Brain Pathology ISSN 1015-6305

MINI-SYMPOSIUM: Etiologies of Focal Epilepsy

Defining Clinico-Neuropathological Subtypes of Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

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Keywords
brain, development, hippocampus, mesial temporal sclerosis, neuropathology, seizure.

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Received 11 January 2012
Accepted 12 January 2012

doi:10.1111/j.1750-3639.2012.00583.x

Abstract

Hippocampal sclerosis (HS) is the most frequent cause of drug-resistant focal epilepsies (ie, mesial temporal lobe epilepsy with hippocampal sclerosis; mTLE-HS), and presents a broad spectrum of electroclinical, structural and molecular pathology patterns. Many patients become drug resistant during the course of the disease, and surgical treatment was proven helpful to achieve seizure control. Hence, up to 40% of patients suffer from early or late surgical failures. Different patterns of hippocampal cell loss, involvement of other mesial temporal structures, as well as temporal neocortex including focal cortical dysplasia, may contribute to the extent of the epileptogenic network and will be discussed. An international consensus is mandatory to clarify terminology use and to reliably distinguish mTLE-HS subtypes. High-resolution imaging with confirmed histopathologic diagnosis, as well as advanced neurophysiologic and molecular genetic measures, will be a powerful tool in the future to address these issues and help to predict each patient's probability to control their epilepsy in mTLE-HS conditions.

HISTOLOGICAL CLASSIFICATION AND GRADING SYSTEMS FOR MTLE-HS

The earliest neuropathology study in epilepsy patients dates back to 1825, in which Bouchet and Cazauvielh described a hardened and shrunken hippocampus in autopsy brains from patients with clinical history of epilepsy (12). Wilhelm Sommer was first presenting microscopic features of hippocampal sclerosis in an autopsy brain from a patient with temporal lobe epilepsy (88). He observed loss of pyramidal neurons in a portion of the hippocampus that was later on termed "Sommer's sector," and corresponded to the sector CA1 of Lorente de Nó (52). Sommer already noted neuronal loss within the hilus of the dentate gyrus. In 1899, Bratz made available a detailed description of unilaterally atrophic hippocampus, illustrating severe loss of pyramidal neurons and gliosis in the Sommer's sector of the Ammon's horn, less severe neuronal loss in the hilus of the dentate gyrus and adjacent sector CA3, and preservation of neurons in the CA2, subiculum and the granule cell layer of the dentate gyrus (13). Of note, his illustration confirmed the boundary between lesional CA1 sector and a well-preserved subiculum as oblique, which represents the subicular-CA1 border zone or "prosubiculum" of Lorente de Nó. In 1966, Margerison and Corsellis defined two types of hippocampal damage (55). One was similar to that described by Bratz showing severe to total neuronal loss in CA1 and hilus of the dentate gyrus with sparing of CA2, termed "classical" Ammon's horn sclerosis. Another pattern of hippocampal damage that they described was characterized by neuronal loss confined to the hilus of the dentate gyrus or "end folium," termed "end folium sclerosis." In addition to those two patterns of hippocampal sclerosis, Bruton added, in his monograph published in 1988, the third pattern of hippocampal sclerosis called "total" Ammon's horn sclerosis showing almost complete neuronal loss in all sectors of the hippocampus (15). These specific patterns of hippocampal sclerosis could easily be assessed by qualitative observation; however, Bruton found no apparent correlation between any of those specific types of hippocampal sclerosis and the clinical history among 107 patients in his study.

The first systematic attempt to semiquantitatively evaluate the severity of hippocampal neuronal loss for the histological grading of hippocampal sclerosis was proposed by Wyler *et al* in 1992 (106). Four grades for hippocampal sclerosis along with a diagnosis of no hippocampal sclerosis were provided in Wyler's grading system. Grade I referred to mild mesial temporal damage (MTD) showing gliosis with slight (<10%) or no neuronal cell loss in CA1, CA3, and/or CA4; grade II presented moderate MTD and was characterized by gliosis with 10%–50% neuronal cell loss in CA1, CA3 and/or CA4, and "end folium" sclerosis if the lesion is limited to CA3 and CA4; grade III was classified as moderate to marked MTD equivalent to "classical" Ammon's horn sclerosis defined as gliosis with more than 50% neuronal dropout in CA1, CA3 and CA4, with sparing of CA2; and grade IV refers to marked MTD that is equivalent to "total" Ammon's horn sclerosis,

