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REVIEW

# Epilepsies associated with hippocampal sclerosis

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**Abstract** Hippocampal sclerosis (HS) is considered the most frequent neuropathological finding in patients with mesial temporal lobe epilepsy (MTLE). Hippocampal specimens of pharmacoresistant MTLE patients that underwent epilepsy surgery for seizure control reveal the characteristic pattern of segmental neuronal cell loss and concomitant astrogliosis. However, classification issues of hippocampal lesion patterns have been a matter of intense debate. International consensus classification has only recently provided significant progress for comparisons of neurosurgical and clinic-pathological series between different centers. The respective four-tiered classification system of the International League Against Epilepsy subdivides HS into three types and includes a term of "gliosis only, no-HS". Future studies will be necessary to investigate whether each of these subtypes of HS may be related to different etiological factors or with postoperative memory and seizure outcome. Molecular studies have provided potential deeper insights into the pathogenesis of HS and MTLE on the basis of epilepsy-surgical hippocampal specimens and corresponding animal models. These include channelopathies, activation of NMDA receptors, and other conditions related to $Ca^{2+}$ influx into neurons, the imbalance of $Ca^{2+}$—binding proteins, acquired channelopathies that increase neuronal excitability, paraneoplastic and non-paraneoplastic inflammatory events, and epigenetic regulation promoting or facilitating hippocampal epileptogenesis. Genetic predisposition for HS is clearly suggested by the high incidence of family history in patients with HS, and by familial MTLE with HS. So far, it is clear that HS is multifactorial and there is no individual pathogenic factor either necessary or sufficient to generate this intriguing histopathological condition. The obvious variety of pathogenetic combinations underlying HS may explain the multitude of clinical presentations, different responses to clinical and surgical treatment. We believe that the stratification of neuropathological patterns can help to characterize specific clinic-pathological entities and predict the postsurgical seizure control in an improved fashion.

**Keywords** Temporal lobe epilepsy · Seizures · Long term epilepsy · Neurodegeneration · Gliosis · MRI · Treatment · Surgery · Outcome

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## Introduction

Temporal lobe epilepsy (TLE) is the most frequent form of focal epilepsy in adults [63]; however, the incidence of hippocampal sclerosis (HS) or mesial TLE (MTLE) in the general population is unknown, because most studies are based on surgical series. It is also unknown what is the

real percentage of patients with MTLE with HS who have few or well-controlled seizures [90]. Nevertheless, seizures related to HS are often resistant to antiepileptic drugs (AEDs) [87, 136].

The relationship between seizures and HS spans more than 180 years [104]. It was initially described by early neuropathologists based on autopsy [29]. Only decades later the potential importance of this lesion in epilepsy was recognized [68]. Autopsy and neuroimaging studies indicate that patients with MTLE with HS often have bilateral asymmetric hippocampal damage, with one side showing HS and the other side varying degrees of damage, going from mild nonspecific neuronal loss to well-characterized milder HS [60, 103].

Neuropathologists have described different patterns of neuronal cell loss within hippocampal subfields and adjacent temporal lobe structures in surgical specimens, and there have been several classifications of HS over the years, which were based on the distribution and extent of neuronal loss and gliosis in different hippocampal subfields [33, 48, 115, 138]. A recent consensus classification system, validated through the neuropathology taskforce of the International League Against Epilepsy (ILAE) [25], tried to incorporate aspects of all previous schemes [24, 33, 48, 100, 115, 125, 138].

Since first histological descriptions, the question whether HS is a cause or consequence of seizures was raised [34, 60]. As in many other biological issues, the truth is most likely in between. While HS may be produced by seizures (in particular during *status epilepticus*), the development of MTLE as a syndrome does not depend solely on cell loss or neuroplasticity within the hippocampus [34, 60]. This would be a gross oversimplification and cannot account for frequent associated features, as for example, the bi-directional relationship between depression and MTLE [75].

## Histopathological characterization including the new International League Against Epilepsy hippocampal sclerosis classification

Neuropathological key features of HS encompass segmental neuronal cell loss of the Ammon's horn and concomitant astrogliosis. The astrogliosis pattern is comprised of the presence of prominent reactive astrocytes and a dense fibrillary scar-like pattern [84, 120]. Further key neuropathological aspects of HS are mossy fiber sprouting and granule cell dispersion [82, 98].

An international classification system should have high reproducibility among different centers and should be based on rather straightforward neuropathological approaches. Considering such aspects, the ILAE classification taskforce has suggested a four-tiered classification system based on hematoxylin-eosin staining and NeuN immunohistochemistry [25]. This classification subdivides HS into three types and includes a term, "gliosis only, no-HS".

### HS ILAE type 1

This characteristic neuronal cell loss pattern is the most frequent finding in epilepsy surgical series of MTLE, comprising about 60–80 % of the cases. The CA1 area shows more than 80 % of neuronal cell loss. However, other segments are also severely affected by neuronal cell loss such as 30–50 % of pyramidal neurons in CA2, 30–90 % of neurons in CA3, and 40–90 % in CA4 (Fig. 1a). The dentate gyrus granule cells also show loss by 50–60 % [24, 25, 48, 125]. The dentate gyrus can be variably affected and present in association with different patterns of CA pathology cell loss, dispersion, and bilamination (Fig. 2). However, the large variability of granule cell layer pathology cannot be clearly correlated so far with seizure outcome [23, 121]. With respect to the differentiation between the so-called classic versus severe/total cell loss pattern in HS, the evaluation of the ILAE taskforce considered this distinction as not significantly reproducible and, therefore, omitted it [24, 125]. Therefore, this HS ILAE type 1 comprises the formally classic and total forms of HS.

