Surgical Pathology of Temporal Lobe Epilepsy.
Experience with 216 Cases

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Abstract. The surgical treatment of chronic epilepsies is increasing rapidly. Here we report the histopathologic findings in 216 consecutive surgical specimens of patients with chronic pharmacoresistant temporal lobe epilepsy. In 75 cases (34.7%) there were tumors, all but two of which were of low histopathologic grade (WHO grade I or II). The most common tumors were gangliogliomas (34 cases), pilocytic astrocytomas (17 cases), oligodendrogliomas (9 cases), fibrillary astrocytomas (6 cases), and dysembryoplastic neuroepithelial tumors (6 cases). There were 51 cases with non-neoplastic focal lesions and an additional 13 cases with tumors and non-neoplastic focal lesions within the same specimen. The most frequent non-neoplastic focal lesions were microscopic glioneuronal hamartias (32 cases), glioneuronal hamartomas (7 cases), and vascular malformations (13 cases). The hippocampal formation was structurally well preserved in 71 specimens. In 51 of these (71.8%) there was Ammon's horn sclerosis. Presurgical placement of depth electrodes was invariably associated with circumscribed defects of the brain parenchyma. The implantation of subdural electrodes was sometimes followed by chronic inflammatory changes of the leptomeninges. Our findings indicate that in the majority of patients with medically intractable temporal lobe epilepsy there are significant histopathologic findings, many of which are only rarely encountered otherwise.

Key Words: Ammon’s horn sclerosis; Dysembryoplastic neuroepithelial tumor; Ganglioglioma; Hamartia; Hamartoma; Hippocampus; Temporal lobe epilepsy.

INTRODUCTION

Patients with complex partial seizures, the characteristic form of seizures in temporal lobe epilepsy (TLE), account for roughly one-half of all patients with epilepsy. In approximately one-third to one-half of these patients the seizure disorder is refractory to pharmacotherapy (1, 2). Fortunately, many of these patients can still be cured by a partial resection of the temporal lobe which typically includes the corpus amygdaloideum, portions of the anterior temporal hippocampal formation and, if present, an epileptogenic zone elsewhere in the temporal lobe (for review see 3, 4). In many countries, centers specializing in the diagnosis and treatment of seizure disorders have been established. Thus, the number of seizure patients who are being treated surgically is increasing steadily (1).

Based on conservative figures it has been estimated that in the U.S. alone there are 100,000 patients who are potential candidates for epilepsy surgery, with 7,500 new candidates per year (1). These data highlight the medical and social significance of epilepsy surgery. In the past, the pathologist’s contribution to the study of epilepsy was largely confined to the field of morbid anatomy. With the rising numbers of surgical specimens from patients with epilepsy the pathologist now assumes an increasing role in the care of patients in this subspecialty of medicine.

Here we describe the findings in 216 surgical temporal lobe specimens from patients with TLE who were operated on at the University of Bonn Medical Center between November 1987 and January 1993. The results point out some aspects which are of special interest for surgical pathologists dealing with this highly selected patient population.

MATERIALS AND METHODS

All slides and pathology reports of surgical temporal lobe specimens from patients with chronic epilepsy between November 1987 and January 1993 were retrieved from the files of the Department of Neuropathology. The corresponding clinical charts and all available CT and MRI scans were reviewed. Only patients with well-documented chronic and medically intractable epilepsy were included in the study. All patients had had temporal lobe seizures for at least 2 years (average 12.5 years) and had been unsuccessfully treated with maximum doses of anticonvulsant drugs according to current protocols by neurologists experienced in the treatment of seizure disorders. All but three patients had been referred for surgery by the Department of Epileptology at the University of Bonn Medical Center. All glass slides were reviewed by two pathologists/neuropathologists. Hematoxylin and eosin-stained sections were available from all specimens. In the vast majority of specimens there were also Nissl stains and combined hematoxylin and eosin-luxol fast blue stains. In selected cases, additional special stains (Elastin-van Gieson, reticulin, Bodian) were performed. In all tumor cases some or all of the following immunohistochemical reactions were carried out: glial fibrillary acidic protein (GFAP), synaptophysin, neurofilament protein (NFP), neuron specific enolase (NSE), S100-protein. Tumors were classified according...
to the revised WHO classification for tumors of the nervous system (5).

