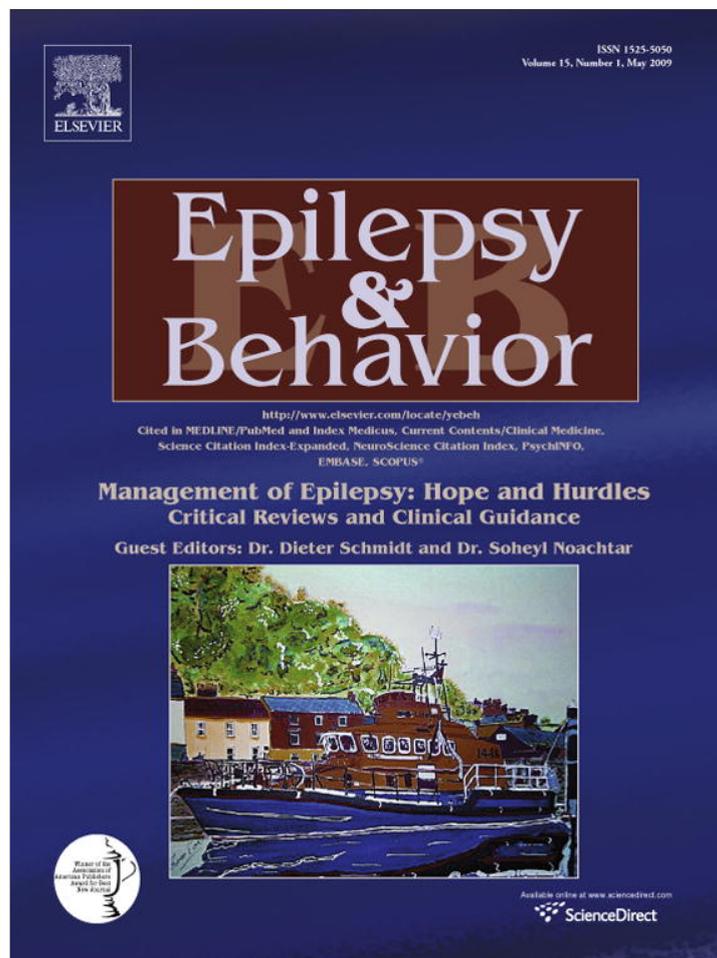


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## Review

## Neuropathology of focal epilepsies: A critical review

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## ARTICLE INFO

## Article history:

Received 18 February 2009

Accepted 19 February 2009

Available online 25 February 2009

## Keywords:

Epilepsy surgery

Hippocampus

Tumor

Neoplasia

Dysplasia

Malformation

## ABSTRACT

A broad spectrum of structural lesions can be histopathologically identified in surgical brain specimens obtained from patients with focal, therapy-refractory epilepsies. In our experience with 4512 tissue samples collected at the German Neuropathological Reference Center for Epilepsy Surgery, three clinicopathological entities are most common: mesial temporal sclerosis (40%), long-term epilepsy-associated tumors (27%), and malformations of cortical development (13%). Notwithstanding, a systematic histopathological and molecular-genetic analysis is mandatory to unravel the underlying pathogenic mechanism of epilepsy-associated lesions and may contribute to our current understanding of pharmacoresistance and epileptogenesis. However, an interdisciplinary approach is necessary to further explore predictive parameters with respect to postsurgical seizure relief and memory impairment, and also to identify new pharmacological targets.

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### 1. Histopathological evaluation of surgical tissue specimens obtained from patients with focal intractable epilepsies

Epilepsy surgery has been established as a reliable treatment option in pharmacoresistant focal epilepsies [1]. With the advances in imaging technology, structural lesions are increasingly recognized in patients with chronic focal seizures. However, the epileptogenic area often extends beyond the structural/visible lesion and requires careful electrophysiological evaluation, for example, surface or invasive EEG recording [2]. Thus, an interdisciplinary approach combining histopathological and molecular-biological studies of electrophysiologically well-characterized brain tissue will be helpful in clarifying the etiology, biological behavior, and functional impairment of epilepsy-associated structural lesions. Addressing molecular pathomechanisms may also unravel novel pharmacological targets in the human brain.