### HS ILAE type 2

In this rare form of HS, pathology is affecting entirely the CA1 sector (Fig. 1b). Whereas approximately 80 % of pyramidal neurons are lost in the CA1 sector, all other subfields may show rather mild reduction of neuronal densities, generally <25 % of respective neuronal populations. Only 5–10 % of all MTLE surgical cases reveal this pathology pattern. It is similar to the former description of a pathology pattern by de Lanerolle and colleagues [48]. Concomitant astrogliosis in CA1 is generally prominently present, but this pathology pattern generally lacks significant granule cell dispersion.

### HS ILAE type 3

This type of HS is characterized by predominant neuronal cell loss (approximately 50 %) in CA4 as well as in the dentate gyrus, where more than 30 % of granular neurons are lost (Fig. 1c). All other subfields show moderate loss of pyramidal cells, i.e. <30 % [21]. This form is less frequently observed as compared to the previous two with an incidence of 4–7 % of all the MTLE surgical series [24, 125]. This CA4 predominant sclerosis according to

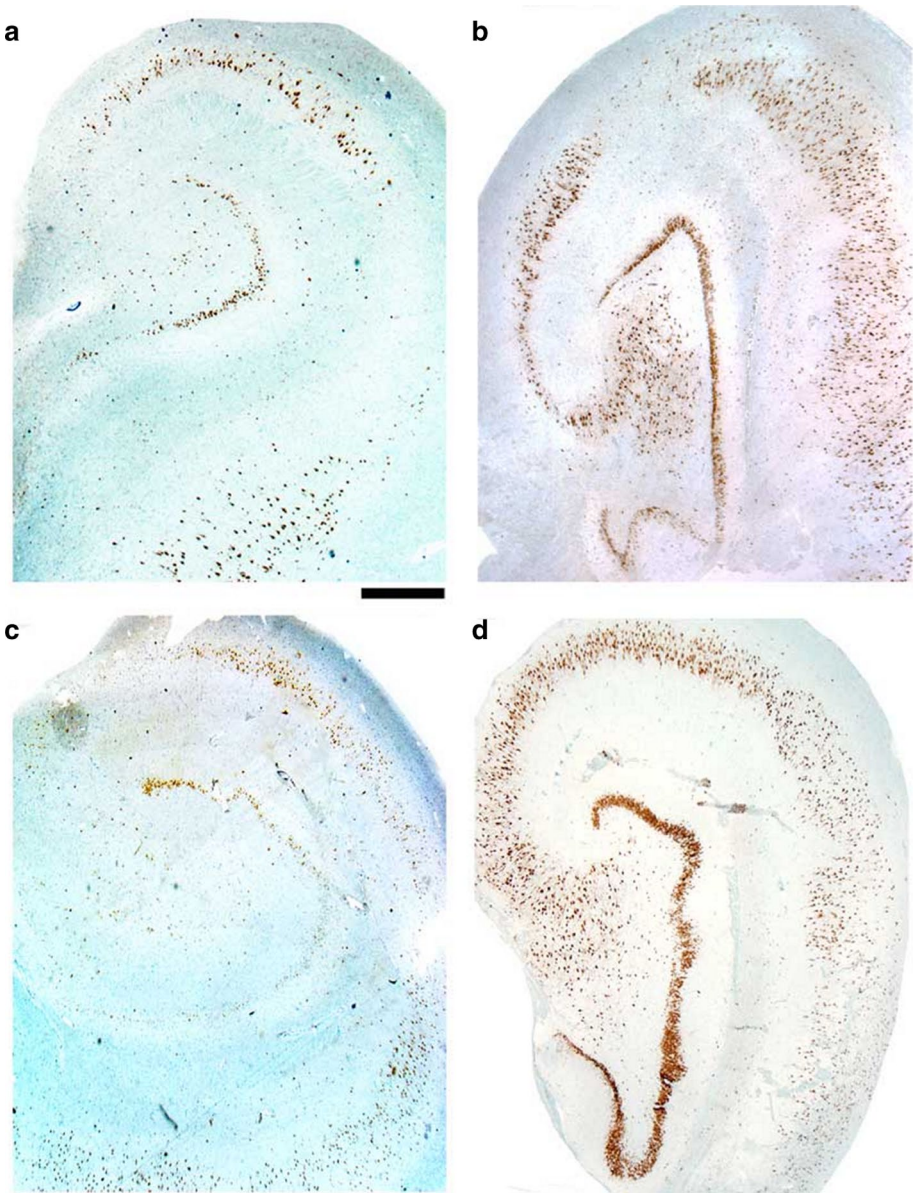


**Fig. 1** Histological subtypes of hippocampal sclerosis in TLE patients according to ILAE classification: **a** HS ILAE type 1 reveals neuronal cell loss in areas CA1 and CA3/4 of the hippocampal formation. There is variable loss of neuronal density in the dentate gyrus granule cell layer as well. CA2 is relatively preserved in neuronal cell density. **b** HS ILAE type 2 shows predominant neuronal loss in the CA1 area. This lesion pattern is relatively rare. **c** In HS ILAE type 3 the hippocampal formation's neuronal cell loss is focused on sector CA4. Also dentate gyrus granule cells are substantially reduced in densities. In the other subfields relatively moderate loss of pyramidal neurons is observed. Limbic encephalitis is frequently associated with this variant of HS. **d** Finally, some hippocampi in pharmacoresistant MTLE patients do not show hippocampal sclerosis, but only astrogliosis in the affected hippocampus. NeuN immunohistochemistry reveals no substantial neuronal loss in the hippocampal formation (**a**–**d** NeuN immunohistochemistry on 4 µm paraffin sections. *Scale bar* for all 1.0 mm)

HS ILAE type 3 has been claimed as associated with dual pathologies [102] and perhaps in HS associated with limbic encephalitis [17].

Gliosis only, no-HS

Approximately 20 % of MTLE patients in larger series lack significant neuronal loss although reactive gliosis is present and electrophysiological evidence suggests a respective seizure focus (Fig. 1d) [24]. Corresponding findings have been derived from surgical as well as postmortem MTLE patients' series [27, 126]. Whereas in the so-called "Wyler" classification [138] a 10 % difference in neuronal cell counts has been classified as HS grade 1, the recent ILAE classification does not designate such changes as HS, but as 'no-HS, gliosis only'. However, recent evidence indicates glial infiltrates as putatively potent epileptogenic triggers [132].

## What to do when the surgical specimen is incomplete

In order to carry out a neuropathological diagnosis according to the above-mentioned classification scheme, en bloc resected hippocampal specimens are required that allow cuts in a way to represent the entire anatomical presence of all subfields. However, clinical practice shows that ideally preserved hippocampal specimens are not available for neuropathological assessment and subsequent experimental approaches in all patients. The ILAE HS-classification