and defined as gliosis with more than 50% neuronal cell loss in all sectors of the hippocampus. Fascia dentata, subiculum and parahippocampal gyrus can also be involved in this category. Wyler's grading system revealed that classical and total Ammon's horn sclerosis were the most frequent pathologies in mesial temporal lobe epilepsy (mTLE). Inverse clinicopathological correlation has been reported between Wyler's grade and postsurgical memory impairment (43), as patients having the most postoperative memory loss were the ones with normal or grade I pathology, whereas those patients with high-grade pathology III and IV showed little postoperative memory decline. Mossy fiber sprouting in the dentate gyrus as demonstrated by Timm's staining can be observed in cases with Wyler's high-grade lesions (74). In terms of memory impairment, histological patterns of granule cell pathology in the dentate gyrus has been reported to be associated with learning dysfunction in addition to the higher age at epilepsy surgery and longer duration of illness (8). A more recent study has demonstrated that the *in vitro* capacity of proliferation and differentiation into neurons of neural stem cells isolated from the dentate gyrus in patients with pharmacoresistant mTLE was predictive for preoperative memory performance and the number of granule cells in the resected specimen (23). Another study has shown that the younger age at seizure onset was associated with Wyler's high-grade pathology (25). In 1996, Watson *et al* proposed a modification of Wyler's grading system (101). They introduced a six-tiered system by inserting an additional grade between Wyler's grades II and III, that is, Watson's grade III refers to gliosis with more than 50% neuronal loss in CA1 and 10%–50% neuronal loss in CA3/CA4, with sparing of CA2, and the definitions of grades IV and V are the same as Wyler's grades III and IV, respectively. Watson's grade II is defined as gliosis with 10%–50% neuronal cell loss in CA1 and/or CA4, indicating that, although not clearly mentioned in the literature, this category also includes end folium sclerosis and CA1 sclerosis (patient 5 in their 18 cases). In 2007, Blümcke *et al* proposed a clinicopathological classification system for hippocampal sclerosis, based on semiquantitative measurements of neuronal loss in CA1-CA4 (7). Based on the fact that extrahippocampal mesial temporal structures such as parahippocampal gyrus and amygdala may also be involved in pharmacoresistant mTLE (107), they used the term "mesial temporal sclerosis (MTS)" instead of "hippocampal sclerosis (HS)." A cluster analysis of the semiquantitative measurements revealed five distinct patterns of hippocampal pathology (Table 1), that is, no MTS refers to a group without histopathologically classifiable hippocampal sclerosis including no or only 10% neuronal loss that is within the first standard deviation of age-matched autopsy controls, corresponding to "no hippocampal sclerosis" and Wyler's grades I; MTS types 1a and 1b are equivalent to "classical" and "total" hippocampal sclerosis, respectively; MTS type 2 is identical with CA1 sclerosis; and MTS type 3 refers to "end folium sclerosis." They found that these patterns were associated with specific clinical histories and postsurgical outcome; for example, the age of the initial precipitating injury (IPI) appeared to be an important predictor of hippocampal pathology, as it was younger in patients with MTS types 1a and 1b (<3 years) than those with MTS types 2 (mean 6 years) and 3 (mean 13 years) as well as no MTS (mean 16 years). While successful seizure control was associated with MTS types 1a and 1b, MTS type 3 (end folium sclerosis) appears to be a predictor of poorer postsurgical seizure control. By contrast, Thom *et al* (99) found better outcomes for patients with end folium sclerosis and poorer outcomes for no HS group. Such differences in the results among various studies appear to be a major problem in elucidating the clinicopathological correlation of mTLE-HS, and seem to be associated, at least in part, with differences in the number of patients studied, inclusion and exclusion criteria, surgical procedures as well as postsurgical follow-up periods. Interobserver reliability would also affect the histological diagnosis and correlational studies, as anatomical boundaries between CA subfield and regions of interest are not uniformly applied. As mentioned above, trials for establishing the histological classification and grading systems for hippocampal sclerosis have begun with qualitative observations identifying several patterns of hippocampal injury, followed by semiquantitative evaluations for classifying the severity of neuronal loss with clinicopathological correlation studies. Current knowledge is to establish a classification of histological

Table 1. A neuropathologic grading system of hippocampal sclerosis.

	% neuronal cell loss				
CA1	≤10%	≥80%	≥80%	≥80%	≤20%
CA2	≤10%	≤30%	≤50%	≤30%	≤30%
CA3	≤10%	≤30%	≥70%	≤30%	≤30%
CA4	≤10%	≥40%	≥80%	≤30%	≥50%
Category	No HS	Classical HS	Severe HS	CA1 sclerosis	CA4 sclerosis

% neuronal cell loss: Semiquantitative microscopic examination of the human surgical hippocampus resected *en bloc* and evaluated at the midbody level. Formalin-fixed, paraffin-embedded sections at 4–7 μm thickness are recommended for H&E, CV/LFB, NeuN and glial fibrillary acidic protein (GFAP) stainings. Values refer to differences from age-matched post-mortem controls. Please note limitations of visual inspection, as first visible sign of cell loss is usually in the range of 30–40% (H&E stains, shown by quantified neuronal density measurements). Quantitative methods are, therefore, more reliable for scoring. CA1–CA4: Anatomical sectors of the human hippocampus according to Lorente de Nó (52). CA4: The center of CA4 was assessed but not the endfolium (bordering the polymorphic layer of DG). Dentate gyrus pathology was not predictive for postsurgical seizure outcome and relates rather to preoperative memory impairment (72). Granule cell counts were, therefore, not applied for this classification scheme. Scores best suited for differentiating HS subtypes are highlighted in gray. Modified from (7).

types based on the semiquantitative evaluation of neuronal loss. However, quantitative measurements for neuronal loss may require special equipments including computer and/or special technical support for labor-intensive, highly specialized examinations not readily available in most routine pathology laboratories.