Characteristic histological patterns can be recognized in 93% of patients with intractable focal seizures who undergo epilepsy surgery (Table 1); these include mesial temporal sclerosis (also known as Ammon's horn sclerosis, hippocampal sclerosis), long-term epilepsy-associated tumors (gangliogliomas, dysembryoplastic neuroepithelial tumors), malformations of cortical development (focal cortical dysplasia, polymicrogyria), malformative vascular lesions (cavernomas, arteriovenous malformations), glial scars (ischemic or traumatic brain injuries), and encephalitic lesions. In a small proportion (7%), however, thorough and systematic histomorphological analysis cannot identify a specific anatomical alteration.

The history of neuropathological studies in brains of patients with intractable epilepsy is, however, often characterized by a controversial debate concerning the primacy of structural abnormalities in seizure genesis. In this regard, only an interdisciplinary approach will be successful in identifying the "epileptogenic potential" of distinct morphological alterations and should include clinical faculty as well as basic sciences. Most evident examples relate to astrocytic tumors or cavernomas, which do not have an innate ability to generate action potentials, but rather compromise adjacent neuronal networks and/or architecture, if manifesting at an early age.

### 2. Clinicopathological findings in MTS

Histopathological studies in patients with pharmacoresistant temporal lobe epilepsy (TLE) have identified mesial temporal sclerosis (MTS, Ammon's horn sclerosis, hippocampal sclerosis) as the major pathological finding [3,4]. In a large series of 3311 patients with TLE operated in Germany between 1995 and 2007, MTS was identified in 48%. Within our entire cohort of 4512 patients with epilepsy who underwent surgical resection for various etiologies, MTS was recognized in 35.2%, with additional presenting as dual pathology, that is, MTS combined with focal cortical dysplasia (FCD), tumors, or scars (see below). Although the pathogenesis of MTS remains to be identified, clinical histories follow a characteristic clinical course in most patients. Approximately 50% of patients had an "initial precipitating injury" before the age of 4 [3]. In this cohort, complex febrile seizures were the most frequently noted events. Birth trauma, head injury, and meningitis were other early childhood lesions observed in patients with TLE. The mean age at

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**Table 1**  
Histopathological findings in 4512 patients with focal intractable epilepsies.

Entity	Variant <sup>a</sup>	Number	Mean age at surgery	Hemisphere	Gender	Mean age at onset <sup>b</sup>	Mean duration <sup>c</sup>
Mesial temporal sclerosis		1591	34.6	659 L/611 R	786 M/805 F	11.5	23.3
Dual pathology		218	24.8	78 L/112 R	127 M/ 91 F	9.7	14.6
Long-term epilepsy-associated tumors		1236	28.5	407 L/397 R	638 M/565 F	16.5	12.8
	Ganglioma	570	25.4	184 L/158 R	285 M/263 F	12.7	13.5
	DNT	189	26.3	59 L/68 R	105 M/84 F	15.2	12.3
Dysplasia		577	18.5	228 L/242 R	299 M/276 F	5.6	12.4
	FCD I	66	11.5	35 L/26 R	16 M/33 F	3.5	7.2
	FCD II	216	18.4	76 L/96 R	112 M/104 F	4.1	14.1
Vascular		271	36.4	91 L/108 R	157 M/114 F	23.5	13.4
Scars		239	25.2	92 L/91 R	147 M/90 F	10.3	14.8
Encephalitis		73	22.0	26 L/29 R	43 M/29 F	13.9	9.4
No lesion		307	29.2	117 L/58 R	161 M/146 F	12.7	16.1

Note. All data were obtained from the German Neuropathological Reference Center for Epilepsy Surgery. FCD, focal cortical dysplasia; DNT, dysembryoplastic neuroepithelial tumor.

<sup>a</sup> Frequent variants of specific entities are highlighted.

<sup>b</sup> Mean age at onset of spontaneous seizure activity (in years).

<sup>c</sup> Mean duration of seizure disorder before surgical treatment (in years).

onset of spontaneous complex partial seizures was 11.5 years (Table 1). In fact, structural, molecular, or functional analysis cannot usually be done in this early and clinically silent period, and the diagnosis of MTS is verified after a long period of refractoriness to antiepileptic medication. The mean age at the time of surgery is about 34.6 years after a duration of epileptic seizures of 23.3 years (Table 1). As in most other series reported so far, both genders were equally affected and a familial history of TLE was very rare, indicating that hereditary factors do not play a role in MTS-associated TLE.