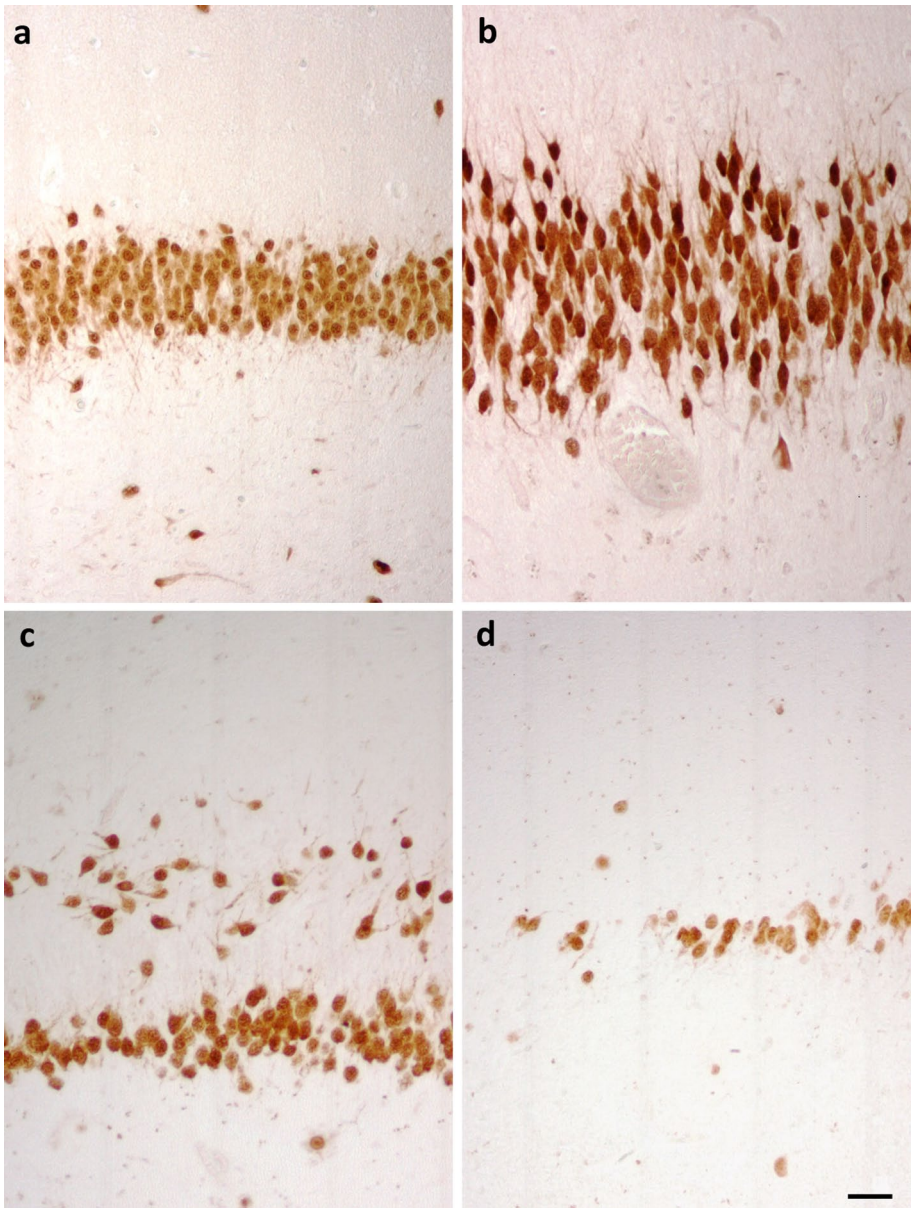


**Fig. 2** Histopathologic spectrum of dentate gyrus pathology in patients with HS as visualized by NeuN immunostaining. **a** Normal densely packed granule cells with sharp borders; **b** granule cell dispersion; **c** bilaminar architecture; **d** thinning of dentate gyrus with granule cell loss. Of note the pathologic changes of DG are not specifically associated with the subtypes of HS. (*Scale bar* 40 µm)

taskforce suggests that in the case of fragmented hippocampal specimens the microscopic analysis should cover at least the hippocampal areas CA1 and CA4, whenever possible [22, 25].

Considering electro-clinical and neuroimaging findings characteristic of MTLE in respective patients, such scenario may allow the diagnosis of 'probable HS'. As soon as more anatomical areas are available for more accurate neuropathological assessment, the diagnosis of HS gains a more solid basis and the ILAE score may be applied. In contrast, if less tissue specimens are available for neuropathology, particularly lacking CA1 and CA4, the diagnosis of HS according to ILAE classification may neither be confirmed nor ruled out. This aspect should be considered and stated in neuropathological reports and also in the scientific context [25].

## Molecular findings which help to explain the production and progression of the HS lesion

A major problem for comparative molecular and functional analyses of surgical specimens from patients with pharmacoresistant MTLE is the unavailability of age-matched controls. Comparative analyses between two groups of MTLE patients, i.e. HS versus TLE associated with other lesions such as highly differentiated tumors or cortical dysplasias can be applied with respect to some clinico-pathological features such as extent of structural changes and neuronal damage. Only a few hippocampal samples from tumor patients without epileptic seizures can be obtained as biopsy non-epileptic controls. Autopsy specimens should be regarded with precaution as "controls" due to variable