For the purpose of this study some terms which are not used consistently in the literature are defined as follows:

Anatom's Horn Sclerosis: This term describes the presence of marked segmental neuronal loss and astrogliosis which predominantly involves the most vulnerable neuronal populations of Ammon's horn. In the 19th century, the term Ammon's horn sclerosis was coined based on gross atrophy and increased firmness of Ammon's horn in patients with chronic epilepsy. Subsequently, the typical histological findings were described (for review see 6–8). Accordingly, in the present study the diagnosis “Ammon's horn sclerosis” was used only if the classical gross and/or histologic changes were present. The presence of varying degrees of diffuse gliosis or slight neuronal loss which would have required morphometric analysis for confirmation were not considered Ammon's horn sclerosis (8). The terms hippocampal sclerosis and mesial temporal sclerosis are similar but not identical to Ammon's horn sclerosis because they describe changes that extend beyond Ammon's horn and involve the adjacent portions of the mesial temporal lobe (8). For the present analysis of surgical specimens we prefer the term Ammon's horn sclerosis because Ammon's horn is readily identifiable, even in many suboptimal specimens. In contrast, the parahippocampal structures may be difficult to identify unless the specimen is removed en bloc.

A critical evaluation as to the presence or absence of Ammon's horn sclerosis in a surgical specimen requires that the anatomic integrity of the hippocampal formation is sufficiently preserved to allow an unequivocal identification of its different segments (CA1–CA4, dentate gyrus, presubiculum, subiculum). If this condition was not met, the presence of Ammon's horn sclerosis was considered uncertain. Similarly, in some cases other pathological processes such as infiltrating glioma or encephalitis involving the hippocampus precluded a meaningful evaluation as to the presence or absence of Ammon's horn sclerosis. This study focuses on those changes that are pertinent to diagnostic surgical pathology, and a quantitative evaluation of neuronal loss and nonspecific gliosis was not performed. As these changes are difficult to assess reproducibly and even more difficult to quantify without special studies such as GFAP immunohistochemistry and morphometric analysis, they are not treated as specific diagnostic entities in the present context (9, 10).

Hamartoma: A hamartoma is a mass of disorganized but mature cells or tissues indigenous to the particular site. The term designates a tumor-like but primarily non-neoplastic malformation or error of tissue development (11, 12). Despite their tumor-like gross appearance, hamartomas display little or no evidence of growth and cellular proliferation microscopically (12).

Glioneuronal Hamartia: The term hamartia designates a defect in tissue combination during development. In contrast to hamartoma, glioneuronal hamartias are not well circumscribed and do not produce grossly visible masses. Related terms are “focal cortical dysplasia” (13–17), “heterotopia” (6, 15, 18–20) and “microdysgenesis” (21–23). The term heterotopia has been used for a wide variety of findings ranging from ectopic ganglion cells to dermoid cysts and other gross anomalies (6, 11). We prefer the term glioneuronal hamartia because it clearly indicates a developmental flaw, specifies the cellular elements involved, and does not connote a neoplastic lesion.

Focal Lesion: This term characterizes any gross or microscopic focal abnormality. In an attempt to separate probable primary lesions from changes that may be a result of previous seizure activity or an invasive diagnostic procedure, Ammon's horn sclerosis and iatrogenic changes (e.g. defects due to depth electrodes) are not included in this category but are dealt with separately.

RESULTS

There were a total of 216 temporal lobe resection specimens from 104 male and 112 female patients. Of these, 212 patients had had complex partial seizures. In 94 patients there were also secondary generalized grand mal seizures. The specimens were obtained from combined anterior temporal lobectomies and hippocampectomies in 205 cases (94.9%) and corticectomies in 11 cases (5.1%).

Focal lesions as defined above were present in 125 specimens (58.1%). In 75 specimens (34.7%) there was a neoplasia. The histological tumor diagnoses are summarized in Table 1.

Gangligliomas were the most common tumors en-
countered. In all cases there was an intimate mixture of neoplastic astrocytes and atypical ganglion cells (Fig. 1). Nissl stains and immunohistochemical stains for neuronal (synaptophysin, NFP, NSE) and astrocytic (GFAP) markers were useful in highlighting the neuronal and glial cell populations, respectively, and provided a valuable aid for the diagnosis of small and fragmented tumor samples. Six specimens contained both ganglioglioma and one or more glioneuronal hamartias in the same specimen. This represents roughly 18% of all gangliogliomas, a figure that is not significantly different from the fraction of all tumor specimens with coexisting glioneuronal hamartias (15%).