Recently, the International League Against Epilepsy (ILAE) constituted a Task Force of Neuropathology within the Commission on Diagnostic Methods, which tries to compile an international consensus for the clinicopathological classification of hippocampal sclerosis. It is based on the agreement to define common terminology issues first and on the recognition of the importance to identify distinct morphological patterns. Further work will then allow us to clarify if these patterns relate to clinicopathological subtypes of mTLE-HS. Novel techniques including high-field imaging may be suitable to translate this knowledge into clinical perspectives and help to predict each patient's response to drug vs. surgical treatment as well as to related comorbidities, that is, memory impairment and mood disorders.

THE CLINICAL SPECTRUM OF MTLE-HS

In a large European series of 3311 patients suffering from temporal lobe epilepsies (TLE), HS can be identified in 48% (3). Within the entire cohort of 5392 epilepsy patients undergoing surgical resection for various etiologies, HS is recognized in 33.6%, with additional 5.1% presenting as dual pathology, that is, combination with tumors or scars (see also Blümcke and Spreafico in this issue). However, there is no reliable epidemiological information available for mTLE-HS. In a hospital-based study, 25% of TLE patients were reported to have hippocampal atrophy on magnetic resonance imaging (MRI) (83). There is evidence for familial history of seizures and familial forms of hippocampal sclerosis (18). There is no predilection for sex or affected hemisphere (14). It is important to note, however, that HS is present also in a non-epileptic elderly population and may be related to anoxic and/or ischemic injury or TDP-43-related neurodegeneration (108). Clinical histories in mTLE-HS patients often refer to an "initial precipitating injury" before the age of 4 years (6). In this patient cohort, complex febrile seizures are most frequently noted events. Birth trauma, head injury or meningitis were other early childhood lesions. The time between onset of habitual seizures and initial precipitating injury is the "latent period" (29). Seizures usually start by the end of the first decade although there are few reports for late onset (>50 years) (54). Seizure semiology often includes auras with psychic, perceptual or dysamnestic phenomena. Motor arrest with impairment of awareness and responsiveness and a blank staring appearance with pupillary dilatation are common in the beginning of a seizure. Seizures may either stop at this stage or semi-volunteered coordinated motor movements may follow (103). Contralateral posturing of the upper extremity indicating the involvement of basal ganglia, ictal speech (nondominant TL), ictal anomia and postictal dysphasia (dominant TL) are well-known lateralizing signs (49). Head and/or eye deviation is usually to the same side of seizure onset (at the early stage) where late and foreword deviation is generally contralateral (103). A seizure lasts typically less than 2 minutes, and is often followed by confusion and disorientation postictally, which resolves gradually over a period of minutes. Characteristic electroencephalogram (EEG) findings are blunt sharp waves with maximum field in sphenoidal and/or fronto-temporal T1/2 > F7/8 > T3/4 electrodes. EEG abnormalities may occur unilaterally, isolated or run at one per second repetition rates (10). They may be facilitated during drowsiness and non-rapid eye movement (REM) sleep stages 1–2, whereas REM stages are likely to exert inhibition. Ictal scalp EEG is usually characterized by secession of interictal spikes and flattening of background activity followed by rhythmic crescendo-like theta activity with decreasing frequency and increasing amplitudes (103, 105). Impaired declarative and episodic memory disturbances (long-term memory consolidation or recall of newly learned information) are frequent in mTLE-HS patients and will be discussed further below. MRI is highly sensitive and specific for the diagnosis of HS. Atrophy is detected in almost 90%–95% of patients when volumetric measurements are applied (17). T2 signals are increased in 80%–85%, T1 signals decreased in 10%–95% and loss of internal structure is visible in 60%–95% (103). There are also extrahippocampal abnormalities to be considered. However, all MRI modalities may fail to detect signal abnormalities in atypical HS variants, which can be demonstrated only by histopathology (see below). Functional imaging has become very helpful, with interictal ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography (mapping glucose metabolism) showing an ipsilateral anterior temporal hypometabolism. PET abnormalities may be visible on both hemispheres but usually aggravate on the HS side and with extratemporal involvement of insula, thalamus, basal ganglia, inferior frontal cortex and lateral parietal cortex (103).