post mortem delays of observations and frequent lack of the availability of age-matched samples.

The complementary scrutiny of parallel epilepsy-associated changes in human epilepsy tissue and experimental animal models may provide more insights into the pathogenic significance [72, 101]. In contrast to human surgical specimens that generally reflect late stages of epilepsy, animal models provide the potential to analyze cellular and structural changes in consequence of transient insults to the brain [61, 97]. Commonly used animal models for focal limbic epilepsies comprise kainate-, pilocarpine-, and electrical kindling–induced chronic seizures and individual protocols elicit a wide spectrum of hippocampal HS-like damage patterns and provide a useful basis for unraveling molecular neuropathologic mechanisms of MTLE [9, 128, 129].

A unique human parallel to the animal model of kainate-induced epilepsy comes from the outbreak of an illness, in 1987 in Canada, due to the consumption of mussels contaminated with domoic acid, an excitotoxic in analogous to kainic acid and structurally related to glutamate [123]. Neuropathological evaluation in four patients who died after mussel-induced intoxication demonstrated acute lesions with necrosis and neuronal loss, predominantly in the hippocampus and amygdala, in a pattern similar to that observed experimentally in animals after the administration of kainic acid [123]. In addition, an 84-year-old man who survived had generalized convulsions and then dyscognitive status epilepticus during the acute domoic acid intoxication and later developed MTLE, after a "silent" period of 1 year. Three years and three months after the intoxication he died due to pneumonia and the autopsy showed severe bilateral HS, providing further evidence of glutamate-receptor excitotoxicity as one of the causal factors of HS [36].

