Acta Neurochir (Wien) (1995) 135: 19–24

Acta Neurochirurgica

Seizures in Patients with Supratentorial Oligodendroglial Tumours

Clinicopathological Features and Management Considerations

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Summary

In this study of 34 consecutive histologically confirmed oligodendroglial brain tumours (15 oligoastrocytoma, 12 oligodendroglioma, 7 anaplastic oligodendroglioma) twenty five patients (75%) presented with symptoms related to seizures. Although the seizure incidence was lowest in anaplastic oligodendroglioma (57%) it was not statistically different from either pure (75%) or mixed (80%) oligodendroglial tumours. Patients with seizures had a significantly lower age ($p < 0.001$) at diagnosis (median 36 years) than those without seizures (57 years). The types of seizure disorder, that were present for a median of 15 months prior to surgery, were variable with 32% having generalised, 36% partial and 32% mixed patterns. There were no significant differences between either the type or incidence of seizures and the particular cerebral location of the oligodendroglial tumour.

Twenty four of the patients presenting with seizures underwent surgery (5 stereotactic biopsy, 5 stereotactic guided resection and 14 conventional craniotomy and resection) without intraoperative electrocorticography (ECoG). Eighteen (75%) of these patients also had postoperative radiotherapy (40 to 54 Gy in 30 fractions.

Following these treatments the percentage of patients fit free at 6, 12, and 24 months were 67%, 56%, and 53%, respectively. Median time to first post operative seizure was 32 weeks (range 5 weeks to 5.3 years). After a median follow up time of 30 months 20 of the 25 patients who presented with seizures were still alive. Eight (40%) were seizure free and three other patients (15%) had experienced less than three postoperative seizures in follow-up periods ranging from 42 to 62 months. Although the numbers of patients on preoperative (87%) and postoperative (83%) anticonvulsant medications were similar, some had their medications either withdrawn (17%) or reduced (4%) whilst others had it introduced (12%) after interventional management. Only five (20%) patients who presented with seizures, compared to 6 (67%) who had not presented with seizures had died during median follow-up of 28 months. Three of nine patients (33%), who were initially seizure free, developed seizures between 25 and 36 months after initial sugery and radiotherapy.

This study (i) confirms the high incidence of epilepsy in supratentorial oligodendroglial tumours; (ii) has shown that seizures associated with these tumours are significantly more common in younger patients; (iii) suggests that younger age, but not the presence of seizures, is a significant independent prognostic variable; (iv) that seizure control following a second operation is generally disapponting and (v) suggests that tumour resection and radiotherapy often facilitate control of the seizures by anticonvulsants.

Because of the multiple clinicopathological and management variables involved a prospective study would be required to assess the optimal management of patients with seizure disorders associated with oligodendroglial brain tumours.

Keywords: Epilepsy; oligodendroglioma; oligoastrocytoma; surgery; radiotherapy.

Introduction

Supratentorial oligodendroglial brain tumours represent an unusual clinicopathological subgroup of gliomas. Although comprising around 5% of gliomas [9, 13, 17], they generally respond favourably to surgery and radiotherapy and the anaplastic subgroup also seem to be particularly chemosensitive [3, 15, 17]. Many patients with these tumours present with seizure disorders, and epilepsy may predate tissue diagnosis by many years [6, 18]. Despite several comprehensive reviews of the clinicopathological features of these tumours [6, 11, 18] little has been written about the clinicopathology of seizure disorders associated with oligodendroglial tumours and the response of the epilepsy to interventional therapies.

This paper examines the incidence, nature and clinicopathological significance of seizures in these patients. Since there is evidence from several clinical trials and anecdotal reviews of malignant astrocytoma that seizures, prior to histological diagnosis, and younger age are favourable prognostic features, these parameters were specifically evaluated. The effects of interventional management strategies on control of

Table 1. *Incidence of Seizures According to Subtype of Oligodendroglial Tumour, Together with Sex Distribution and Median Age of Disease Diagnosis for Each Category*

Histology	Without seizures			With seizures		
	n	M/F	Age (yrs)	n(%)	M/F	Age (yrs)
Oligodendroglioma	3 (25%)	2/1	58.1 yrs	9 (75%)	8/1	36.4
Oligoastrocytoma	3 (20%)	2/1	57.8 yrs	12 (80%)	8/4	35.1
Anaplastic oligo	3 (43%)	2/1	56.6 yrs	4 (57%)	1/3	37.6

M = male, *F* = female.

the seizure disorder at 6, 12, and 24 months, anticonvulsant requirements and patient rehabilitation was also assessed.