Antiepileptic drug (AED) treatment may achieve favorable seizure control at the beginning of the disease, but most patients develop drug resistance during puberty or early adulthood (29, 32). The most recent definition of drug-resistant epilepsy has been proposed by an *ad hoc* Task Force of the ILAE Commission on Therapeutic Strategies and is described as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (50). For drug-resistant mTLE-HS patients, epilepsy surgery is beneficial as proven in a randomized, controlled trial (102). However, the analysis of our large database revealed a mean age at time of surgery around 34 years with a history of epileptic seizures for almost 23 years! There is no consensus protocol to evaluate postoperative outcome and a large range (33%–97%, median 70%) of seizure freedom has been reported so far (89). Favorable postsurgical seizure control can be usually envisaged when a distinct abnormality is visible on preoperative MR images, absence of status epilepticus, concordant lateralizing memory deficit and absence of seizures in the first postoperative week (22, 59). No significant differences were found regarding different resection types nor resection volumes (80, 81). However, neuropsychological testing usually reveals better postoperative results after limited resections compared with standardized procedures, especially with regard to attention level, verbal memory and calculated total neuropsychological performance (42). In a study where surgical failures were carefully reevaluated, no major risk factors, demographic, electrophysiological or radiological findings have been identified and seizure relapse occurred within 1 year in this patient population (76). Cure was defined to be totally seizure free for 2 years after AED discontinuation and was achieved in 36%–42.7% of patients (67, 104). Long-term relapse must also be taken into account and may affect 15% of operated patients (89).

DENTATE GYRUS PATHOLOGY IN MTLE-HS

It remains an intriguing observation that dentate granule cell loss significantly associates with deficient memory acquisition and recall in TLE patients (8, 23, 72). Indeed, the population of dentate granule cells is pathologically affected in the majority of HS patients. Lesional patterns in this anatomical distinct compartment range from granule cell dispersion (GCD), which occurs in almost 50% of patients (8) to severe cell loss in HS type 1a and 1b (Figure 1). Neuropathological criteria for granule cell alterations include increased granule cell lamination above 10 layers with smaller perikarya and larger intercellular gaps, as well as ectopic cluster and bilamination into the molecular layer. As grading scales for granule cell pathology are not yet internationally standardized, clinicopathological studies yielded complementary but also controversial results (8, 44, 58, 77, 97).

Our current understanding of these pathology patterns were much influenced from developmental neurobiology studies of the dentate gyrus and its propensity to generate neurons throughout life. Assembly of the granule cell layer follows different migration streams building first its internal limb, from which newly generated granule cells progressively expand into lateral direction, thus forming the external limb (1). Most intriguingly, the neurogenic capacity of the dentate gyrus maintains throughout life, also in human brain (30). Within the adult mammalian hippocampus, multipotent precursor cells have been characterized in the dentate gyrus, residing directly below the granule cell layer (34). These cells proliferate upon diverse functional and molecular stimuli, generate migratory neuroblasts and further differentiate into granule cells upon migration into the dentate gyrus (73, 84). Migratory guidance is provided by a scaffold of radial glial cells within the dentate gyrus as well as by Reelin molecules secreted by Cajal-Retzius cells (33, 47, 109). Newborn granule cells functionally integrate into the trisynaptic hippocampal pathway (37, 75, 100), expand dendrites into the molecular layer and axonal collaterals into the CA3 region (mossy fibers), where they form synaptic connections on large excrescences of pyramidal neurons within the stratum lucidum (41). The time period from proliferation to functional integration has been estimated in the range of 4 weeks in adult rodents, although maturation of newborn neurons extends over several months (100). In the mouse, axons reach the CA3 region about 2 weeks after neurogenesis (110). In adult rats, the number of newly added hippocampal neurons per day has been estimated to approximate 9000 or 250 000 per month, respectively (16), while cell proliferation in humans is likely to be much lower (27). The number of new and functionally integrated neurons is challenged by apoptosis and most of these cells die within 1–2 weeks after their generation (38).

