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Clinical Features and Surgical Outcome of Patients with Indolent Brain Tumors and Epilepsy

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ABSTRACT

Introduction: In this study the authors review the outcomes of 22 patients with medically refractory epilepsy and slow growth brain tumors. **Objectives:** Evaluate the clinical, electrophysiological, operative, and histopathological features. **Patients and Results:** The majority of the tumors were located in the temporal lobe (n = 20) and involved the cortical gray matter. The most frequent tumors were gangliogliomas (n = 9), astrocytomas grade I and II (n = 6), dysembryoplastic neuroepithelial tumors (n = 5) and ganglioneuroma (n = 2). The biological behavior of the tumors was strikingly indolent, as indicated by a long preoperative history of chronic seizures (mean, 14 years). Mean follow-up time after resection was 27 months, and according to Engel's classification, 85% were seizure-free, 10% showed a reduction of seizure frequency of at least 90%, and 5% had reduction in seizure frequency at least 75%. **Conclusion:** The data indicate that neoplasms associated with pharmacoresistent epilepsy constitute a distinct clinicopathological group of tumors that arise in young patients, involve the cortex, and exhibit indolent biological behavior for many years. Complete surgical removal of these tumors, including the epileptogenic area, can achieve excellent seizure control.

Key words: indolent brain tumors, epilepsy, surgical outcome.

RESUMO

Avaliação clínica e tratamento cirúrgico de pacientes com tumores cerebrais indolentes e epilepsia

Introdução: Neste estudo os autores avaliaram retrospectivamente 22 pacientes tratados cirurgicamente com diagnóstico de epilepsia refratária e tumor cerebral de crescimento lento. **Objetivos:** Avaliar os aspectos clínicos, eletrofisiológicos, cirúrgicos e histopatológicos. **Pacientes e Resultados:** A maioria dos tumores estava localizada no lobo temporal (n = 20) com envolvimento da substância cinzenta. Ganglioglioma foi o tumor mais frequente (n = 9), seguido do astrocitoma grau I e II OMS (n = 6), tumor neuroepitelial disembrioplástico (DNET) (n = 5) e ganglioneuroma (n = 2). O comportamento biológico dos tumores foi estritamente indolente como indicado pela longa história pré-operatória de (média, 14 anos). O tempo de acompanhamento pós-operatório médio foi de 27 meses e de acordo com a Classificacão de Engel, 85% ficaram sem crises (Classe I), 10% obtiveram redução maior de 90% das crises (Classe II), e 5% tiveram redução menor que 75% (Classe III). **Conclusão:** Os dados indicam que neoplasias associadas à epilepsia crônica refratária constituem um grupo de tumores com características clinico-patológicas distintas que se iniciam em pacientes jovens, envolvem o córtex e apresentam comportamento biológico indolente. A ressecção cirúrgica completa destes tumores, incluindo a zona epileptogênica, levou ao controle total das crises na maior parte dos casos estudados.

Unitermos: tumores cerebrais indolentes, epilepsia, tratamento cirúrgico.

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INTRODUCTION

Seizures constitute the presenting manifestation of intrinsic brain tumors in 37 to 92% of patients.[7] The incidence of seizures is related to the location and the growth and pathological characteristics of tumors.[2] Slowly growing and cortically located low-grade tumors, such as gangliogliomas and oligodendrogliomas, represent the tumors with the greatest epileptogenic potential. With the use of neuroimaging techniques, these lesions are more readily diagnosed.[1,2]

The optimal treatment of epilepsy-associated tumors is a controversial issue because the very benign nature of many of these lesions seems to differ from the more common glial tumors in other settings.[3] Therapeutic goals include not only the removal of the lesion with its risks for malignant dedifferentiation or hemorrhage but also the control of seizures. The relationships between lesions and epileptogenicity, however, are complex. Therefore, different surgical approaches have been used successfully, such as lesionectomy,[4] nontailored en bloc resection,[3,5] and tailored surgery.[6]

During the past decade, high-resolution magnetic resonance imaging (MRI) as well as improved pre- and intraoperative electrophysiological mapping procedures have greatly increased our knowledge about the epileptogenic lesion and the extent of the resective surgery. The aim of the present study was to analyze the clinical, radiological, and histopathological features in a recent series of 22 patients with tumor-associated chronic epilepsy and to evaluate their seizure outcomes in relation to various parameters.

