was associated with the highest risk of seizures (OR: 7.1; CI 95% 2.9-17.3). At a median follow up of 24 months (IQR$^{25°\text{-}75°}$: 15-48), 22 /35 (63%) with seizures, had a single seizure episode, 15/35 (43%) were seizure free (SF) on AEDs, 13/35 (37%) were SF off AEDs, and 7/35 (20%) experienced continuing epileptic seizures. Overall 34/35 (97%) were treated with AEDs after a seizure, of whom 12/35 (35%) withdrew from AED medication, and although 4/35 (12%) had seizure relapse, all were after further acute events. The median duration of AED before withdrawal was 11 months (IQR$^{25°\text{-}75°}$ 5-14 months), and the median follow up after withdrawal was 15 months (IQR$^{25°\text{-}75°}$ 5-34 months).

Conclusions: Seizures affect about 1/3rd of children and young people presenting with and being treated for brain tumours particularly when the tumour is in the cerebral cortex.

The low risk of recurrent seizures after AED treatment justifies consideration of early withdrawal of AED after seizure control.

Key Words: Brain Tumour Paediatric Seizure Anti-epileptic drug

Introduction

Epileptic seizures are a common symptom of brain tumours previously reported in 7% to 16% of children and young people in the very limited literature on this topic [1]. Other studies reported a 15-25% incidence [2]. Seizures were reported as the first symptom in 38% of children with supratentorial tumours [3].

The mechanism of epileptogenesis is incompletely understood and it seems to be multifactorial and may include cytotoxic oedema, haemosiderin deposition, and the disruption of brain circuits by morphological changes in the tumour and peri-tumoural tissues [4, 5]. Moreover tumour treatment-related toxicity is another important cause of epileptic seizures [6]. A recent study identified individual risk factors for epileptic seizures in children with brain tumours at any time: cortical tumour location, histology as glioneuronal tumour, and low or high grade glioma, incomplete resection, and tumour recurrence [5].

Currently there is no consensus on the treatment of brain tumour related/provoked acute symptomatic epileptic seizures in children and young people.

The American Academy of Neurology recommends tapering antiepileptic drugs (AEDs) if used prophylactically at the time of craniotomy, after the first postoperative week and declares that anticonvulsant medications are not effective in preventing a first seizure and that prophylactic AEDs should not be used routinely in adult patients with a new diagnosis of a brain tumour [7]. Moreover a review by Stevens in 2006 found that 11 out of 12 studies did not show any substantial benefit from routine prophylaxis in adult patients [8].

There are few clear recommendations on which AED to choose following one or more epileptic seizures in children and young people presenting with a brain tumour or while being treated for a brain tumour, although carbamazepine and phenytoin are mentioned in the SIGN guideline for adults [9].

When choosing an AED, even for short term use, it is necessary to consider the potential drug interactions and adverse effects, especially where complex chemotherapy and supportive care drug combinations may be in use [10].

Moreover the optimal tming of AED withdrawal in children with brain tumours and epileptic seizures is not known. There is limited literature on predictors of seizure recurrence upon AED withdrawal in the brain tumour population. Some authors suggested that children with pre-operative seizures, which resolve completely after surgery, may be weaned off AEDs within 3 months after surgery [11]. One study found a seizure recurrence rate of 27% over 5 years, with half the recurrences occurring within the first 6 months [12]. A more recent study examined AED discontinuation in an adult population with meningioma and low grade glioma. It found 10% seizure recurrence after AED withdrawal [13]. The principal aim of this retrospective study was to determine patient and tumour characteristics; seizure type, frequency and duration; AED treatments used, their duration; and the associated outcomes in a representative paediatric neuro-oncology population to eventually identify the seizure risk factors in children with brain tumours, and assess current use and withdrawal of AEDs.

Identifying children with the highest risk of developing further epileptic seizures would be very useful clinically. Understanding the current clinical practice, especially the duration of AED use before withdrawal, will help the development and implementation of new treatment policies.

Methods

Inclusion criteria

A retrospective case note review of newly diagnosed brain tumour patients referred between January 2010 and December 2014 to the regional paediatric neuro-oncology service was carried out to determine patient, tumour, and seizure characteristics, their treatment, and outcome.

The inclusion criteria were: 1) age from birth to 16 years old, 2) children with primary brain tumours classified using WHO 2016 classification [14]. The seizures were classified according to the International League Against Epilepsy 2016 terminology [15, 16]. The exclusion criteria were: children with prior epilepsy or with syndrome related-epilepsy.