MTS is characterized at the histopathological level by segmental pyramidal cell loss in CA1 (Sommer's sector), CA3, and CA4 (endfolium), whereas CA2 pyramidal and dentate gyrus granule cells are the most seizure resistant. Nevertheless, several interneuronal cell populations are also affected, that is, neuropeptide Y- and somatostatin-immunoreactive interneurons and/or mossy cells in the CA4 sector [5,6]. Neuronal cell loss is invariably associated with reactive astrogliosis, which results in stiffening of the tissue and is the basis for the traditional term *Ammon's horn sclerosis* [7]. An intriguing question relates to the mechanisms of selective neuronal vulnerabilities between these morphologically similar neuronal cell populations. This topic is a matter of ongoing studies and is not discussed further here. Major pathomechanisms include, among many others, abnormal neuronal circuitries (aberrant mossy fiber sprouting) [8] and molecular rearrangement/plasticity of ion channel and neurotransmitter receptor expression [9].

The majority of hippocampal specimens also reveal alterations within the dentate gyrus, that is, granule cell dispersion [10]. In addition, variable cell loss can be detected within adjacent cortical regions, including the subiculum, entorhinal cortex, and amygdala. Cortical dyslamination and increased numbers of ectopic white matter neurons within the ipsilateral temporal lobe may also occur in MTS [11].

### 3. A critical review of current MTS classification systems

Several histopathological classification systems have been proposed in recent years that rely on qualitative or semiquantitative analysis of regional cell loss, extent and severity of gliosis, or axonal reorganization [12,13]. However, the predictive value of such measures requires further confirmation with particular emphasis on postsurgical seizure relief and memory impairment. We propose a new classification system for MTS based on a quantitative survey of segmental cell loss within the hippocampal formation (Fig. 1, Table 2). This classification system may be helpful in the

further study of clinical determinants, that is, psychophysiological outcome of memory and learning performance, which is also differentially compromised in patients with TLE undergoing tailored neurosurgical resections. This applies particularly to the significant association between neuronal cell loss in the dentate gyrus and the patient's ability to store and recall memories [15].

Molecular-biological and electrophysiological efforts to distinguish MTS-related pathomechanisms are likely to benefit from a systematic classification of MTS specimens and establish an important basis to better understand the various MTS syndromes [16].

### 4. Clinicopathological findings in epilepsy-associated tumors: a critical review

One thousand two hundred thirty-six long-term epilepsy-associated tumors (LEATs) were identified in our series, with ganglio-



**Fig. 1.** MTS classification system. Modified from Blümcke et al. [14]. Cluster analysis of microscopically examined hippocampal specimens revealed five distinct neuropathological subgroups [14]. Classic patterns of hippocampal sclerosis are characterized by major cell loss in all pyramidal cell layers (MTS types 1a and 1b in 19% and 53% of cohort studied, respectively) and are associated with favorable seizure relief after surgical resection (see Table 2). Early disease onset with precipitating injuries before age 4 years is common in these patients. However, atypical patterns with pronounced cell loss only in the CA1 region (MTS type 2) or the hilus (MTS type 3) are also identified. These patients experienced their first seizures at a significantly later time and have less favorable seizure relief after surgery. It has also been proven that patients with TLE without hippocampal neuronal loss (no MTS) benefit from epilepsy surgery.

**Table 2**  
Clinicopathological correlation between MTS patterns and seizure relief 12 months after surgery.

MTS	Engel 1 (%)	Engel 2 (%)	Engel 3 (%)	Engel 4 (%)	Total (n)
No MTS	58.6	13.8	17.2	10.3	29
Type 1a	72.0	12.0	12.0	—	25
Type 1b	72.9	21.2	4.7	1.2	85
Type 2	66.7	11.1	11.1	11.1	9
Type 3	28.6	14.3	42.9	14.3	7
Total	67.7	17.4	10.3	4.5	155