PATIENTS AND METHODS

Between May 2002 and November 2006, a total of 22 patients underwent resective surgery (temporal, n = 20; extratemporal, n = 2) for medically intractable epilepsy. All patients had well-documented chronic and medically intractable epilepsy lasting for a minimum of 4 years. For all patients, incomplete seizure control at maximal tolerable serum levels of at least two first-line anticonvulsant agents, such as carbamazepine, phenytoin, phenobarbitone, or valproic acid, had to be proven before they were referred for presurgical evaluation. Complex partial seizures were observed in 18 patients, and simple partial seizures were observed in 4 patients. A history of secondarily generalized tonic-clonic seizures was present for 11 patients.

All patients underwent continuous, noninvasive video electroencephalographic monitoring with scalp and sphenoidal electrodes. Noninvasive evaluation was considered sufficient if the site of seizure origin was congruent with the location of the tumor. Electrocorticographic (ECoG) studies were performed in 6 of the 22 patients (27%).

The decision about the site and the extent of the resection was based mainly on the delineation of the zones of seizure origin and persistent interictal epileptiform activity as well as the location of the neoplasm, as determined by MRI. Hippocampal tissue was resected only if there was clear evidence from ictal recordings and sclerosis signs on MRI. The diagnosis of Ammon's horn sclerosis was based on the following criteria: increased signal on T2-weighted images and temporomesial atrophy. The extent of the hippocampal resection depended on the memory performance of neuropsycologic tests, and ranged between 1.5 and 2.8 cm.

All preoperative MRI studies were retrospectively evaluated by the same neuroradiologist. The imaging procedure usually included sagittal T1-weighted images (TR, 500-600 ms; TE, 15-25 ms; slice thickness, 8-10 mm), axial proton-density and T2-weighted images (TR, 2000-2500 ms; TE, 20-30 and 80-120 ms; slice thickness, 6-8 mm), and spin echo scans. T2-weighted gradient echo scans were performed only rarely. In addition, coronal and axial T1-weighted images with and without gadolinium diethylene triamine penta-acetic acid were acquired with similar parameters. For patients with an assumed temporal lobe epilepsy, axial images were acquired with a modified angulation at about 25 degrees off the orbitomeatal line and parallel to the long axis of the hippocampus.

All operations were performed under general anesthesia. In the temporal lobe (n = 20), the following surgical procedures were performed: anterior temporal lobectomy with hippocampectomy (n = 11), lesionectomy without hippocampectomy (n = 5) and temporodorsal lesionectomy (n = 4). These different forms of temporal resections were primarily determined by the location of the tumor and the distribution of the epileptiform activity. Extratemporal resections (n = 2) included frontal (n = 1) and parietal (n = 1) lesionectomy, according to the results of the electrophysiological evaluation. Intra-operative electrocorticography for the delineation of the limits of the resection was performed in 6 cases. In all cases a complete removal of the lesion was intended. The function of intraoperative monitoring was to provide data regarding whether an additional resection of tissue beyond this margin was necessary and where it was located.

All slides of operative specimens were reviewed by the same neuropathologist. Hematoxylin-and-eosin-stained sections were available from all the cases. For the majority of specimens, there were also Nissl stains and one or all of the following immunohistochemical reactions were performed: glial fibrillary acid protein, synaptophysin and neurofilament protein. The tumors were classified according to the revised WHO classification for tumors of the nervous system.

Follow-up information, available from all 22 patients, was based on regular visits at 3- to 6 month intervals.

The postoperative observation times ranged from 6 to 35 months (mean, 27 months). With respect to the postoperative seizure state, patients were assigned to four different outcome classes, as described by Engel et al.:[12] I, seizure-free or only auras since surgery; II, rare seizures (> 90%); III, reduction of seizure frequency[3] 75%; and IV, unchanged (< 75% reduction of seizure frequency).

