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Epilepsy surgery in children with developmental tumours

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ABSTRACT

We report our experience regarding evaluation, surgical treatment and outcomes in a population of 21 children with histopathologically confirmed developmental tumours [nine dysembryoplastic neuroepithelial tumours (DNET), ten gangliogliomas (GG) and two gangliocytomas (GC)] and related epilepsy, analyzing video-EEG, MRI and neuropsychological data, before and after surgery.

Most children had focal epilepsy correlating well with lesion location. One patient had epileptic spasms and generalized discharges. Tumours were located in the temporal lobe in 13 patients. Mean age at surgery was 11.16 years. Postsurgical MRI showed residual tumour growth in one DNET. One child had a recurrent ganglioglioma with anaplastic transformation. At latest follow-up (mean 4.68 years) 95.2% of patients were seizure-free and no significant neuropsychological declines were observed. Evidence from our study suggests that, in this setting, surgery should be performed before criteria for refractory epilepsy are met, particularly in cases with early seizure onset, in order to optimize cognitive outcome.

1. Introduction

Around twenty to thirty per cent of long-standing medically intractable epilepsies are caused by tumours of neuroepithelial tissue, especially neuronal–glial tumours.[1] Gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumours (DNETs) are the most common causes and constitute a major pathologic substrate of children referred for epilepsy surgery. Magnetic resonance imaging (MRI) reveals characteristic findings, although rarely specific.[2] The identification of these tumours is of particular importance, with therapeutic and prognostic implications, due to their benign behaviour and tendency to mimic more aggressive tumours, such as oligoastrocytomas.[3] DNETs and GGs, together with gangliocytomas, have been included in Barkovich's classification of malformations of cortical development, as malformations due to abnormal neoplastic neuronal and glial proliferation with abnormal cell types, associated with disordered cerebral cortex.[4]

Epilepsy is usually the main manifestation of developmental tumours and, in most cases, the presenting feature. Its electroclinical findings are usually, but not always, concordant with the location of the lesion. Children with these tumours can be cognitively normal or present specific deficits or epilepsy-related deterioration, including psychopathological manifestations.

Surgery in this setting offers very good results overall, although some controversy still exists over the best surgical strategies. In selected cases, intracranial electroencephalogram (EEG) recordings and brain mapping may aid in tailoring the resection. Seizure frequency and oncological morbidity are the most frequently assessed outcome measures in the literature. However, the consequences on the neurocognitive and behavioural functioning domains have been insufficiently analyzed to date.

We report our experience regarding the evaluation and surgical treatment in a paediatric population with developmental tumours and related epilepsy. Our purpose was to review their pre-surgical and post-surgical clinical, neurophysiological, neuroimaging and neuropsychological data and to analyze and specifically delineate the findings with regard to each other. Outcomes were assessed in terms of a variety of measures, including thorough neuropsychological testing, in addition to seizure control and oncological morbidity.

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2. Materials and methods

2.1. Study population and data collection

All children (<18 years) with histopathologically confirmed developmental tumours and epilepsy as the cardinal presenting neurological manifestation, surgically treated at the Niño Jesús Children's University Hospital in Madrid, between January 2000 and December 2007, with a postoperative follow-up of at least one year ($N = 21$), were selected for this retrospective analysis. Patients were identified through our Epilepsy Unit database, which includes all epilepsy surgery candidates at our centre.

2.2. Description of procedures

All patients had been evaluated under the same pre-surgical work-up and post-surgical follow-up protocols. Postoperative seizure outcome was assessed by using Engel's classification.[5] Surgical and post-surgical complications were documented.