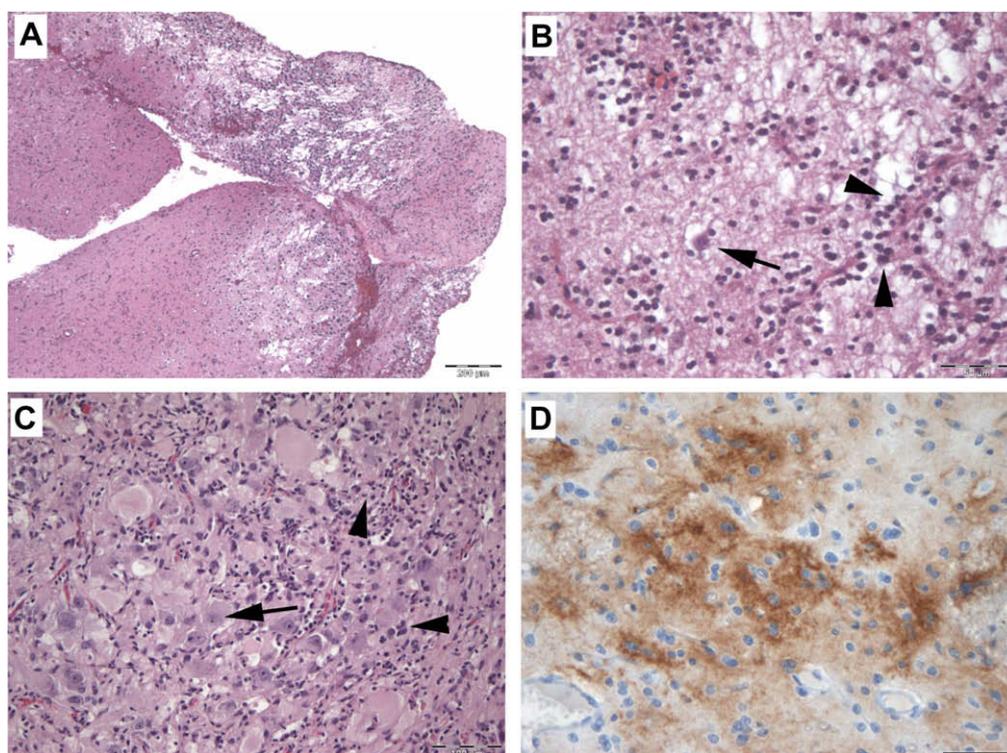
gliomas being the most frequent tumor entity. About 80% of these tumors were located in the temporal lobe and were WHO grade I [17,18]. The biphasic differentiation of tumor cells into glial and neuronal lineages is yet difficult to explain (Fig. 2). Abundant expression of the oncofetal marker CD34 in gangliogliomas may open new avenues to study this tumor entity [19]. Indeed, recent molecular-genetic studies have pointed out that compromised neurodevelopmental signaling pathways [20–22], rather than well-recognized glioma-associated tumor genes (i.e., TP53, PTEN; EGFR), are affected.

Unfortunately, many tumors escape early detection in young patients with epilepsy (mean duration of epilepsy before detection = 13.2 years), and the various consequences of long-term seizure disorders on cognitive as well as social development and behavior are considerable. Histopathological diagnosis of LEATs remains challenging. There is a large spectrum of morphological phenotypes, even within neuropathologically defined entities (Table 3). Neuropathological evaluation should therefore be obtained at experienced centers. The need for such expertise is critical, because the variability in histopathological phenotypes may often result in

diagnosis of a high-grade tumor, whereas the long-term clinical course of LEATs is very modest, without enhanced risk of recurrence and/or malignant transformation.

Three major issues are of considerable interest in this field: (1) refinement of the current classification of LEATs, (2) molecular pathogenesis and biological behavior, and (3) neoplasia and epileptogenesis.

Pathogenic mechanisms underlying focal hyperexcitability in patients with LEATs require further clarification. Two major hypotheses should be considered. The neuronal component of the tumor itself may contribute to epileptogenic activity. Immunohistochemical studies have identified aberrant expression of neuroactive molecules in dysplastic neurons, such as glutamatergic neurotransmitter receptors. Whether these neurons functionally integrate and excite neuronal pathways remains to be shown. In a recent study, intracerebral recordings from electrodes implanted to localize seizure onset identified early ictogenic discharges from a ganglioglioma. Such findings would support a hyperexcitable neuronal tumor component functionally integrated into excitatory circuitries [23–25]. In addition, recent evidence includes the inflammatory response as a contributing factor in the epileptogenicity of these developmental lesions [26,27]. An alternative mechanism involves tumor-associated, epileptiform changes in the adjacent brain. Altered patterns of expression of neuroactive molecules within the perilesional brain parenchyma [28,29], as well as the clinical observation that the epileptogenic area may be substantially larger than the tumor mass itself, would be consistent with this hypothesis. In many patients, seizure relief cannot be achieved if only the lesion is resected. Neuronal hyperexcitability within perifocal brain areas may be evoked by kindling mechanisms in limbic structures such as hippocampus and amygdala, as has been observed in experimental animal models. In addition