Astrocytomas were the second most frequent tumors in this series. The pilocytic variant (Fig. 2) was almost three times as common as fibrillary astrocytomas (Fig. 3) which are generally far more numerous than pilocytic tumors. Histologically, the pilocytic astrocytomas of the temporal lobe had all features of those located in more typical areas such as the cerebellum or brainstem. There were nine oligodendrogliomas (Fig. 4).

The dysembryoplastic neuroepithelial tumor (DNT) is a benign tumor composed of ganglion cells, oligodendrocyte-like cells and astrocytes (24). All six DNT in this series showed the typical histologic features, namely a predominantly intracortical location, multinodularity, a mixture of neuronal and glial cells and a myxoid matrix (Fig. 5). The age of seizure onset ranged from 4 to 23 years (mean 14). At the time of surgery, the patients’ age ranged from 23 to 44 years (mean 31) and there was a 4 to 36 year duration of the seizure disorder (mean 18 years).

Except for two cases, all tumors were of low histopathologic grade (WHO grade I or II). One exception was that of a 24-year-old man with an 8 year history of complex partial seizures resistant to pharmacotherapy. A tem-

![Fig. 2. Pilocytic astrocytoma. Note the bipolar nature of many tumor cells (Hematoxylin-Eosin ×272).](image)

![Fig. 3. Fibrillary astrocytoma (Hematoxylin-Eosin ×225).](image)

![Fig. 4. Oligodendroglioma (Hematoxylin-Eosin ×340).](image)

![Fig. 5. Dysembryoplastic neuroepithelial tumor. Area with prominent microcystic architecture, myxoid matrix and predominantly oligodendroglia-like cells (Hematoxylin-Eosin ×140).](image)
poropolar lesion had been documented on MRI scans 4 years previously and had not increased in size since. Histologically, the tumor was composed of highly pleomorphic GFAP-positive astrocytes with numerous mitotic figures. The large size and pleomorphism of the tumor cells and the presence of occasional vacuolated cells were reminiscent of pleomorphic xanthoastrocytoma. However, due to the high mitotic index this tumor was classified as an anaplastic astrocytoma (WHO grade III). It seems reasonable to assume that this malignant lesion had evolved only recently from a low grade precursor lesion—possibly a pleomorphic xanthoastrocytoma—which had been documented radiologically for several years. The second high grade tumor was that of a 13-year-old boy with a 12 year history of complex partial seizures. At the age of 6, a CT scan was reported to be unremarkable. However, 5 years later seizures became more frequent and CT and MRI scans revealed a mass in the mesial temporal lobe. Histologically, the tumor was composed of astrocytes and atypical ganglion cells with features diagnostic for ganglioglioma. However, the astrocytic component was highly cellular and contained numerous mitotic figures. The lesion was therefore classified as an anaplastic ganglioglioma (WHO grade III).

There were seven cases of glioneuronal hamartomas and 32 specimens with microscopic glioneuronal hamartias (Fig. 6). None of the hamartomas showed features typical of cerebral tubers in tuberous sclerosis. In 11 cases, both tumors and glioneuronal hamartias were present within the same specimen. Coexisting tumors and hamartomas were present in two cases.

Vascular malformations were identified in 13 specimens. This group consisted of 11 cavernomas and two vascular malformations which could not be further classified due to severe calcification. Other less frequent focal lesions included the following entities: cortical pseudocyst (three cases), old necrosis (three cases), old hematoma (two cases), glio-mesodermal scar (one case), fibrous adhesions of the arachnoid (one case), arachnoid cyst (one case) and numerous ectopic neurons in the white matter (three cases; Fig. 7). Whereas the latter two entities are generally thought to be of developmental origin, the etiology of the other lesions remained unclear. In no case were abundant ectopic neurons in the white matter seen in association with other malformations.