Patients and Methods

All patients with a histological diagnosis of oligodendroglioma, oligoastrocytoma or anaplastic oligodendroglioma managed in the Department of Clinical Neurosciences from March 1987 to August 1993 were included in this review. Data was retrieved concerning sex, age at diagnosis, precise histology (Dr. J. Ironside), tumour location, type and frequency of seizure disorder(s), anticonvulsant medications before and after treatment, and survival time both from diagnosis and from first symptoms. Statistical methodology included Cox's proportional hazards model, the chi squared test with Yates modification and the Wilcoxon signed rank test.

Results

The cohort comprised 34 patients (11 female and 23 male) and accounted for 4% of all hemispheric brain tumours diagnosed in the Department during this time. Twenty-eight (84%) of patients experienced one or more seizures during the course of their disease. Seizures were the presenting clinical problem in 25 patients (75% of the total cohort). These patients had a significantly lower ($p < 0.001$) median age (36 - years, range 10 to 61 years) than those without seizures (58 years; range 19 to 60 years). Three patients, who were initially seizure free, developed a seizure disorder 25, 28, and 36 months after diagnosis. Although seizures were more common with pure or mixed oligodendroglial tumours than in patients with anaplastic oligodendroglioma this difference was no statistically significant difference. The incidence of seizures in males (76%) and females (73%) was almost identical (Table 1).

Seizure types were generalized tonic-clonic (n = 8; 32%), complex partial (n = 4; 16%), partial with secondary generalisation (n = 3; 12%), and partial motor (n = 2; 8%). Mixed seizure patterns were also common (n = 8; 32%). The combination of a partial seizure and generalised tonic-clonic seizure occurring at different times being the most frequent. There was no significant correlation between location of oligodendroglial tumour and seizure type (Table 2). There was a considerable variation in the incidence of seizures prior to surgical and radiotherapeutic intervention (Fig. 1). Some patients had only one or two seizures, others had infrequent seizures over many years whilst some patients regularly had in excess of ten partial seizures per day. In the latter two groups omit seizures were generally stereotyped in terms of pattern, intensity and duration for each patient. Most patients were treated with one (58%) or more (29%) anticonvulsants, although 13% received no pre-operative anticonvulsants. There was also a wide range in the duration of the seizure disorder prior to a tissue diagnosis (median 15 months: range 1 month to 14 years). One patient had a seizure disorder that had begun with childhood febrile convulsions. In this patient the diag-

Table 2. *Oligodendroglial Tumour Location, Seizure Incidence at Each Location and Response Following Treatment (n = 24) at Specific Follow-up Times*

Location	n	Seizure incidence	Fit free		
			6 mth	12 mth	24 mth
Frontal pole	10	8 (80%)	6 (75%)	5 (63%)	3 (38%)
Temporal pole	7	6 (86%)	4 (66%)	2 (33%)	2 (33%)
Callosal-cingulate	8	6 (75%)	4 (66%)	4 (66%)	3 (50%)
Other	5	3 (60%)	2 (40%)	2 (40%)	2 (40%)
Perirolandic	3	2 (66%)	0	0	0
Occipital pole	1	0			
	34	25	16 (67%)	13 (56%)	10 (53%)

Twenty three patients had been followed up for 12 months and 19 for 24 months. "Other" location refers to non-polar subcortical lesions that were either diffuse hemispheric lesions and not predominantly callosal-cingulate or perirolandic.