**Fig. 2.** Histopathological findings in glioneuronal tumors associated with focal intractable epilepsies. (A) Dysembryoplastic neuroepithelial tumors are characterized by a nodular growth pattern and the appearance of a "specific glioneuronal element". (B) This element exhibits "floating neurons (arrow in B)" in a mucoid matrix and columns of oligodendroglial-like cells (arrowheads). (C, D) In gangliogliomas (GGs), dysplastic neurons (arrow in C) are admixed with neoplastically transformed glial cell elements (arrowhead). The oncofetal marker protein CD34 (D) frequently immunoreacts with GGs, which is helpful in differentiating them from other neoplastic as well as dysplastic lesions.

**Table 3**  
Neuropathological spectrum of brain tumors in patients with epilepsy.

Diagnosis	% <sup>a</sup>	Mean age at surgery	Mean age at onset	Mean duration (years)
Ganglioglioma				
WHO I	46.0	25.1	25.1	13.7
WHO II	5.0	26.3	12.2	11.7
WHO III	0.9	38	29.3	4.7
Dysembryoplastic neuroepithelial tumor WHO I	16.4	26.6	13.8	12.7
Astrocytoma I				
Isomorphic variant	1.7	28.9	5.3	16.2
Pilocytic variant, WHO I	4.9	25.4	11.9	14.5
Not otherwise specified <sup>b</sup>	4.8	29.1	16.1	16.0
Pleomorphic xanthoastrocytoma WHO II	2.4	30.8	19.2	15.2
Subependymal giant cell astrocytoma WHO I	1.4	18.8	4.5	14.8
Astrocytoma				
WHO II	4.4	33.8	25.7	6.8
WHO III	2.4	39.5	37.0	10.3
Oligodendroglioma				
WHO II	2.7	35.6	20.6	13.9
WHO II	0.9	40.7	14.7	22.3
Mixed oligo-astrocytoma				
WHO II	2.6	34.8	18.8	10.7
WHO III	1.2	43.0	21.0	16.3
Cysts <sup>c</sup>	1.9	33.4	21.0	14.2
Other	0.4	6.3	3.0	3.3

Note. The upper half of the table refers to typical LEAT entities, which represent more than 80% of all brain tumors detected in patients with chronic focal epilepsies. The remaining cases (lower half of table) belong to the group of common glial tumors, although malignant variants are rare.

<sup>a</sup> Percentage of the 938 tumor samples obtained from the German Neuropathological Reference Center for Epilepsy Surgery.

<sup>b</sup> These tumors cannot be classified according to the revised WHO classification system (2007).

<sup>c</sup> Epidermoids, dermoids, or arachnoidal cysts.

to molecular reorganization phenomena in adjacent brain tissue, enhanced epileptogenicity may also evolve from architectural dis-

turbances of cortical layering (similar to those observed in focal cortical dysplasia type I) [30]. Such alterations are frequently encountered in patients with LEATs, in particular those with dysembryoplastic neuroepithelial tumors (DNTs). Whether such cortical dysplasias should be considered “dual pathology,” that is underlying a different pathomechanism compared with adjacent tumorigenesis, awaits further clarification.

It is reasonable to conclude, that amongst the cohort of LEAT novel entities may be hidden. It is worthwhile to identify these tumors with respect to a significantly better outcome and prognosis of these neoplasms.

### 5. Clinicopathological findings in epilepsy-associated cortical malformations: a critical review

Malformations of cortical development (MCDs) are also increasingly recognized in patients with intractable focal epilepsies [31]. The histopathological spectrum of MCDs is large, ranging from prominent to only minute changes (Table 4). Whereas gross MCDs can be reliably diagnosed *in vivo*, for example, hemimegalencephaly, polymicrogyria, nodular or band heterotopias, and focal cortical dysplasia (FCD) often escape imaging techniques (MRI) and may considerably vary in their size and localization [32]. According to the current classification system [33], FCD can be histopathologically distinguished into types I and II. FCD type IA refers to architectural disturbances of cortical lamination, and FCD type IB has additional cytoarchitectural abnormalities, that is, hypertrophic neurons outside layer V [34]. Also, mild forms of cortical malformations (mMCD) should be distinguished, including heterotopic neurons in layer I (mMCD type I) or within white matter location (mMCD type II). However, different cohorts of patients with epilepsy can present with similar histopathological findings. FCD type IA may occur within the temporopolar region of adult patients with MTS, and tailored resection strategies usually achieve successful seizure control [35]. FCD type IA can also be identified outside the temporal lobe and in young children with “catastrophic” multilobar epilepsies and psychomotor retardation [36]. Neurosurgical resection does not always sufficiently control seizure activity in these young patients [37]. Nevertheless, the underlying pathomechanisms in all FCD variants need to be specified. FCD type II presents with bizarre configured dysmorphic neurons (FCD type