Statistical analysis

Descriptive analysis was performed to characterise the study population. Chi-square, Mann-Whitney U test or Fisher's exact test were used to compare groups, as appropriate. Logistic regression was used to estimate odds ratios and 95% confidence intervals for potential predictors. All analyses, other than decision trees, were performed with IBM SPSS 23.0 for Windows (IBM Corp. Armonk, NY, USA), and a $p < 0.05$ was considered statistically significant in all analyses.

Ethical approval

In the UK Health Research Authority (HRA), which coordinates and regulates ethical approval of research involving human subjects, specifically excludes projects from requiring ethical approval if they fall into the categories of clinical audit, service evaluation, and usual practice/surveillance work in public health. This was an observational study, a retrospective chart review, which was undertaken as a clinical baseline audit of current practice and outcome. The data were collected, analysed and reported according to ethical standards, in an anonymous database.

Results

The cohort included 120 patients with a new diagnosis of brain tumour in a regional paediatric neuro-oncology service serving a population of 4.5 million. It was representative of the UK population, in terms of tumour histology distribution, compared to cases registered with the Children's Cancer and Leukaemia Group (CCLG)'s national childhood cancer treatment network between1996-2005 (χ^2: $p>0.05$). Two patients with tuberous sclerosis were excluded because of their previous long history of seizures, and 1 patient was lost in follow up (Figure 1). 67/117 (57%) were male, median age at tumour presentation was 8.1 years (IQR $^{25°\text{-}75°}$: 3.6-12.7). None were referred primarily for epilepsy surgery. Of these, 23/117 (20%) patients had died, 15/117 (13%) had progressive disease, and 79/117 (67%) were in remission or had stable disease, at the time of case note review, at a median follow up of 33 months (IQR $^{25°\text{-}75°}$: 24-56). The 35 (29%) who experienced seizures were not significantly younger (median 6.3 years, IQR$^{25°\text{-}75°:}$ 2.8-10.4) than those without seizures (median 8.2 years,

IQR$^{25°-75°}$: 3.8-13.3) (p=0.295). The population characteristics are summarised in Table 1and the types of tumours and the age at diagnosis in Figure 2.

There was a correlation using logistic regression analysis, between cerebral hemisphere tumour localisation and seizure occurrence (OR: 7.07 IC 95%: 2.9-17.3).

Although there was a high incidence of seizures in children with neuroglional tumours (75%), no statistical correlation was found between type of tumour, age, and seizure occurrence.

Seizure activity

A total of 35/117 (30%) patients had seizures, 22/35 (62%) were males. The median seizure follow-up was 33 months (IQR $^{25°-75°}$: 24-56). The seizure characteristics are described in Table 2.

12/13 patients with seizures at tumour diagnosis had a cortical hemisphere localisation. The most frequently used AED at diagnosis was levetiracetam, used in 17/34 (50%), followed by phenytoin and carbamazepine each used in 6/34 (18%), sodium valproate in 4/34 (11%) patients, and phenobarbital 1/34 (3%). Only one patient did not receive any AED after their acute seizure. Three patients were treated with phenytoin as prophylaxis during craniotomy, which was subsequently changed to sodium valproate (2/3) or levetiracetam (1/3).

6/34 patients were documented to have AED related adverse effects leading to dose reduction or withdrawal: 1 had a rash (phenytoin), 2 had memory difficulties (levetiracetam), 2 had lethargy and somnolence (levetiracetam), and 1 had regression of speech and somnolence (carbamazepine).

The median follow up before, and after AED withdrawal was 11 months (IQR$^{25°-75°}$ 5-14 months) and 15 months (IQR$^{25°-75°}$ 5-34 months), respectively. Of the 34 patients who received AED therapy, 11 (32%) patients were treated with a single AED, 6 (18%) with 2 AEDs, 3 (9%) with 3 AEDs, and 2 (6%) with 4 AEDs. 12 (35%) had discontinued AEDs. Referral for epilepsy surgery occurred in 4 patients after they had failed to respond to levetiracetam, carbamazepine, sodium valproate, and clobazam. Seizure relapse after withdrawal of AEDs occurred in 4/12 (33%) linked to new emergent disease or neurological complications: two associated with acute hydrocephalus requiring ventriculo-peritioneal drainage (12 and 14 months after the end of therapy), one with acute sepsis 1 month after

AED withdrawal, and one with ventriculitis associated with a ventriculo-peritoneal shunt revision. All later had their AEDs withdrawn again without further relapse.