The obvious association between HS and GCD led to the hypothesis that newly generated granule cells were aberrantly integrated into the dentate gyrus and compromised the trisynaptic hippocampal pathway, thereby increasing seizure susceptibility (69). Recurrent mossy fiber sprouting (mossy fibers are axonal projections of granule cells) has long been recognized in animal models of temporal lobe epilepsy (94) as well as in surgical human hippocampal specimens (92). Indeed, seizure-induced granule cell neurogenesis and/or dispersion may then represent a major pathomechanism underlying hippocampal seizure activity (69). Further studies on this intriguing topic challenged this assumption. Irradiation of hippocampal precursor cells did not abolish mossy fiber sprouting after experimental induction of status epilepticus (70) and fostered the discussion on the relevance of neurogenesis for architectural abnormalities within the epileptogenic hippocampus and the etiology of temporal lobe epilepsy (78). However, newly generated granule cells integrate not only anatomically and functionally into the granule cell layer (as destined) or ectopically into the molecular layer (GCD) but also ectopically into CA4 (71). Ectopic granule cells at the CA4/CA3 boundary have been first identified and functionally characterized in animal models for TLE (79). Using immunohistochemical preparations for Prox-1, a homeobox gene specifically expressed in postmitotic dentate granule cells (73), a significant number of ectopic granule cells can now be reliably recognized in rat models as well as human surgical specimens (71). These findings are compatible with the notion that aberrant anatomical organization of the epileptic hippocampus contributes to increased seizure susceptibility and that neurogenesis is critically involved in this process. The majority of findings points to a predominately young age of seizure-induced neurogenesis, which contributes to aberrant network integration and seizure progression. The decreased propensity of neurogenesis in chronic TLE stages, whether reflecting a depletion or exhaustion of the precursor cell pool (5), would rather result in the well-recognized cell loss patterns and severe cognitive deterioration (72) (see below). This hypothesis is in good agreement with a recently proposed pathogenic model on the "two faces" of seizure-related neurogenesis in human TLE (78).

The hippocampus serves a major role in all aspects of conscious, declarative memory, that is, semantic memory for facts and concepts, episodic memory and spatial memory (91). Notwithstanding, bilateral damage of both hippocampi induces profound anterograde amnesia in humans (82). Neuropsychological lesion studies, functional imaging in humans, as well as experimental animal models, linked memory function particularly to the dentate gyrus (46). Thus, standardized cognitive evaluation programs in epilepsy patients submitted to surgical treatment offer the unique opportunity to study such higher brain function in humans. Evidence has already been achieved pointing to the impact of dentate granule cell neurogenesis on learning and behavior in rodents (51, 85). We have studied this issue in human hippocampus obtained from epilepsy surgery. Comparing memory performance [tested by amobarbital anesthesia (WADA) in patients subsequently submitted to surgical resection of either the left or right hippocampus] with the extent of hippocampal cell loss identified granule cell density within the internal limb as the most significant predictor, accounting for 78% of the total memory capacity in an individual patient (72). It "suggestively" points to neurogenesis as the neurobiological substrate of memory acquisition (rather than seizure etiology) and that a rundown of the neurogenic propensity in chronic seizure disorders compromises higher cognitive brain functions. Indeed, we experimentally confirmed this hypothesis when isolating proliferating and differentiating adult human stem cells from the dentate gyrus of TLE patients with HS (23). There was a highly significant correlation between the proliferation and differentiation capacity of adult stem cells with the same patient's memory performance, when each hemisphere was tested separately using WADA. These results suggest that encoding new memories is related to the regenerative capacity of the hippocampus also in the human brain.