Among 71 specimens in which the hippocampal formation was adequately represented, anatomically well preserved and not involved by tumor or inflammation, Ammon's horn sclerosis (Fig. 8) was present in 51 cases (71.8%). In different subgroups of patients with TLE the frequency of Ammon's horn sclerosis was as follows: no
focal lesions, 88.4%; focal lesions (neoplastic and non-neoplastic), 46.4%; tumors, 30.7%. Of the 51 cases with Ammon’s horn sclerosis, 22 patients had a history of secondary generalized tonic clonic seizures (43.1%). Of the 20 patients without Ammon’s horn sclerosis, secondary generalized tonic clonic seizures had been reported in seven patients (35%).

Table 2 lists the frequencies of Ammon’s horn sclerosis and focal lesions among the 71 specimens with an anatomically preserved hippocampal formation. It is evident that the presence of Ammon’s horn sclerosis and focal lesions are not independent variables. This is significant as determined by chi-square test at a 0.001 level of significance. Ammon’s horn sclerosis is more common in patients without focal lesions as compared to those with focal lesions.

Table 3 lists the age at onset of seizures, the age at surgery and the duration of the seizure disorder in the present series. As determined by Student’s t-test the patient’s age at the time of surgery and the age at the first onset of temporal lobe seizures were significantly lower in patients with focal lesions as compared to those without focal lesions (p < 0.01). However, there still was marked overlap between the two populations. No statistically significant differences were present between any of the other groups.

A reliable presurgical mapping of epileptogenic cortical

zones frequently requires the placement of subdural electrodes of various size and/or depth (intracerebral) electrodes. Stereotactic depth electrodes in the hippocampus and corpus amygdaloideum and multiple subdural grid electrodes were implanted bilaterally in approximately 20% of the patients in this study. Additional patients had only subdural electrodes implanted. Histologically, depth electrodes were invariably associated with small, sharply circumscribed defects of the brain parenchyma accompanied by aggregates of macrophages and/or reactive astrogliosis, depending on the age of the lesion (Fig. 9). Many of these lesions resembled small infarcts. In no case, however, did we observe defects that were significantly greater than the diameter of the electrode. Subdural electrodes were sometimes accompanied by a circumscribed, slight inflammatory infiltrate of the leptomeninges. In a few cases, however, there was a prominent layer of granulation tissue involving the leptomeninges and the subarachnoid space.

The overwhelming majority of the specimens included in this study contained minor and nonspecific changes such as focal gliosis of the end folium or other parts of the hippocampal formation, subpial gliosis or diffuse white matter gliosis, irrespective of the presence or absence of specific focal lesions or Ammon’s horn sclerosis as defined above. However, as a representative specimen of the hippocampus was not available in a substantial portion of cases, we cannot give a specific figure on the number of entirely normal samples for the whole series.

DISCUSSION

The pathological evaluation of surgical specimens from patients with chronic TLE focuses on two main issues: focal lesions and Ammon’s horn sclerosis. Both findings have been shown to indicate a better prognosis with respect to the seizure disorder as compared to patients with-
out anomalies in the surgical specimen (10, 17, 25, 26). Thus, the histopathological evaluation provides prognostically relevant information in addition to any therapeutic implications that the finding of a specific lesion such as a tumor might have. Finally, the pathology report documents the extent of the surgical resection.

The results of a study on the histopathology of epilepsy greatly depend on the selection of cases. Here we describe the findings in 216 consecutive surgical temporal lobe specimens of a highly select group of patients with chronic medically intractable epilepsy. All specimens were obtained during a 5 year period between November 1987 and January 1993. Preoperatively, all but two patients had MRI and CT scans and all patients were refractory to treatment with a variety of current anticonvulsant medication protocols. All patients with a seizure history of less than 2 years and those with significant extratemporal radiological abnormalities were excluded. This selection reflects current developments in epilepsy surgery. The patient profile of this study with complete and detailed documentation of clinical, electrophysiological and CT and MRI findings is different from some studies in the past that have covered surgical specimens from extended time periods ranging up to several decades (10, 27, 28) and from postmortem studies which frequently lacked detailed clinical data on every case and generally included a more diverse set of patients (18, 21, 29).

Many previous reports on surgical specimens in TLE have focused on clinical aspects without detailed reference to the histopathology of focal lesions. Some authors have cautiously avoided distinguishing between tumors and malformative lesions in favor of the noncommittal term “alien tissue lesion” (10). Here we have applied the current diagnostic terminology that is also used for lesions that are not related to epilepsy. We believe that this practice best meets the needs of the clinical staff. It is admitted, however, that the exact nature and pathogenesis of some lesions such as ganglioglioma and DNT have not yet been satisfactorily established.