## Molecular factors promoting hippocampal lesions

Patients' history as well as animal models suggests that transient insults to the brain can induce a process, often referred as epileptogenesis, that can finally result in HS and the emergence of chronic recurrent seizures [86]. Such insults can comprise prolonged febrile seizures, brain trauma, status epilepticus, and other causes [34, 45]. The induced pathogenetic cascades and involved molecules are potential targets for therapies to retard or antagonize the onset of spontaneous seizures [113]. These insults can substantially alter the expression and distribution of neurotransmitter receptors and ion channels in hippocampal neurons. This has been shown in human hippocampal specimens for metabotropic glutamate receptors [20, 96]. Particularly in animal models, acquired channelopathies were demonstrated to substantially alter the excitability of distinct neuronal hippocampal populations such as altered expression of $GABA_A$ receptor subunits in dentate gyrus granule cells to underlie detrimental failure of inhibition after status epilepticus [32]. Other transcriptional channelopathies may even sensitize neurons for selective degeneration. In an exemplary fashion this may hold true for a voltage-dependent calcium channel. One study demonstrated that deletion of the $Ca_V3.2$ calcium channel subunit prevented the hippocampal segmental neuronal cell loss pattern of HS [7]. $Ca^{2+}$ ions entering through T-type channels may sensitize neurons vulnerable by activation of specific signaling pathways including the calpain system [116]. $Ca_V3.2$ transcriptional augmentation and subsequent increase in T-type $Ca^{2+}$ current density, apical dendritic $Ca^{2+}$ spikes, and somatic bursting may synergistically cause $Ca^{2+}$ overload in CA1 pyramidal cells. $Ca^{2+}$ influx into neurons can be even further augmented by the reversal of $GABA_A$ receptor-mediated currents from hyperpolarizing to depolarizing based on a decrease of the 'KCC2' chloride potassium symporter expression [112]. In this scenario, GABA mediated postsynaptic excitation goes along with massive $Ca^{2+}$ influx through various types of voltage-gated $Ca^{2+}$ channels [2]. Furthermore, chemoanatomical studies have shown that the vulnerable sectors of the hippocampus are rich in kainate (endfolium and sector CA3) and NMDA receptors (sector CA1) [60, 119]. Activation of NMDA receptors and of a subclass of kainate receptors leads to considerable $Ca^{2+}$ influx into postsynaptic neurons and if, as is the case in prolonged seizures, these neurons are not protected by $Ca^{2+}$—binding proteins, they may become irreversibly damaged and die. In the human hippocampus, the principal cells of the vulnerable sector, i.e. the endfolium, sectors CA3 and CA1, contain virtually no $Ca^{2+}$—binding proteins (calbindin or parvalbumin), while the relatively resistant structures such as the dentate granule cells and sector CA2 are rich in calbindin [60, 119]. The destruction of neurons in the vulnerable sectors of the hippocampus that characterizes HS may thus be facilitated by two of their features: (a) the high content of the type of glutamate receptors that promotes $Ca^{2+}$ entry into the neuron during a seizure and (b) their lack of protection against $Ca^{2+}$ overload due to their virtual lack of $Ca^{2+}$ binding proteins [60, 119].

Other acquired channelopathies that increase neuronal excitability can in parallel promote neuronal vulnerability. Those include A-type potassium channels. In CA1 pyramidal cells, the density of A-type $K^+$ currents ($I_A$), mediated by the potassium channel $K_V4.2$ substantially increases with distance to the soma [66]. $I_A$ shows substantial activity-dependent changes. Tetanic stimulation of afferent fibers, which induces long-term potentiation (LTP) of synapses, is followed by a shift in the voltage-dependence of $I_A$ [55]. The functional consequences include increased back-propagation of action potentials into the dendrites and augmented excitatory postsynaptic potential (EPSP)

propagation to the soma [55]. Phosphorylation of $K_v4.2$ by several protein kinases can relate to these shifts in voltage-dependence [65]. Further, clathrin-mediated internalization of $K_v4.2$ channels was found after LTP induction [77].

After induction of status epilepticus by pilocarpine, a similar reduction in $I_A$ develops. In analogy to the consequences of tetanic stimulation, increased phosphorylation of $K_v4.2$ channels relates to impaired function of dendritic $I_A$ [15]. Transcriptional downregulation of $K_v4.2$ subunits was shown to contribute to $I_A$ reduction in epileptic animals [15].

Furthermore, downregulation of hyperpolarization activated cyclic-nucleotide-gated (HCN) channel subunits and the *h*-currents ($I_h$), which they mediate, has been described in hippocampal and entorhinal neurons of chronic epileptic animals after pilocarpine induced status epilepticus [73]. Downregulation of $I_h$ has substantial functional consequences including hyperpolarization of the resting membrane potential, increase in input resistance, and in the summation of dendritic EPSPs [73, 99]. Intriguingly, different insults as well as the developmental time point at which they occur in brain structures, may lead to opposite alterations of $I_h$; i.e. in contrast to downregulation after pilocarpine-induced SE, experimental febrile seizures during early development upregulate $I_h$ and the corresponding subunits in CA1 neurons [30, 42]. Interestingly, the upregulation of $I_h$ could also be pro-epileptic, bringing neurons closer to firing threshold [50]. Many of these channelopathies have been demonstrated particularly in CA1 neurons and may act in concert to increase their excitability and vulnerability to degeneration.

Accumulating evidence, however, suggests that also other factors with strong impact on neuronal excitability, recently referred to as acquired synaptopathies, contribute to epileptogenesis and respective impairment underlies selective vulnerability of neuronal populations other than CA1. Analyses in knockout mice revealed that presynaptic plasticity and proper function of RIM1α play an important part in neuronal adaptive responses to aberrant electrical activity such as status epilepticus [114]. Whereas wild-type mice after SE downregulate hippocampal RIM1α and decrease excitability after status epilepticus, respective RIM1α knockout mice do not show this capacity and demonstrate not only substantially higher seizure activity but also a hippocampal lesion pattern reflecting HS ILAE type 3. Complementary expression analyses in human tissue are difficult due to low available numbers of hippocampi with this lesion pattern and need further studies. Acquired synaptopathies have recently been shown as interesting candidate mechanisms also for pharmacoresistance to Levetiracetam [62]. Certainly, the emergence of distinct hippocampal lesion patterns in epilepsy is multifactorial and intriguing indication is present for correlation of pathomechanisms with particular lesion patterns in human MTLE such as inflammatory changes and HS ILAE type 3 [17].

## Inflammatory mechanisms

In the past years, particularly in patients with adult onset MTLE, a prominent role of paraneoplastic and non-paraneoplastic inflammatory events has been shown [17, 18]. Intriguingly, in those forms of limbic encephalitis, the type of antigens, i.e. intracellular or on the cellular surface has been demonstrated to foster substantial clinical implications.