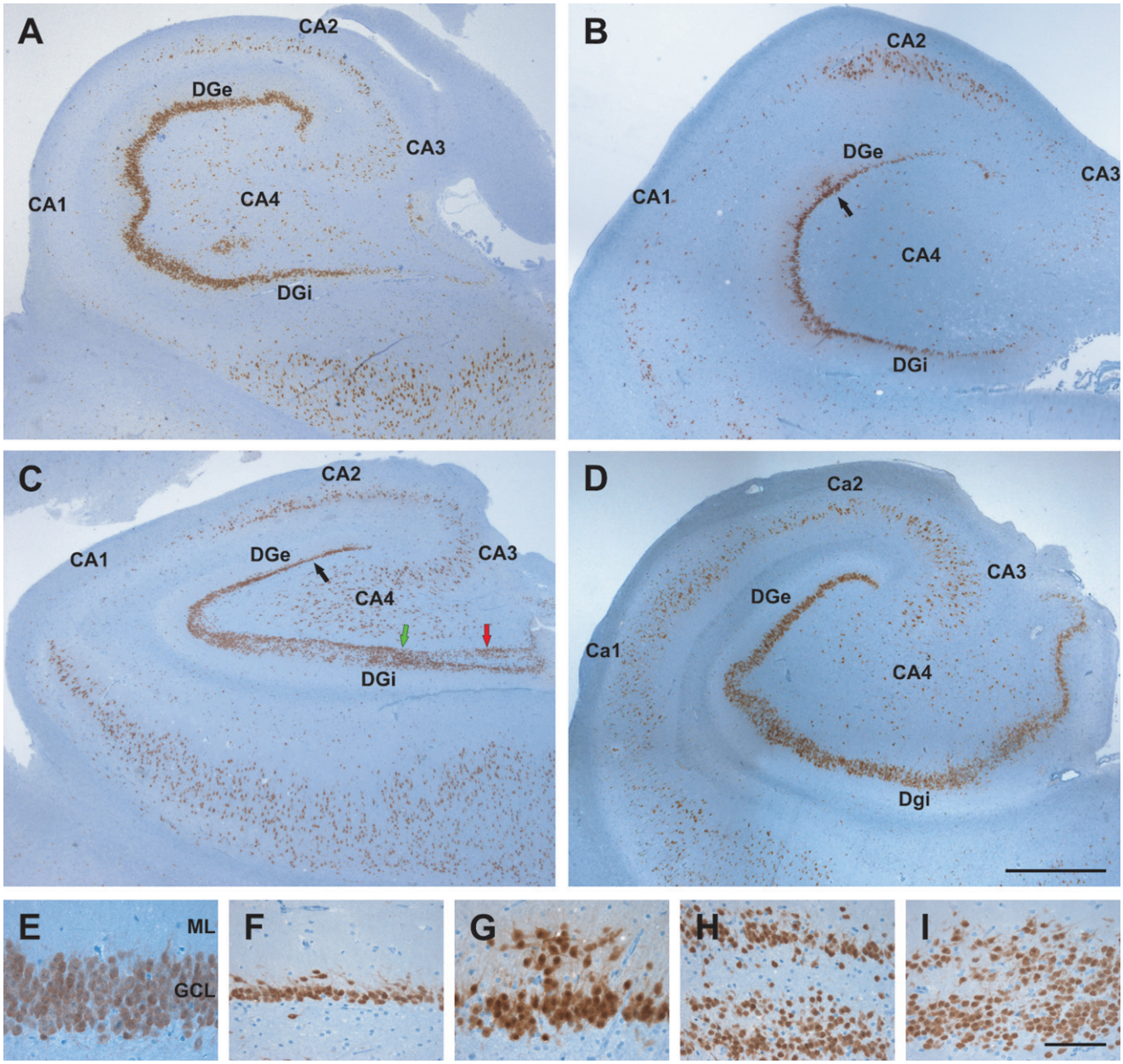

Figure 1. *Neuropathological subtypes of hippocampal sclerosis.* **A.** Classic hippocampal sclerosis with pronounced neuronal cell loss in CA4 and CA1. Note severe cell loss also in the internal limb of the dentate gyrus (DGi), compared to the mid portion or DGe area. Experimental data has shown that this patterns correlates with the patient's impairment to store and recall memory [WADA-testing of the isolated hemisphere; (23)]. **B.** Severe hippocampal sclerosis is characterized by abundant neuronal cell loss in hippocampal CA4, CA3 and CA1 sectors. **C.** CA1 Sclerosis is a rare and atypical HS pattern characterized by predominated cell loss in CA1. Semiquantitative measurements reveal pyramidal cell loss in other sectors as well, but at a lower extent that is not really visible by visual inspection (<30%; Table 1). Please also note the different patterns of granule cell loss in this patient (higher magnifications shown in **E**–**I**). Granule cell loss is evident at the external limb (black arrow). Granule cell dispersion visible at the mid portion (green arrow). Bilaminar architecture at the internal limb (red arrow). **D.** A patient with limbic encephalitis and late onset of her MTLE. The surgical specimen showed restricted cell loss within the CA4 region. This rare pattern is classified as atypical CA4 sclerosis (Table 1). **E.** Higher magnification of a normal human dentate gyrus with densely packed granule cells and sharp borders to subgranular and molecular layers. **F.** Granule cell pathology with significant granule cell loss indicated by layer thinning. **G.** granule cell dispersion with spreading of granule cell clusters into the molecular layer, as described by (44). **H.** Aberrant bilaminar architecture of the granule cell layer is visible. **I:** Granule cell dispersion with spreading of granule cells into the molecular layer. NeuN immunohistochemistry with hematoxylin counterstaining (4 μm thin paraffin-embedded section; applies to all Figure 1 images). GCL = granule cell layer; ML = molecular layer. Scale bar in **D** (applies also to **A–C**) = 1000 μm; scale bar in **I** (applies also to **E–H**) = 100 μm.

HIPPOCAMPAL SCLEROSIS AND ASSOCIATED FOCAL CORTICAL DYSPLASIA (FCD TYPE IIIA)

An intriguing issue remains in the association between mTLE-HS and focal cortical dysplasia (4). Despite the many published results, neither a distinct etiology nor a clinicopathological phenotype for HS with FCD has been identified, which elicits continuous debate (90). Notwithstanding, HS is frequently associated with other pathologies (6), and electroclinical as well as imaging abnormalities in mTLE-HS patients are often larger than the hippocampus, suggesting a more widespread substrate for the generation or persistence of seizures (19, 20, 31). An *ad hoc* Task Force of the ILAE diagnostic commission has classified, therefore, some distinct aberrant histopathological patterns in mTLE-HS patients as associated FCD type IIIa (9). It could yet not been clarified whether FCD type IIIa is an acquired pathology with accompanying reorganizational dysplasia resulting from hippocampal sclerosis, or a distinct developmental entity. The latter would favor the hypothesis that HS is the consequence of chronic epileptogenicity of the temporal lobe caused by the dysplasia. Several aspects argue, however, for a common etiology between HS and FCD type IIIa. Patients from both groups have a similar age at onset and a similar history of febrile seizures as an initial precipitating injury (56); no other clinical differences have yet been identified between isolated HS and HS/FCD type IIIa cases (98). Accordingly, postsurgical outcome is similar in patients with HS only and with FCD type IIIa (93).