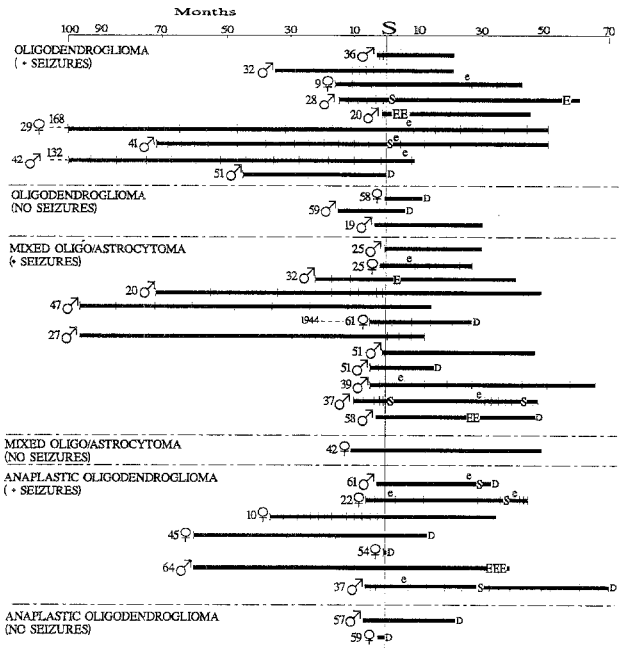

Fig. 1. Representative diagram of the cohort of patients. The length of each bar corresponds to the period of time from the onset of symptoms to either the latest follow-up interview, or to date of death. Time zero is arbitrarily set at the date of the first surgical intervention (*S*). Two patients had pre-operative symptoms for in excess of 100 months–these are indicated by dotted lines, with the period of time in months. Values next to the male/female symbols correspond to the patients' age in years at the onset of symptoms. The cohort is grouped according to pathological diagnosis, and presence or absence of seizures. Vertical lines indicate periods of time when the patient was suffering a seizure disorder of any sort; spacing between them semi-quantitatively represents the frequency of fits. e indicates the return of a seizure disorder after post-surgical amelioration; *E* also indicates the return of a seizure disorder post-operatively, but represents a single fit, in cases where they could be measured as such. *S* is a second or third surgical procedure, *D* indicates the time of the patients' death. One 28 year old male patient, who had a solitary seizure prior to resection of a temporal lobe oligodendroglioma, and who has been fit free for 30 months is not shown on the figure

nosis of an oligodendroglial tumour was made 53 years later.

Most patients with epilepsy had no focal neurological deficit (60%), 20% had focal neurological signs and 20% had signs and symptoms of raised intracranial pressure. Overall pre-operative performance status was good (median Karnovsky score = 80). An EEG was performed pre-operatively in 9 (38%) patients. Three were normal, three showed focal spiking activity and three showed slow wave abnormalities. No patients underwent either EEG videotelemetry or invasive EEG monitoring prior to surgery [1, 13].

Surgical management of patients presenting with seizure disorders included CT guided stereotactic biopsy (n = 5), stereotactic CT guided microcraniotomy and resection (n = 5) or resection using conventional neurosurgical techniques (n = 14). Three patients had a stereotactic biopsy before planned resection of the lesion. One patient aged 54 years who had a diffuse lesion causing epilepsy presented in poor clinical condition after an episode of status epilepticus. This patient was deemed not suitable for any surgical intervention and diagnosis was confirmed at autopsy one month later.

The surgical management of patients who did not have seizures prior to diagnosis included stereotactic biopsy (n = 1) and tumour resection (n = 7). One of these nine patients presented with a large intracerebral haemorrhage and died two days after admission. Autopsy confirmed a diagnosis of oligodendroglial tumour. One patient, with a diffuse anaplastic oligodendroglioma, died on the first postoperative day otherwise there was no surgical morbidity.

Cerebral irradiation (ranging from 48 Gy to 54 Gy in 30 fractions) was administered to 18 patients presenting with seizures (72%) and 8 patients who did not have pre-operative seizures (88%). Chemotherapy (either TCNU or the combination of CCNU, procarbazine and vincristine) was administered to 7 patients.

The percentage of the cohort that had presented with seizures, and underwent treatment, and were fit free at 6, 12, and 24 months were 67%, 56%, and 53%, respectively. After a median follow up of 30 months (range 5 months to 5 years and 5 months) 8 (40%) of the surviving 20 patients were fit free and three (15%) had experienced less than three postoperative seizures in follow up periods ranging from 42 to 63 months. Median time to first postoperative seizure was 32 weeks (range 5 weeks to 5.3 years). The response of the seizure disorder to therapy was not significantly related to patient age, pre-operative seizure type, tumour location or subtype (Fig. 1 and Table 2). The 13 patients who experienced only isololated seizures and a seizure history shorter then ten months generally hat a similar outcome, in terms of seizure control, to the 11 patients with seizure disorders of more than 10 months duration (Fig. 1). Following surgery 67% of patients remained on the same anticonvulsant regime, 4% have had their drugs reduced, 17% have been taken off anticonvulsants totally, and 13% have had them begun or increased.