Presumably, intracellular antigens are not accessible for distinct antibodies. So they are more of diagnostic than pathogenic relevance. This holds true for antigens such as Hu, Ma2, and glutamic acid decarboxylase (GAD). It was demonstrated that epileptogenic encephalitides associated with such antigens are preferentially mediated by cytotoxic T-lymphoid reactions targeting hippocampal neurons [18]. Such neurotoxic T-lymphocyte mediated effects are well compatible with progressive atrophy of affected brain structures in respective patients.

By contrast, potassium channels are the typical surface structures against which epilepsy-associated antibodies were found to be targeted (voltage-gated potassium channel complex; VGKC), NMDA- and AMPA receptors [67, 91–93]. In the case of VGKC, antibodies are targeted against distinct motifs of this channel protein, i.e. typically the ‘contacting associated protein 2’ (CASPR2) as well as LGI1. Binding of the channels by such IgG antibodies has been shown to increase the spontaneous depolarization frequency of respective neurons [93]. Another mechanism eliciting neuronal hyperexcitability has been demonstrated by internalization of NMDA receptors after crosslinking by IgG antibodies [67].

Whereas antibodies against NMDA- and AMPA receptors are often associated with primary cancers or teratomas, this is not the case for GAD targeted antibodies. Intriguingly, epilepsies which can be attributed to antibodies against surface structures generally show a more favorable response to immunotherapies compared to respective disorders associated with antibodies against intracellular target epitopes, e.g. GAD-targeted antibodies [133]. Considering the notion that in a number of patients suspicious for limbic encephalitis, known pathogenic auto-antibiodies are not found, we may expect additional new antigens/auto-antibody combinations to be recognized in the future.

## Epigenetic regulation promoting the emergence of epileptogenic hippocampal alterations

Epigenetic dynamics after brain insults represent powerful mechanisms to trigger rather globally aberrant gene expression alterations and the action of AEDs interfering with epigenetics, such as valproic acid, may at least partially act by interfering with such mechanisms as has been

shown for blocking seizure-induced neurogenesis [71]. Intriguingly, reelin promoter methylation was observed to correlate with granule cell dispersion in human MTLE specimens suggesting a prominent role of reelin signaling for aberrant structural reorganization in hippocampi under epileptic conditions [82]. A recent massive parallel sequencing approach in a chronic rat MTLE model demonstrated aberrant methylation patterns to be inversely correlated with gene expression changes using mRNA sequencing from same animals and tissue specimens. Interestingly, such data may have substantial implications for therapy, i.e. a ketogenic high-fat- versus low-carbohydrate-containing diet attenuated seizure progression and antagonized DNA methylation-mediated transcriptional alterations [83]. Surprisingly, a certain accumulation of differentially methylated motifs was particularly observed in coding genome regions.

### Genetic predisposition

Familial MTLE is a subgroup of MTLE in which most affected individuals have a benign clinical course, and in some families all affected members have good seizure control or remit after a short period of seizures [12, 13, 81, 108]. However, as in patients with non-familial MTLE, some affected family members may have poor seizure control and require surgical treatment. Although magnetic resonance imaging (MRI) signs of HS, including hippocampal atrophy and hyperintense T2 signal, are more frequent and more pronounced in patients with refractory seizures [79, 81], these changes are also observed in patients with good clinical outcome [108], and even in asymptomatic family members [80]. These are strong indicators that genetic factors play a role in the genesis of HS in patients with familial MTLE. While the pattern of inheritance is autosomal dominant with incomplete penetrance, the genetic background in familial MTLE does not imply a more widespread structural abnormality on MRI.

The presence of HS in both affected and asymptomatic family members in familial MTLE suggests that the hippocampus abnormalities themselves could be inherited, and not necessarily lead to epilepsy [80, 108]. The phenotype would then be dependent on interaction with other modifying factors. These data together with the existence of a number of syndrome-specific genes for febrile seizures emphasize the importance of genetic factors as one of the causes of HS [14].

Available pathology from surgical specimens obtained from operated familial MTLE patients showed the typical pattern of HS: selective neuronal loss in CA1, CA3, and CA4 with relative preservation of CA2, and variable involvement of the amygdala and parahippocampal region [1, 78].

Most likely, familial MTLE will be found to have a major gene leading to hippocampal abnormalities, and the phenotype could be influenced by additional genetic and environmental modifying factors, including known and unknown initial precipitating injuries (IPIs).

These multiple pathogenetic aspects of epileptogenic hippocampal lesions may underline the perception of MTLE/HS as multifactorial disease patterns, i.e. no individual pathogenetic factor is either necessary or sufficient to generate these pathologies. The obvious variety of pathogenetic combinations underlying HS may contribute to the multitude of clinical presentations and may even be further enhanced by more complex neuropathological patterns such as dual pathology.

## Typical and atypical clinical presentations

The diagnosis of MTLE requires a constellation of signs and symptoms, but the main criterion for the diagnosis is the presence of characteristic seizure semiology [136]. The accurate recognition of MTLE with HS is usually based on MRI findings, EEG, and Video-EEG, neuropsychological tests and sometimes positron emission tomography (PET) or ictal single photon emission computed tomography (SPECT) [39].