Another well-recognized clinical challenge is that of ipsilateral temporal atrophy with temporo-polar gray/white matter blurring, visible by MRI in up to 70% of mTLE-HS patients (21, 60, 62). It is often regarded as a sensitive radiological FCD marker, although no reliable pathological substrate has been identified. Histopathologically proven cortical abnormalities in mTLE-HS patients are less frequent and usually present in two variants. In approximately 10% of temporal lobe surgical specimens from HS patients, an abnormal band of small and clustered "granular" neurons can be observed in the outer part of neocortical layer 2, and was classified as temporal lobe sclerosis (TLS) (35, 98). TLS is likely to present severe neuronal cell loss in layers 2 and 3 with associated laminar gliosis (GFAP-positive astrogliosis) and cortical reorganization (Figure 2). Horizontal bundles of myelinated axons can be observed to a variable degree in these cases. However, there is no correlation between this FCD variant and MRI findings from the same patients (36, 98). Small "lentiform" nodular heterotopias can be identified as another structural abnormality in the temporal lobe of patients with mTLE-HS. They usually remain undetected by MRI (61). Radial orientation along the gray/white matter junction is characteristic and cellular composition is usually formed by projecting neurons (61). These small "lentiform" heterotopias, which are distinct from the larger nodular heterotopias that are readily identified by MRI, may be present in any location of the white matter and are histologically characterized by projecting and local circuit neurons (61). A diagnostic pitfall results from a similar but normal anatomical structure located within the depth of the temporal lobe close to the claustrum. In addition, lentiform heterotopias should be separated from the frequent observation of "isolated" heterotopic neurons either at the gray/white matter junction or in deep subcortical white matter location. Both findings are very often encountered in surgical specimens obtained from epilepsy patients, although its pathogenic or epileptogenic significance remains undetermined (64). The nature and developmental stage of these heterotopic neurons have been addressed in previous studies (28, 40, 95, 96). They may also derive from resting adult stem/precursor