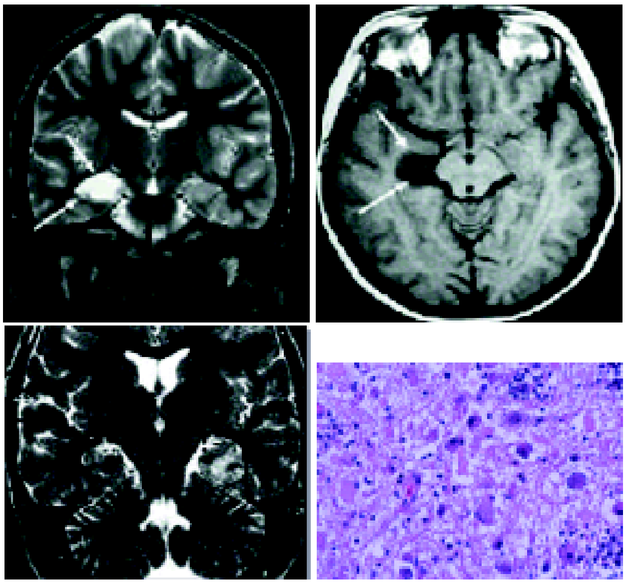

Figure 1. Ganglioglioma.

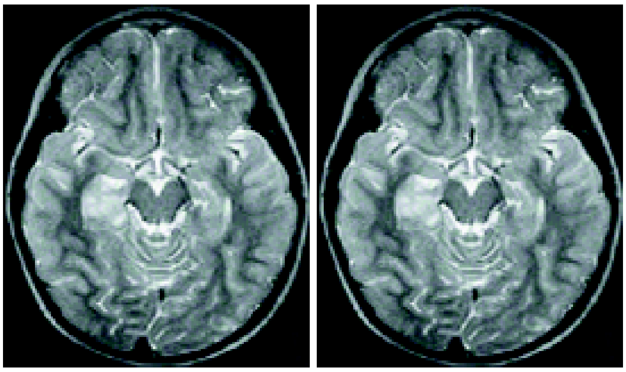

Figure 2. Dysembrioplastic Neuroepithelial Tumor (DNET).

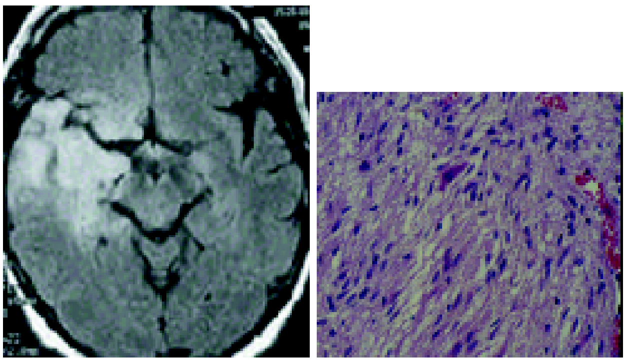

Figure 3. Astrocytoma Grade II.

Student's t test was used for a statistical comparison of continuous variables, if the distribution was normal, and Wilcoxon's test was used if it was not. Discrete variables were compared by cross tabulation tests.

RESULTS

There were 9 male and 12 female patients, ranging in age from 18.2 to 42.3 years (mean, 26.7 years). The mean age at the onset of seizures was 12.7 years. The duration of epilepsy varied between 3 and 21 years, with a mean of 14.0 years. Seizure onset and duration related to the histopathological diagnoses showed no statistical significance.

The majority of tumors (n = 20) were located in the temporal lobe. Sixteen of them (80%) involved mesial temporal structures (hippocampus, parahippocampal gyrus, amygdala, and uncus). The remaining temporal tumors (20%) were in a neocortical location. Extratemporal tumors involved cortical structures (frontal and parietal). The tumor location was not related to the histopathological diagnoses (no statistical significance).

The most frequent tumors were gangliogliomas (n = 9), astrocytomas grade I and II (n = 5), dysembryoplastic neuroepithelial tumors (n = 5) and ganglioneuroma (n = 2). The presence of Ammon's horn sclerosis in addition to a neoplasm (dual pathology) occurred in 11 of 22 patients in whom the hippocampus was resected.

There was no permanent morbidity in our patients or mortality. According to Engel's classification, 85% were seizure-free, 10% showed a reduction of seizure frequency of at least 90%, and 5% had reduction in seizure frequency at least 75%.