Following surgery and/or radiotherapy (62%) of those patients (n = 29) having employment returned to their previous occupation. Of the ones who did not reasons varied from the loss of their driving licence in two cases, early retirement in one case and rapid post-operative relapse in the others.

Responses to a second operation (n = 4) performed because of progressive neurological deficit, worsening seizure disorder or signs of progressive raised ICP, a median 34 months (range 30 to 44) after a first operation, included abolition of seizures until death in one case, transient (8–10 weeks) reduction in seizure frequency and intensity in two patients and worsened seizure frequency in the fourth patient. Three of these patients who underwent re-operation and resection had intra-operative electrocorticography (ECoG) which showed contiguous and non-contiguous perilesional brain dysrhythmia and regions of spiking activity. The resections, however, were limited to tumour tissue only [20].

Median follow up time since first surgery was 30 months (range 5 months to 5 years 5 months) during which time 11 (34%) of the cohort had died. Two of these had died prior to any treatment. Four (17%) of the patients presenting with epilepsy had died (median survival 15 months, median age 51 years) whilst 5 (63%) of those presenting with other symptoms (median survival time 11 months, median age 59 years) had died. Using a Cox's proportional hazards model young age is a favourable independent prognostic variable but the presence is epilepsy in patients with oligodendroglial tumours is not.

Discussion

This review has confirmed the high incidence of seizures in patients with oligodendroglial tumours. The 84% incidence in this consecutive series of patients is not dissimilar to the 50–92% described in previous reports although many of these series contained selected patients and predated CT scanning [6, 9, 12, 15, 18]. The pattern of seizures documented in this study represent the most detailed analysis of seizure disorders in oligodendroglial tumours. In many previous studies the breakdown and classification of seizure type has not been recorded. However, in the only report giving some detail of seizure type and frequency both the incidence and type of seizures (circa 80% for generalized seizures and 70% for partial seizures) is remarkably similar to the 76% and 60% found in this study [6].

The high seizure incidence in patients with oligodendroglial tumours appears to be independent of both tumour subtype and location. In most series, including this one, the most frequent tumour loci are the frontal or temporal regions [6, 15]. Although our series had a lower incidence of seizures in patients with anaplastic oligodendroglioma (57%), the Mayo clinic experience with this tumour (54% of a cohort of 80 patients with oligodendroglial tumours) suggested a seizure incidence of at least 75% [15]. The strong influence of young age in determining the presence of epilepsy in patients with oligodendroglial tumours is also a mystifying factor. The observation of a significantly younger age in patients who had epilepsy and brain tumours compared to those brain tumour patients without epilepsy has previously been noted [16] but its mechanism is open to speculation. In clinical trials of high grade glioma favourable prognostic features have been noted to be young age at time of diagnosis and the presence of a seizure disorder [21]. The former has been confirmed for this heterogenous collection of oligodendroglial tumours, but since most young patients had epilepsy, the presence of a seizure disorder was not an independent prognostic feature.

In this series the median duration of the seizure disorder (15 months) prior to surgical diagnosis was considerably shorter than others. Pre-CT series describe median seizure durations of 7 years [9, 18], whilst those that include patients accrued in pre- and post-CT eras describe 2.5 to 2.9 years [15, 16]. Our shorter median duration of epilepsy is almost certainly explained by the use of CT and MR imaging and stereotactic surgical techniques being available throughout the period of cohort acquisition. Nonetheless the percentage of brain tumours that were oligodendroglial (4%) is remarkably similar to the ranges described elsewhere 3–7% [9, 13] and it remains a predominantly (2 : 1) male lesion [9]. The incidence of oligoastrocytoma (45%) is, however, higher than other older series (23–25%) [9, 17].

Two of the major difficulties in assessing the role and contribution of interventional (resective surgery and radiotherapy) managements in patients with oligodendroglial tumours arise because of varying clinical indications for intervention and different technical approaches to aspects of the surgical procedure. Patients with oligodendroglial tumours comprise clinical cohorts in which the primary indications for surgery include (a) control of established seizure disorder; (b) alleviation of the signs and symptoms of a

mass lesion as well as controlling seizures and (c) diagnosis of a mass lesion causing either one or more seizures and a focal neuroradiological abnormality. The latter cohort does not have an established seizure disorder and the intervention here is primarily diagnostic as well as cytoreductive. This group of patients is now tending to dominate the presentation of oligodendroglial tumours because of both improved brain imaging leading to earlier diagnosis of a focal lesion and safer, stereotactic techniques of both biopsy and resection. Since the seizure disorder is not chronic "lesionectomy" shortly after clinical and radiological diagnosis, would be expected to be more effective than in patients having similar surgery for established epilepsy due to an oligodendroglial tumour. Surprisingly this hypothesis is not confirmed by the results of this study. Within the period of follow up the results, in terms of seizure control were remarkably similar in patients who had infrequent seizures for less than 10 months duration and those who had seizure disorders for at least ten months.