Focal lesions were present in almost 60% of the specimens. More than one-half of these were low grade tumors. Gangliogliomas, which account for only approximately 5% of all brain tumors in children and are even less common in adults (12), were the most common neoplasms. Similarly, although DNT are unusual lesions that have only recently been recognized as a separate entity, there were six DNT in this series. They occur almost exclusively in patients with a longstanding history of seizures, and any pathologist who examines specimens from these patients should be aware of their histological features (24, 30-32). Both gangliogliomas and DNT are composed of a mixture of glial and neuronal elements. This mixture is also a prominent feature of glioneuronal hamartias and raises the question if gangliogliomas and DNT may arise through a neoplastic transformation of a primary malformative lesion. The distinction between ganglioglioma and glioneuronal hamartia/hamartoma may be challenging in small and fragmented specimens. It rests on the larger overall size and increased cellularity of the gangliogliomas as compared to malformative lesions.

Epileptic seizures appear in approximately one-half of all patients with intracerebral tumors (33-35). In this study of patients with chronic TLE, all but two tumors were low grade neoplasms. The two exceptions were unusual neoplasms, i.e. an anaplastic ganglioglioma and an anaplastic pleomorphic astrocytoma. In both cases it may be assumed that the tumors represent a recent malignant progression of a longstanding benign lesion. The absence of the most common high grade brain tumors such as glioblastoma multiforme or metastatic tumors reflects the fact that the material under investigation has been selected for chronicity of the seizure disorder and a surgical approach that is aimed primarily at the treatment of seizures rather than the removal of a lesion.

A total of 205 specimens were obtained from combined anterior temporal lobectomies and hippocampectomies. Although in all of these cases an appropriate resection of the hippocampal formation had been documented intraoperatively and by postoperative imaging studies, a definite evaluation as to the presence or absence of Ammon’s horn sclerosis was possible in only 71 specimens (34.6%). In some cases the presence of segmental neuronal loss and gliosis were obscured by infiltrating tumor or inflammation. More frequently, however, the portion of the hippocampal formation that was actually submitted for pathological evaluation consisted only of small tissue fragments which did not permit a proper orientation during embedding or a reliable identification of the different segments of Ammon’s horn. In many cases the lack of an appropriate specimen was due to the extensive use of ultrasonic aspiration. Other authors have also pointed out difficulties in evaluating the hippocampal formation due to insufficient preservation of surgical specimens (10, 27, 36-38). This is unfortunate because of the prognostic implications of well-documented Ammon’s horn sclerosis as outlined above. Since this aspect of the study has been discussed with the neurosurgical staff the quality of the surgical specimens has improved greatly.

At present, there are only a few reports on complications of subdural or depth electrodes and these have been dealt with primarily from a clinical standpoint (for summary see 39). The histopathological findings here emphasize the need for a detailed clinical history at the time the histological changes are being interpreted. In particular, if cut tangentially the glotic area surrounding an electrode tract may be confused with a small infarct. Similarly, inflammatory changes at the surface of the brain may initiate an extensive search for pathogenic organisms if one is not aware of the recent placement of a subdural electrode.
Any pathologist who studies morphologic changes in patients with epilepsy will find himself in the midst of a discussion as to whether the changes observed histologically are the primary cause of seizures, the result of repetitive seizure activity or hypoxic injury, or just a coincidental finding. There is little doubt about the ability of gross focal lesions such as tumours, hamartomas and vascular malformations to initiate epileptic seizures (33, 35, 40). Similarly, there is clinical and experimental evidence for a role of Ammon’s horn sclerosis and neuronal loss and gliosis of adjacent parahippocampal structures in the pathogenesis of TLE (6, 8, 26). Controversial, however, is the significance of minor microscopic anomalies such as ectopic neurons in the white matter and glioneuronal hamartias (10, 41, 42). While clarification awaits future studies, it seems appropriate to note that the histopathologic examination does not indicate whether a given lesion is epileptogenic. Nevertheless, the presence of significant histopathological changes in all but 7% of those specimens in which the hippocampal formation was anatomically well preserved raises the question as to whether medically intractable TLE is largely an expression of a structural alteration.

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(Received February 22, 1993/Accepted April 15, 1993)