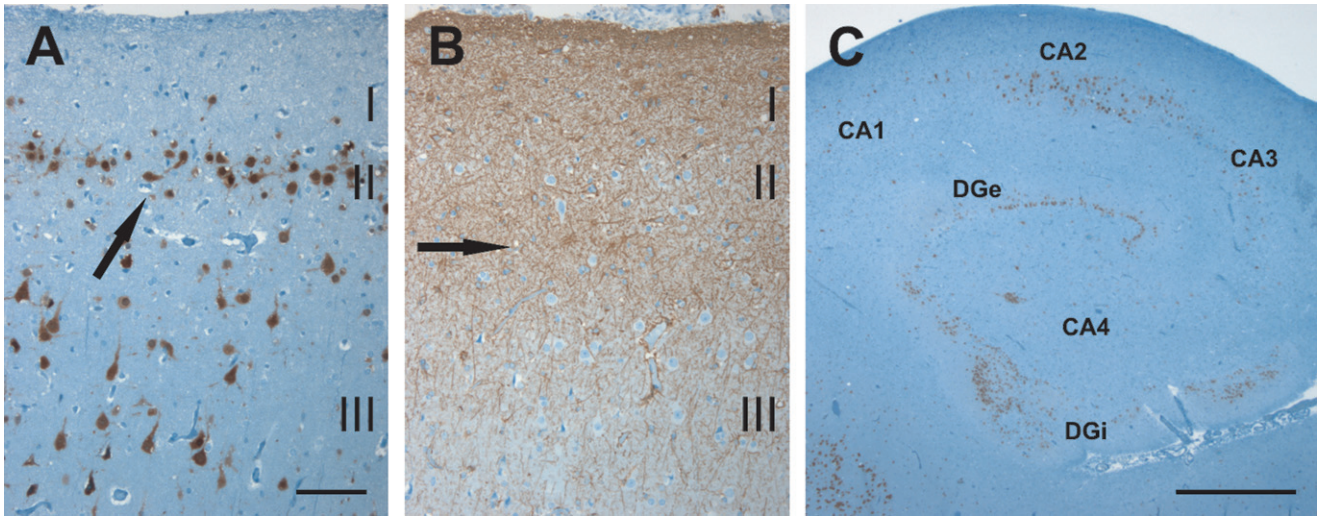

Figure 2. *Temporal lobe sclerosis (FCD type IIIa according to 2011 ILAE classification system).* **A.** "Temporal lobe sclerosis" (98) can be identified in approx. 10% of mTLE-HS patients and is characterized by an abnormal supragranular cell layer (arrow). This pattern should be specified as associated FCD (type IIIa) according to the 2011 consensus classification system for focal cortical dysplasias (9). **B.** Serial section to **A** identifies laminar astrogliosis below the aberrant supragranular cell layer (arrow), indicating severe neuronal cell loss in layers 2/3. Glial fibrillary acidic protein immunoreactivity. **C.** In the same patient, severe HS was evident following microscopic inspection at the midbody level of a NeuN stained and *en bloc* resected hippocampus. I–III = cortical layers; DGe/DGi = external and internal limbs of the dentate gyrus. Scale bar in **A** (applies also to **B**) = 100 μm; scale bar in **C** = 1000 μm.

cells, as recent neurodevelopmental studies provide evidence for neurogenic radial glia in the outer subventricular zone of human neocortex (39), a region that will turn into white matter at later maturation stages. In rat models as well as young children, increased hippocampal neurogenesis was shown following repetitive seizures (86). This may apply also to cortical epilepsies but remains to be shown. The functional impact of aberrantly located white matter neurons to seizure susceptible neuronal networks is another controversial issue, as seizure initiation from white matter location is not very well documented (53). Increased numbers of heterotopic neurons in white matter locations should still be diagnosed, however, as a mild form of cortical malformation using Palmini's classification system (mMCD type II) (68) if occurring as isolated finding without HS, tumors or other principal lesions (9).

MOLECULAR NEUROPATHOLOGY AND ANIMAL MODELS SPECIFYING HS SUBTYPES

It is beyond the scope of this review to illustrate and discuss cellular and electrophysiologic properties of "epileptic" neurons and glial cells in mTLE patients (2) or present the plethora of aberrantly expressed genes, molecules and proteins in this disease condition (87). It may be tempting to speculate, however, that a common trait of upstream regulatory events exists in mTLE. Such upstream regulatory events may involve epigenetic chromatin modifications (48) or the adenosine deficiency hypothesis of epileptogenesis (11). Both mechanisms are able to severely derange downstream gene expression profiles in affected brain regions and are closely related with each other. Animal models remain, therefore, important to study molecular and pathophysiologic sequelae of epileptogenesis (24). A single injection of pilocarpine (or kainic acid) into the animal's peritoneum or directly into the hippocampus elicits status epilepticus, which is most often used to experimentally study pathogenic mechanisms of TLE (65). Other models require subthreshold electrical stimulation of the limbic system following intrahippocampal or amygdala electrode implantation (63). Only few experimental paradigms have tried, however, to reproduce specific human hippocampus pathology or even establish different HS subtypes. Notwithstanding, very long disease duration in many mTLE-HS patients will make this attempt difficult to address in experimental animals. A recent study aimed at this specific issue postulating that classic hippocampal sclerosis results from a single excitatory event by producing prolonged hippocampal excitation in awake rats without causing convulsive status epilepticus (66). Briefly, they triggered two daily episodes of perforant pathway stimulation, which increased granule cell paired-pulse inhibition, decreased epileptiform afterdischarge durations during 8 h of subsequent stimulation, and prevented convulsive status epilepticus. Similarly, one 8-h episode of reduced-intensity stimulation produced hippocampal discharges without causing status epilepticus. Both paradigms immediately produced the extensive neuronal injury that defines classic hippocampal sclerosis, without giving any clinical indication during the insult that an injury was being inflicted. Spontaneous hippocampal-onset seizures began 16–25 days postinjury, before hippocampal atrophy developed, as demonstrated by sequential magnetic resonance imaging. Their results indicated that classic HS is uniquely produced by a single episode of clinically "cryptic" excitation (66), which may well correlate with the early onset hypothesis of classic HS (MTS 1a) in mTLE-HS patients (8).

In conclusion, the clinicopathological and molecular genetic spectrum of mTLE-HS suggests structural and functional disturbances to be more extensive than just affecting the hippocampus (103). We can clinically define subgroups ranging from very focal mesial to widely extended temporal plus types (45). Neuropathological investigations detected different patterns of neuronal cell loss within hippocampal subfields and adjacent temporal lobe structures (26, 57, 106). An intriguing issue will be, therefore, to identify the missing link between clinical and pathology patterns of mTLE-HS. A reliable consensus classification system will be also helpful to define terminology issues and to prospectively evaluate such clinicopathological HS subtypes with respect to postsurgical seizure control and amelioration/aggravation of frequent comorbidities, such as memory impairment and mood disorders.

ACKNOWLEDGMENTS

The work is supported by the European Community (LSH-CT-2006-037315 EPICURE). H.M. is supported by a grant from the Japan Epilepsy Research Foundation (H21-004).

We declare no conflict of interest.

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