This paradox may arise because the pathophysiological basis of seizures associated with oligodendroglial tumours is undoubtedly dependent on the capriciousness of the tumour biology. Seizures in patients with oligodendroglial brain tumour are related to either anatomical, biochemical or pathophysiological effects of the tumour on perilesional brain [1, 5, 19]. These represent dynamic or progressive reactive effects on the perilesional brain rather than regressive neuronal changes normally found with idiopathic epilepsies. The spectrum of biological behaviour of adult oligodendroglial tumours, as compared to pediatric epileptogenic tumours and most low grade tumours encountered in adult temporal lobe resective specimens in patients with chronic epilepsy [5, 10], also militates against a high incidence of good long term seizure control. Resection of the lesion, with or without resection of the seizure focus, in patients with low grade tumours such as dysembroplastic neuroepithelial tumours or ganglioglioma have an excellent chance of both good long term seizure and disease control [5, 10, 13]. Unfortunately with oligodendroglial tumours tumour recurrence is likely. Interestingly all of the 11 patients whose seizure control could be classified as Engel Outcome grades I or II were free of both clinical deficits and radiological recurrence at last follow up (median 30 months).

Since seizure control may be only one of several indications for tumour surgery it is infrequent that an operation for an oligodendroglial tumour will be planned as an "anti-epileptic" procedure with studies such as pre-operative EEG videotelemetry or invasive EEG monitoring [1, 5, 13]. There is no cogent evidence that a routine tumour resection or "lesionectomy" performed without using ECoG gives significantly inferior postoperative seizure control than procedures based upon either ECoG or sub-dural grid guided resections [1, 2, 4, 5, 7, 8, 13, 20]. ECoG often reveals foci of dysryhthmic and epileptogenic brain, often non-contiguous with the tumour, in patients with tumours causing intractable seizure disorders [1, 2, 5, 13, 20]. Resection of dysryhthmic cortex is often not possible since then it may either abut upon functionally important brain or may extend beneath the margins of the surgical field [1, 2, 20]. ECoG data recorded after tumour resection may also reflect acute pathophysiological changes related to tumour or lesional resection and may not reflect incomplete resection of epileptogenic cortex ([1], Ojemann G, personal communication, 1993). In some patients who initially have satisfactory seizure and disease control but then relapse a second operation, in our hands, produced disappointing results. In the three operations in which ECoG was performed large areas of contiguous and non-contiguous brain perilesional brain were found to be dysrhythmic. Similar findings of secondary epileptogenesis have been noted in other electrophysiological studies of perilesional brain [1]. Failure of seizure control is undoubtedly related to persisting disease. Paradoxically in these patients as focal neurological deficits become worse the seizure disorder became easier to control, presumably due to progressive neuronal loss in previously epileptogenic brain.

Some patients with troublesome seizure disorders refractory to treatment with anticonvulsants, and in whom the primary indication for surgery was "anti-epileptic", had complete abolition of seizures with lesionectomy alone. Similar results following lesionectomy for a range of structural lesions causing epilepsy have previously been described [1]. Interpretation of the surgical contribution to Engel Grade I or II outcomes is, however, complicated by postoperative radiotherapy and chemotherapy given to some patients. Seizure frequency may be reduced following radiotherapy [7] and chemotherapy (I. R. Whittle, A. Gregor, unreported observations) for a spectrum of brain neoplasms. Because of the multiple clinicopathological and management variables involved a multicentre, prospective study would be required to assess

an optimal pre-operative investigation programme, aspect of surgical technique and adjunctive management of patients with seizure disorders associated with oligodendroglial brain tumours.

Acknowledgement

This work was supported by a Vacation Studentship (Awarded to Andrew Beaumont) from the Scottish Home and Health Department. The computational and statistical advice of Ms. J. Tocher and Mr. J. Slattery were gratefully appreciated.

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