Discussion

In our retrospective study we found that 30% of children with brain tumours seen over 5 years in this representative population developed seizures, either at (37%), or after (63%) diagnosis, and in particular we highlighted the relationship between tumour site and seizure occurrence. The most frequently used AEDs was levetiracetam, as first line treatment and only 12/34 patients withdrew the AED, during follow-up. Although 4 patients relapsed all had new emergent acute events that had precipitated the new seizures.

Epileptic seizures are one of the most common neurological complications seen in children with brain tumours. This study in a regional neuro-oncology centre is population based, and therefore representative of the type of cases that routinely present. This study highlights the importance of this complication given that brain tumours account for only 1% of people with epilepsies [17].

In this cohort we found a relationship between tumour site (cerebral hemisphere compared with other localizations) and seizure occurrence. This has been reported before: Wilne et al reported seizures to be particularly associated with supratentorial tumours (in 38%) [3], as did Ullrich (in 53%) [5], and Shuper (25%) [18].

Regarding histopathologic type, several studies have shown a relationship between low grade glioma, DNET, pleomorphic astrocytoma, oligodendroglioma, ganglioglioma and seizure occurrence [19]. However, we did not find a statistical correlation between histological type, such as neuroglioneuronal tumours, and seizures in our cohort, although we observed a high percentage of seizures in children with glioneuronal tumours (75%) at the diagnosis. Glioneuronal tumours are characterised by well-differentiated cells that can release neurotransmitters or modulators that could play a role in seizure initiation and propagation [20].

Our study is somewhat limited by the duration of follow-up. Indeed, a 33 month median follow-up may not be sufficient to show long term treatment effects. The Childhood Survivor Study reported seizures in 25% of brain tumour survivors including 7% who had seizures after 5 years or more of follow up [21]. The optimal duration of follow up in future studies should be determined by the specific purpose of the analysis.

In this cohort of seizure patients the most frequently used AED was levetiracetam. It was the most common first line AED at seizure presentation, and also the most common in overall use. The rational for choosing which AED to use in children with seizures and brain tumours is not well established. The potential for interaction between AEDs and chemotherapeutic drugs is one important consideration [22]. Some studies have shown that non-enzyme-inducing AEDs such levetiracetam and gabapentin may work well in monotherapy in children who have failed to respond to other AEDs [23, 24]. Indeed, they are generally better tolerated and easier to use than the older traditional AEDs such as phenytoin, sodium valproate, and carbamazepine.

On the other hand, the good tolerability will not prompt prescribers or patients to seek early AED withdrawal. Indeed, in our cohort, only 12/34 patients withdrew the AED during follow-up. Although 4 patients relapsed all had new emergent acute events that had precipitated the new seizures. Indeed, after the second AED withdrawal 2 of them did not develop seizures again (one had died from unrelated causes).

There are no randomized controlled trials of AED withdrawal after tumour-related seizures in children. So there are no guidelines to help neurologists and neuro-oncologists in this field. In a retrospective study of 62 children with brain tumours and seizures, AEDs were withdrawn after a median of 5.6 years from the first seizure, and seizures recurred in 27% over 5 years, with half the recurrences occurring within the first 6 months [12]. Another study in adult patients with low grade brain tumours and meningiomas reported seizure recurrence in 10% of patients whose AEDs were withdrawn compared to 48% in patients who did not withdraw AEDs [13]. The authors concluded that physicians are able to identify patients with a high risk of developing post-operative seizures, but

they gave no recommendations on when AEDs should be withdrawn. Wells *et al.* in their paediatric review recommended that 3 months after gross total resection is a conventional time to withdraw AEDs in patients with pre-operative seizures, if there were no post-operative seizures or complications [11]. The prolonged use of AEDs may cause unrecognised adverse effects, e.g. on behaviour and learning, in addition to those documented. A possible explanation for the prolonged treatment seen in our cohort may be related to the specialist follow up, where the oncologist is inhibited from discontinuing AEDs and the neurologist may not be familiar with the tumour-related risks.

Our study is limited by the retrospective methodology and relatively small numbers of patients, compared to Ullrich *et al*'s study of 298 and Khan's of 157, and our modest follow-up of 33 months compared to Ullrich's 90 months. However, our experience is probably representative of UK and potentially international practice. The great majority of the children we report had acute symptomatic epileptic seizures precipitated by the brain tumour, at presentation or subsequently (which when recurrent conceptually overlaps with structural epilepsy), or by its' treatment. The 2 year seizure free rule of thumb for withdrawing AEDs in patients with epilepsies was not intended for such acute symptomatic seizures, and we excluded patients with epilepsy e.g. associated with tuberous sclerosis from this cohort. Our data suggest that, in patients with acute symptomatic seizures due to brain tumour, AED withdrawal within 3 months of seizure onset is associated with only a small recurrence rate.