The natural history of MTLE with HS is classically described as a latent period between IPI and/or onset of seizures, although IPI is often not identifiable. Seizures may be initially well controlled for a while before they become medically refractory [136]. However, not all patients with MTLE with HS become refractory to AED and it is not uncommon to encounter patients without a typical history, particularly in the familial forms [90, 108, 136].

The first habitual seizures usually occur in late childhood or early adolescence. The initial ictal event may be a generalized convulsion or a dyscognitive seizure (previously described as complex partial seizure) [10]. Dyscognitive seizures are usually preceded by an aura, typically involving epigastric rising sensation associated with an emotional disturbance such as fear. Other psychic (e.g. déjà vu) and autonomic symptoms (e.g. flushing, pallor, tachycardia) are also seen, and some patients can have olfactory or gustatory sensations. Auras typically occur in isolation (simple partial seizures), as well as in association with dyscognitive seizures [39].

The dyscognitive seizure commonly begins with a motionless stare and oroalimentary automatisms (e.g., lip smacking, chewing) with a progressive clouding of consciousness. Ictal or postictal gestural automatisms and reactive automatisms are also common. When posturing of one extremity occurs, it is usually contralateral to the side of ictal onset. Hand automatisms are frequent and tend to be ipsilateral to the HS, mainly

when associated with a contralateral dystonic posturing. Verbal automatisms may be present in seizures originating in the non-dominant hemisphere. There is transient postictal confusion and there may also be some degree of postictal aphasia in seizures originating in the language-dominant hemisphere. Postictal nose wiping may occur, usually with the hand ipsilateral to the seizure onset. Patients frequently do not recall the ictal period, even though they may respond semi-appropriately during the seizure. The aura, however, is usually remembered [39].

Seizures can occur as often as many times a week, but usually only several times a month. Seizures typically do not occur in clusters (as it is often in frontal lobe epilepsy) and last 1–2 min and are relatively stereotyped in a given patient. Patients may recall occasional auras years before they experienced the first habitual dyscognitive seizure. Secondary generalization as well as status epilepticus is infrequent, but may occur [39]. A nocturnal predominance is either uncommon or under-recognized [16]. Precipitating factors include stress, sleep deprivation, and, in women, hormonal changes associated with the menstrual cycle.

There are no definitive characteristics that distinguish focal seizures in MTLE with HS from seizures generated in the anterior portion of the temporal lobe. The classic presentation as described above may be similar to ictal symptoms described by patients with mesio-temporal lesions other than HS or without any detectable MRI abnormalities. Therefore, the accurate diagnosis of MTLE is based on a constellation of signs and symptoms and diagnostic tests [10, 39, 136].

Seizures with primary visual, auditory or focal somatosensory auras, focal, or violent motor behaviors and extratemporal EEG spikes do not fit with clinical criteria for MTLE with HS [39, 136]. By contrast, even typical, ictal symptomatology may be due to the spreading of ictal discharges from other temporal and even extratemporal areas [39, 64]. However, seizures with mesio-temporal origin can present with atypical clinical features such as hypermotor behavior [109, 130], particularly in young children, in whom hypermotor automatisms similar to those seen in frontal lobe seizures are not uncommon [31]. Sometimes, ictal phenomenology can be quite subtle and difficult to recognize, with only minor changes in visual expression [94] or mild automatisms [107]. Sudden falling, resembling syncopes, has been occasionally reported, particularly in late onset TLE [56].

Intracranial EEG investigations have shown that seizure onset in MTLE is not always confined to the affected hippocampus, but may involve the amygdala, amygdala and hippocampus, parahippocampal gyrus, entorhinal cortex, the temporo-polar region, the insula, the perisylvian cortex [74], and sometimes may involve a complex epileptogenic network including the orbito-frontal cortex, the insula, the frontal and parietal operculum; which has been defined as temporal 'plus' epilepsy [5, 6].

## Neuroimaging

High-resolution MRI is a highly sensitive and specific non-invasive method to diagnose HS in vivo. Images need to be optimized for the evaluation of features indicating hippocampal pathology. Coronal slices are mandatory and they need to be obtained on a plane perpendicular to the long axis of the hippocampus guided by a sagittal scout image. The slices need to be thin enough to allow appreciation of fine details of the different portions of hippocampal anatomy. Ideally, the slice thickness should be 3 mm or preferably less. To evaluate volume, shape, orientation, and internal structure, high-resolution T1-weighted images, particularly with inversion recovery (IR), are highly recommended. T2-weighted or FLAIR (fluid attenuation inversion recovery) images are also important to assess qualitatively the signal intensity [35].

Visual discrimination of a normal from an abnormal hippocampus is straightforward when one is clearly normal and the other is grossly abnormal, but the visual binary paradigm breaks down in symmetric bilateral disease or mild unilateral disease. In this case volumetric MRI can be used to detect mild unilateral disease or bilateral hippocampal volume loss [46].

Most patients with HS undergoing presurgical evaluation will have a clear cut unilateral atrophic hippocampus with increased T2-weighted signal and a normal appearing contralateral hippocampus (Fig. 3). Therefore, qualitative visual analysis is quite sensitive, especially if the MR images are carefully and properly acquired [35].