The most favorable results were observed in patients with gangliogliomas. With this histopathological diagnosis, 89% of patients were seizure-free. The ratio of seizure-free patients with others tumors was lower (64%). These differences were statistically significant ($p < 0.05$).

DISCUSSION

In a number of series, the majority of neoplastic lesions found in patients with intractable seizures were gliomas.[9-11] In our study, all tumors were of a low histopathological grade (WHO Grades I or II), whereas in most other reported series, the ratio of malignant tumors ranges between 10 and 20%.[11,12] In accordance with the experience of Olivier et al.,[13] gangliogliomas were the most common entity, accounting for 45% of all tumors, followed by astrocytomas (25%). The dysembryoplastic neuroepithelial tumors, described in 1988 by Daumas-Duport et al.,[9] is characterized by an intracortical location, multinodular architecture, and a heterogeneous cellular composition, including astrocytes, oligodendrocyte-like cells, and neurons. In the present study, most dysembryoplastic neuroepithelial tumors were localized temporomesially. Despite principal differences in the cellular composition and biological behavior of dysembryoplastic neuroepithelial tumors and oligodendrogliomas, these tumors may show a great resemblance histopathologically. Therefore, it is likely that many epilepsy-associated tumors that previously have been reported as oligodendrogliomas would be classified as dysembryoplastic neuroepithelial tumors according to current diagnostic concepts.[15] This may account for the high incidence of oligodendrogliomas in patients with seizures, as reported in a number of series.[16-19]

According to the recent literature, the median survival of patients with low-grade gliomas ranges between 3 and 8 years.[20] Death usually occurs from the malignant transformation of the original tumor.[21,22] Although post-operative long-term results are not available in this series, the majority of our tumors seem to have a rather indolent course, as suggested by the long history of epilepsy. These data are consistent with the literature.[15,17,22]

In the present series, 85% of patients became seizure-free and all patients experienced a worthwhile improvement after surgery. There were no significant differences in seizure outcome when temporal and extratemporal resections were compared.

Understanding the spatial and causal relationships between structural lesions and epilepsy is essential to rational therapeutic strategies. Favorable results have been reported after lesionectomy, with a percentage of seizure-free patients ranging from 65 to 90%.[22] These data suggest that in a subset of patients, the cortex surrounding the tumor loses the ability to independently initiate and propagate seizures once the tumor itself has been removed.[11,15]

Particularly in the temporal lobe, the results of lesionectomy alone are disappointing. Only 22% (two of nine patients) with temporal lesions in the series presented by Cascino et al.[5] became seizure-free. When the tumor directly involves the hippocampus, the decision to undertake a mesial resection is relatively clear. However, when the tumor presents no involvement of mesial structures, careful consideration must be given to the potential risks and benefits of a mesial resection. In this situation, the data acquired from neuropsychological testing may be useful to support the decision to proceed with mesial tissue removal.

The development of optimal treatment protocols for patients with lesions associated with focal epilepsy would be enhanced by a better understanding of the fundamental pathophysiological or biochemical processes of seizure generation.[17] Further investigations are likely to improve our understanding of the pathophysiological basis of tumor-associated epilepsy and, ultimately, our ability to identify patients in whom a lesionectomy alone is sufficient and those in whom additional resection of the epileptogenic zone is required to achieve optimal seizure control.[12]

If the tumor or the epileptogenic zone involves cortical areas of high functionality, such as the language or motor cortex, a complete resection of these areas would be accompanied by a significant neurological deficit. In these cases, functional considerations have to be weighed against seizure and tumor control. Because of the individual va-ria-bility in the organization of cortical function,[17,18] intra- or extra-operative electrical stimulation mapping has proven to be useful in determining the extent of the resection.

CONCLUSIONS

Low-grade tumors associated with intractable seizures constitute a distinct clinicopathological group of benign intrinsic brain tumors. Characteristically, these tumors involve the gray matter, arise in young patients, and exhibit stable behavior for many years. Complete resection of these tumors provides the most important condition for seizure control. Therapeutic goals include not only the seizure control, but also de histopathologic diagnosis and minimize the risks for malignant dedifferentiation or hemorrhage. Lesionectomy is successful in a limited number of patients, and additional excision of an epileptogenic zone, as determined by intraoperative or extraoperative studies, is needed to achieve satisfactory seizure outcome.

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