- *Brain MRI*: Brain MRI was performed preoperatively and at six months after surgery. Additionally, in all patients with subtotal resections, follow-up was continued at twelve months and yearly thereafter. High-resolution (1.5 or 3.0 T) brain MRI was performed under a specific protocol, including a T1-weighted volumetric study with multiple-plane reconstruction plus coronal 3 mm slices with T2-weighted and FLAIR sequences. Depending on the lesion, additional axial slices on T2-weighted and/or FLAIR images were obtained, as well as additional axial slices on T2* sequences, for detection of possible calcifications. Furthermore, a post-gadolinium injection study was performed with T1-weighted sequences. Tumours were classified as large (>2 cm) or small (<2 cm) according to largest diameter measures on MRI.
- *Video-EEG monitoring*: Pre- and post-operative video-EEG monitoring was performed using a Nicolet machine (BMSI 5000 and 6000 systems), involving scalp electrode placement according to the international 10–20 system. Additional closely spaced electrodes were used when indicated. Three patients underwent additional subdural electrode studies, during a planned two-stage procedure, in one case during a re-intervention. Follow-up video-EEG recordings (nap studies) were performed at three, six and twelve months after surgery and yearly thereafter.
- *Neuropsychology*: Neuropsychological evaluation entailed the use of an extensive and comprehensive battery of tests for pre- and post-operative analysis. A detailed description of the protocols can be found in a recent publication.[6] Postoperative follow-up was performed twelve months after surgery for every patient and, in some selected cases (patients with cognitive/behavioural deficits present after surgery) this period was extended for up to three to seven years postoperatively. General cognitive abilities were assessed using the Full Intellectual Quotient (FIQ) as well as a Verbal and a Performance Intellectual Quotient (VIQ and PIQ). Specific cognitive abilities were also evaluated, involving motor, perceptive visual and auditory domains, non-verbal abilities, receptive and expressive language, verbal and non-verbal memory (with immediate memory, learning and recall measures), attention and executive functions. Academic abilities (reading, writing and arithmetic) were also examined. In addition, a psychopathological study was performed. In order to compare the results obtained in the different tests, mean scores for each group were expressed as Z scores based on the norms for each test.
- *Operative procedure*: Gross total tumour resection was performed whenever possible. Lesionectomies were the operative procedure of choice, as a general criterion. For tumours located on the left (dominant) lateral temporal region, extended tailored resections were carried out when epileptogenic foci were found outside tumour margins, evidenced by subdural electrode extraoperative video-EEG monitoring, and after language mapping using electrical cortical stimulation. Lobectomies were performed in children with very large tumours with/without signs of associated focal cortical dysplasia (FCD), involving extensive areas within the lobe. Re-interventions were planned when seizures remained uncontrolled after the first surgical procedure and residual tumour was deemed present, or when residual tumour progression or recurrent tumour was documented. Intraoperative frameless stereotactic navigation was used in five patients to assist with tumour localization.
- *Histopathology*: Formaline fixed and paraffin-embedded tissues were routinely processed and cut at 3 μm. The sections were stained by haematoxylin and eosin, in all cases supplemented by immunohistochemistry with antibodies against glial fibrillary acidic protein (polyclonal, Dako), Neu N1 (clone A60, Chemicon), Synaptofisin (clone SY38, Dako), Neurofilaments (clone 2F11, Dako), Vimentin (clone V9, Dako) and Ki-67 (clone MIB-1, Dako). A peroxidase/DAB kit (EnVision FLEX, Dako) was used for visualizing. Histopathological diagnosis was performed following latest WHO criteria.

2.3. Statistical analysis

Fisher's exact test, ANOVA test, dependent t-test for paired samples, Mann–Whitney's U test and Spearmann's correlation coefficient, were used for statistics. A p value of 0.05 was considered significant. Statistical analysis was performed using the SPSS (15.0 version) statistical software (SPSS, Inc., Chicago, IL).

3. Results

General results are summarized in Table 1.

3.1. Epilepsy-related and tumour-related pre-surgical clinical data

Our population consists of seven girls and fourteen boys. Mean age at epilepsy onset was 7.14 years [standard deviation (SD): 4.93]. Seizures began before the age of three years in six patients (28.57%). Mean duration of epilepsy before surgery was 4.07 years (SD: 3.37). This duration was of one year or under in six patients (28.57%). A total of 61.90% of the population (13/21) had medically intractable epilepsy (defined by failure of two or more medications to achieve control of seizures), of which three (14.28% of the population) were under treatment with three or more antiepileptic drugs at the time of surgery.

Six patients had a family history of epilepsy, only two with first-degree relatives affected, and one patient had a grandfather with a brain tumour. Two patients had a history of febrile unilateral convulsive status epilepticus during infancy.

3.2. Pre-surgical MRI findings and their correlation with pathology

Histopathologically, all patients showed tumours with mixed neuronal and glioneuronal components: nine DNETs (with evidence of specific glioneuronal element in three cases), ten GGs and two gangliocytomas. Tumours were located to the temporal lobe in 13 patients.

The main MRI characteristics of histopathologically confirmed DNETs (Figs. 1 and 2) were: hypointense MRI signals on T1 sequences in 77.78% (7/9) and mixed in 22.22% (2/9); MRI signals on T2 and FLAIR sequences were hyperintense or mixed in all cases [88.89% (8/9) and 11.11% (1/9), respectively]; multiple nodular