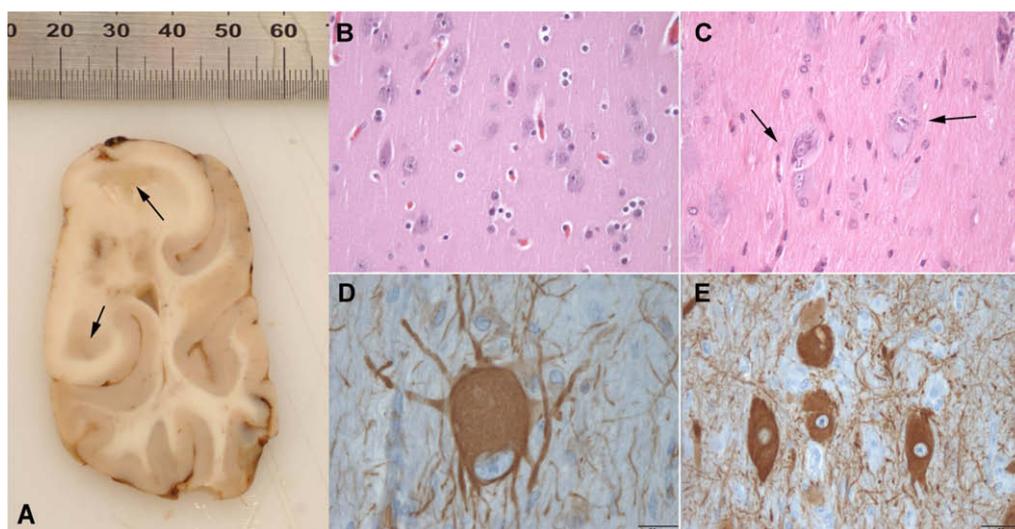
**Table 4**  
Clinicopathological findings for 592 patients with intractable epilepsy and histopathologically confirmed malformations of cortical development.

Entity	Number	Mean age at surgery	Side	Gender	Mean age at onset	Mean duration (years)
Focal cortical dysplasia (FCD)						
Type I	62	11.5	25 L/33 R	32 M/30 F	3.7	7.4
Type IIA	44	17.9	18 L/21 R	25 M/19 F	2.8	14.1
Type IIB	173	17.9	57 L/78 R	88 M/85 F	3.8	13.5
Not otherwise specified	124	20.3	65 L/59 R	83 M/78 F	6.3	12.5
Hamartoma	31	25.3	65 L/59 R	18 M/13 F	8.1	16.4
Hemimegalencephaly	11	2.4	4 L/5 R	3 M/6 F	0.0	2.4
Polymicrogyria	30	8.1	11 L/17 R	14 M/16 F	1.9	5.8
Granule cell dispersion	5	31.0	0 L/4 R	2 M/3 F	17.2	13.8
Heterotopic lesions						
Single neurons	34	25.8	15 L/10 R	20 M/14 F	8.9	16.6
Nodular	12	29.7	5 L/3 R	8 M/4 F	9.3	19.4
Dual pathology <sup>a</sup>						
FCD type I	39	27.6	20 L/15 R	17 M/22 F	10.1	21.0
FCD Type IIA	7	15.7	5 L/3 R	5 M/2 F	4.9	10.9
FCD Type IIB	7	10.8	5 L/2 R	5 M/2 F	1.1	9.7
Hamartoma <sup>b</sup>	4	22.0	3 L/1 R	1 M/3 F	4.5	16.8
Entopic neurons	2	23.0	1 L/-	-/2 F	3.5	6.9
Polymicrogyria	7	5.1	3 L/4 R	5 M/2 F	0.6	4.6

Note. The data were obtained from the German Reference Center for Epilepsy Surgery ([www.epilepsie-register.de](http://www.epilepsie-register.de)) and the European Epilepsy Brain Bank ([www.epicure-bank.org](http://www.epicure-bank.org)).