Conclusions

In this population based cohort from a specialist neuro-oncology centre 1/3 children with brain tumours developed epileptic seizures, either at diagnosis or subsequently, principally associated with cortical tumour location. The most common AED used was levetiracetam, selected for its low risk of interaction with chemotherapy, and good tolerability and efficacy.

The withdrawal of AEDs in children with brain tumours should be assessed after balancing the risk of seizure relapse and the possible adverse effects and interaction with chemotherapy. Further studies in children and young people are required, to confirm that withdrawal after three months of seizure freedom, unless there are specific reasons to continue for longer, is best.

Conflict of interest:-None of the authors has any conflict of interest to disclose.

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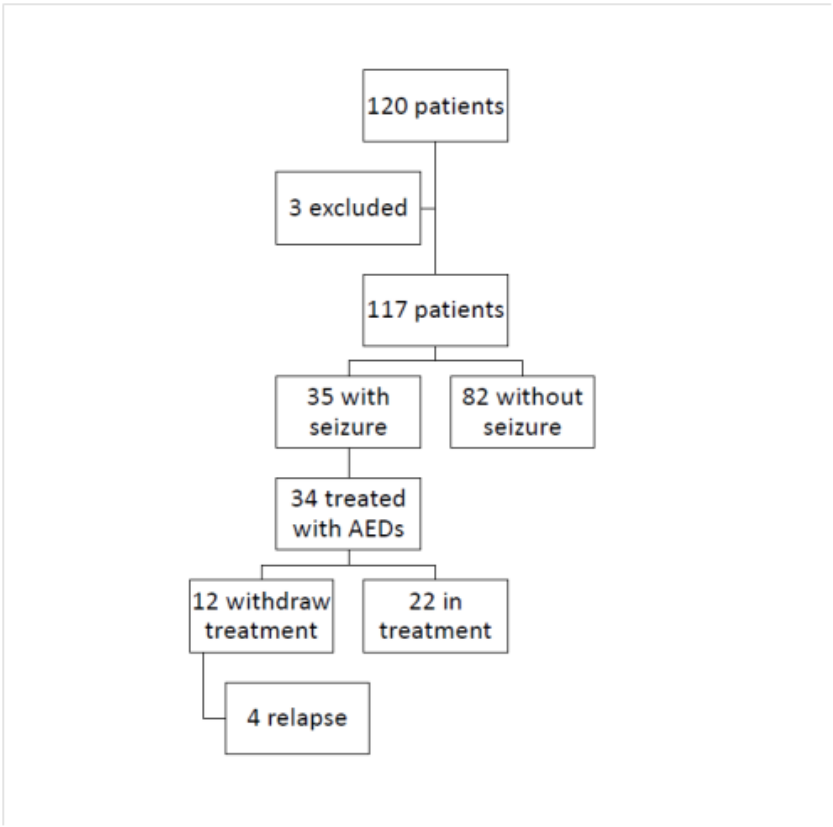