<sup>a</sup> Dual pathology associated with hippocampal sclerosis and the specified malformations.

<sup>b</sup> Glioneuronal hamartoma, not otherwise specified.



**Fig. 3.** Histological hallmarks in focal cortical dysplasia type IIB. (A) Surgical specimen from patient with FCD type IIB. Note the loss of myelin in white matter (arrow). HE staining of a normal (B) compared with dysplastic neocortex (C). The latter reveals many enlarged, clustered dysmorphic (dysplastic) neurons with clustered Nissl substance. Dysmorphic neurons accumulate neurofilament protein (E). Vimentin immunoreactivity is consistently found in balloon cells (D), another hallmark of this disease entity.

IIA) and additional balloon cells (FCD type IIB) (Fig. 3). These lesions were first described by Taylor and colleagues [38], and can be readily observed by the “transmantle” sign on MRI. Histopathological examination of surgical specimens usually corroborates the diagnostic subtype [39]. Recent molecular-biological studies identified the insulin-growth factor receptor cascade to be involved and indicate that FCD types IIA and IIB are pathogenetically distinct [40].

Systematic neuropathological examination of surgical specimens is mandatory to classify variants of cortical dysplasia, which then allows a subsequent molecular-genetic and/or molecular-biological analysis. Different classification systems have been proposed and introduced during the last decade that rely on either histopathological examination [41], imaging and genetic findings [31], or a combination of clinical and histopathological aspects [33]. A clinicopathological approach taking into account many different parameters and disciplines (neurology including electrophysiology, neuropsychology, neuroradiology, neurosurgery, and neuropathology) will be most reliable in achieving prediction of postsurgical outcome. This approach will help to establish a comprehensive classification system as prerequisite for pre- and postsurgical management of patients with chronic intractable epilepsies, but will also support stratification of clinical outcome studies and targeted searches for new antiepileptic drugs.

## 6. Dual pathology

In a proportion of patients with MTS, depth electrode recordings and intraoperative electrocorticography characterize more widespread areas of epileptiform activity involving mesial, lateral, and temporopolar regions [34,35,42]. From neuroimaging and neuropathological studies it is well established that MTS can occur in combination with a second temporal lobe epileptogenic pathology such as cortical dyslamination (i.e., focal cortical dysplasia type I), ectopic white matter neurons, or low grade glioneuronal tumors [3,33,34,43–47]. There are also occasional reports of distinct hippocampal malformations occurring with MTS [48] and structural hippocampal abnormalities on MRI that appear to precede MTS [49,50]. In the German Neuropathological Database for Epilepsy Surgery, dual pathology was identified in approximately 5% of cases (Table 1). There is some evidence for less severe hippocampal

neuronal loss when a “dual pathology” is present (i.e., MTS type 3). In these cases, “kindling” of the hippocampus by the adjacent temporal lobe lesion may play a role. There is some evidence to support the notion that progressive hippocampal atrophy occurs with longer duration of seizures. It has been shown, however, that surgical removal of both lesions results in the best postoperative seizure outcome for dual pathology [43], indicating that each component contributes to the genesis of seizures. The coincidence of dual temporal lobe pathology also raises the important question of a common predisposing malformative process for both lesions. Furthermore, in a larger proportion of TLE cases, less well defined, subtle microscopic malformations may be identified. Such alterations lend further evidence for underlying temporal lobe dysgenesis, which renders it more vulnerable to seizures, neuronal injury, and ultimately MTS [51,52].

A major difficulty, however, reflects the poor inter-rater concordance for the neuropathological classification of dual pathology in patients with MTS. We propose that the term *dual pathology* be restricted to a combination of MTS and those principal lesions that are likely to represent a distinct pathogenic etiology, that is, MTS and LEATs, MTS and vascular malformations, MTS and glial scars/trauma, MTS and limbic/Rasmussen encephalitis, and MTS and MCDs (i.e. FCD type II, polymicrogyria of nodular/band heterotopias). White matter neuronal ectopy (mMCD type II) and cortical dyslamination of the temporal lobe (FCD type 1A) may not inevitably fit into this assumption and, therefore, require careful attention. The same holds true for the frequent association between LEATs and cortical dysplasias, which may not arise from different pathogenic mechanisms.

## Acknowledgment

Financial support was received through a grant from the European Community (EpiCure – Contract no. LSHM-CT-2006-037315) and German Research Council (BI 421/1-2).

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