Figure 1: cohort population

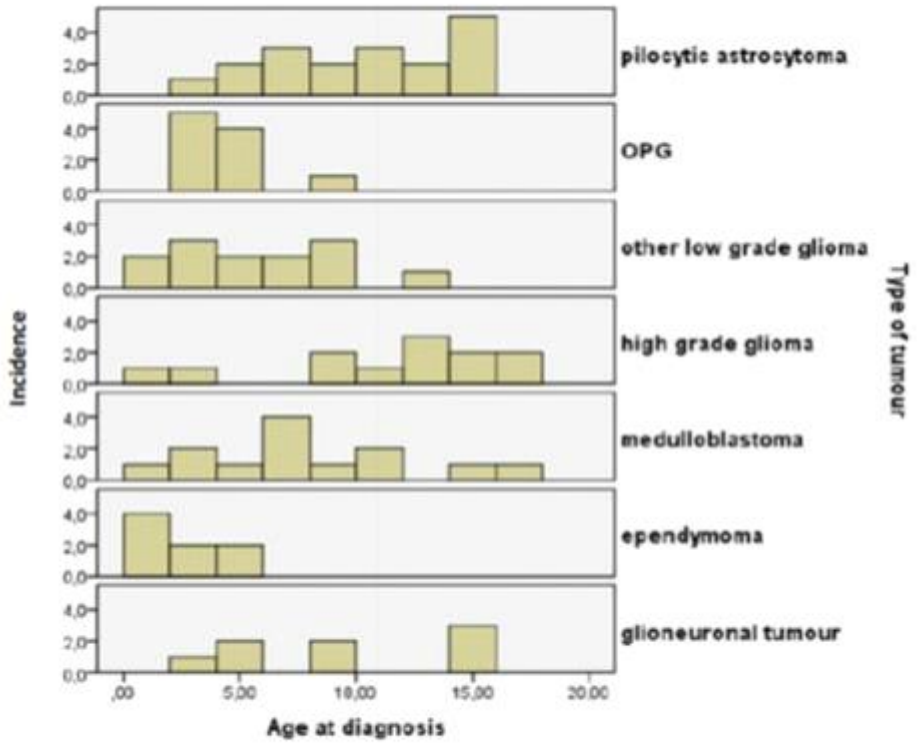

Figure 2: age distribution related with the type of tumour

Table 1: cohort characteristics. OPG: optic pathway glioma, DIPG: diffuse intrinsic pontine glioma, AT/RT: atypical teratoid/rhabdoid tumour.

	Cohort total (%)		**With seizures (%)**		**Without seizures (%)**	
total	117		35	(29.2)	82	(70.8)
female	50	(42.7)	13	(37.1)	37	(45.1)
male	67	(57.3)	22	(62.9)	45	(54.9)
median age at diagnosis	8 years 1 month		6 years 3 months		8 years 11 months	
Site of tumour						
posterior fossa	42	(35.9)	8	(22.9)	34	(41.5)
cerebral hemisphere	33	(28.2)	20	(57.1)	13	(15.9)
supratentorial midline	28	(23.9)	3	(8.6)	25	(30.5)
metastatich/leptomeningeal	8	(6.8)	2	(5.7)	6	(7.3)
spinal cord	6	(5.2)	2	(5.7)	4	(4.9)
Histology						
pilocytic astrocytoma	18	(15.4)	3	(8.6)	15	(18.3)
medulloblastoma	13	(11.1)	5	(14.3)	8	(9.8)
other low grade glioma	13	(11.1)	6	(17.1)	7	(8.5)
high grade glioma	12	(10.3)	3	(8.6)	9	(11.0)
OPG	10	(8.5)	0	(0.0)	10	(12.2)
germ cell tumour	8	(6.8)	1	(2.9)	7	(8.5)
ependymoma	8	(6.8)	4	(11.4)	4	(4.9)
glioneuronal tumour	8	(6.8)	6	(17.1)	2	(2.4)
craniopharingioma	6	(5.1)	1	(2.9)	5	(6.1)
choroid plexus papilloma	5	(4.3)	3	(8.6)	2	(2.4)
other low grade tumour	4	(3.4)	0	(0.0)	4	(4.9)

pineal tumour low grade	3	(2.6)	0	(0.0)	3	(3.7)
DIPG	3	(2.6)	0	(0.0)	3	(3.7)
AT/RT	2	(1.7)	0	(0.0)	2	(2.4)
pineal tumour high grade	2	(1.7)	1	(2.9)	1	(1.2)
choroid plexus carcinoma	1	(0.9)	1	(2.9)	0	(0.0)
other high grade tumour	1	(0.9)	1	(2.9)	0	(0.0)
Surgery						
Complete resection	43	(36.8)	18	(51.5)	25	(30.5)
Biopsy	34	(29.1)	9	(25.7)	25	(30.5)
Partial resection	14	(12.0)	2	(5.7)	12	(14.6)
Other	6	(5.0)	2	(5.7)	4	(4.9)
no surgery	20	(17.1)	4	(11.4)	16	(19.5)

Table 2: Epileptic seizure characteristics

Seizure characteristics	**N**	**(%)**
Timing of first epileptic seizure		
during oncology treatment	14	(40.0)
before the tumour diagnosis	13	(37.1)
within 1 year of treatment completion (3 only had surgery)	5	(14.3)
more than 1 year after treatment completion	3	(8.6)
Type of seizure		
focal	24	(68.6)
generalized	9	(25.7)
unknown onset	2	(5.7)
Frequency of seizure in the last 4 months		
least once daily	5	(14.3)
least once weekly	6	(17.1)
least once monthly	2	(5.7)
other (acute event)	22	(62.9)
Current seizure control		
seizure free on AED	16	(45.7)
seizure free off AED	12	(34.3)
refractory epilepsy	6	(17.1)
no therapy at diagnosis	1	(2.9)