More detailed high-resolution quantitative MRI analyses reveals a network of gray matter atrophy that involves mesial temporal and other structures interconnected with the limbic system, including amygdala, entorhinal, perirhinal and parahippocampal cortices, and thalamus [44, 45, 138].

Proton magnetic resonance spectroscopy ($^1$H-MRS) studies have shown focal reductions of the neuronal marker N-Acetylaspartate (NAA) signal in MTLE with HS, including patients with normal MRI. Both single-voxel and multivoxel $^1$H-MRS have high sensitivity for detecting low NAA indicative of neuronal dysfunction in MTLE. Areas with reduced NAA correlate well with EEG abnormalities and may be a more sensitive measure than structural MRI. However, the NAA decrease is usually more widespread than the epileptogenic focus and may recover after seizure control [40].

The temporal lobe with HS is frequently hypometabolic on interictal [18F]flurorodeoxyglucose (FDG) PET with an area that involves the mesial structures, the pole, and part of the lateral cortex, which is helpful and reliable in localizing temporal lobe foci for surgical treatment [136].

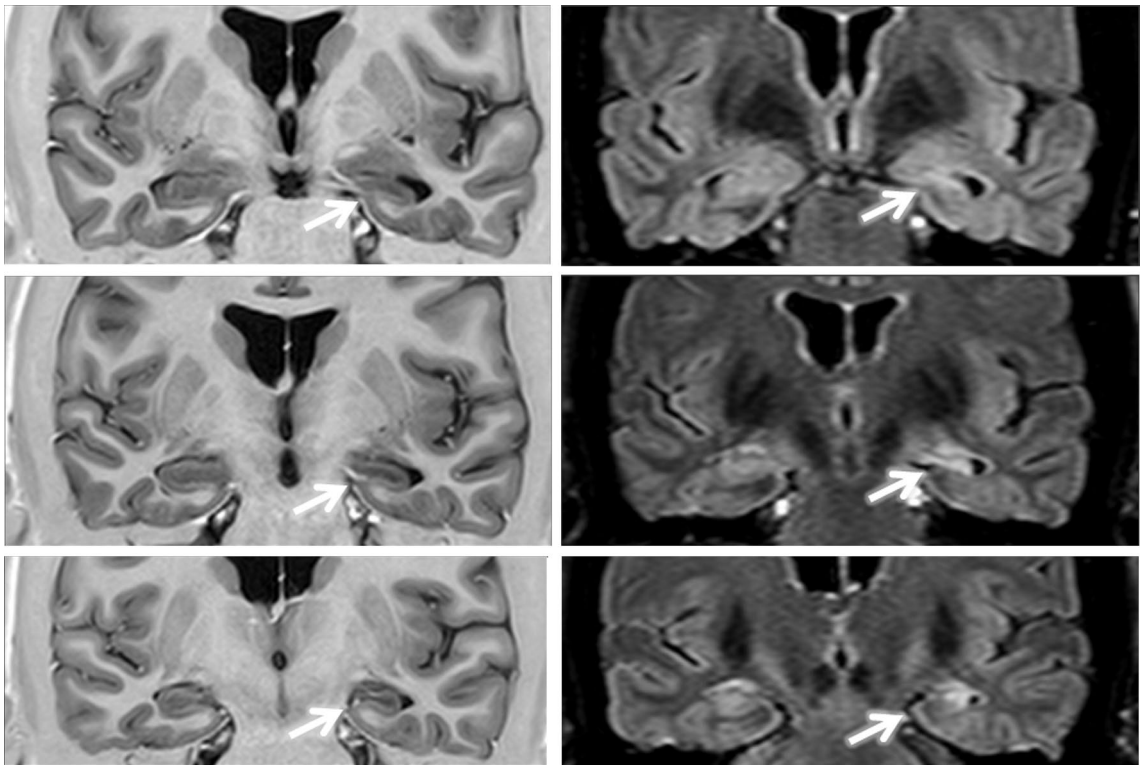

**Fig. 3** MRI from a patient with left mesial temporal lobe epilepsy with hippocampal sclerosis. Coronal T1-Inversion recovery (*left panel*) and FLAIR (fluid-attenuated inversion recovery) images showing typical MRI signs of HS (*arrows*). The left hippocampus is atrophic, with loss of internal architecture, with a decrease in T1 signal (*left panel*) and hyperintense signal in FLAIR images (*right panel*). Note also the loss of hippocampal digitations in left hippocampus compared to the contralateral side (*the top left image*)

Ictal and early post-ictal SPECT scans are also helpful in localizing the epileptogenic focus in patients with MTLE [131]. Interictal SPECT may reveal an area of temporal hypoperfusion, but it is not reliable and should be performed only for the purpose of comparison with ictal SPECT, particularly by using ictal-interictal subtraction images co-registered to MRI [110]. True ictal injections show almost always hyperperfusion of the whole temporal lobe with hypoperfusion of the surrounding cortex.

### Neuropsychological evaluation

Neuropsychological evaluation commonly demonstrates memory dysfunction, which is material-specific according to the hemisphere involved and has been related to the degree of HS as measured by postoperative histopathology and by hippocampal volumetry. Verbal memory is mostly affected with HS in the language dominant hemisphere (usually the left), whereas visuo-spatial memory is more affected with non-dominant (usually right) HS [8]. However, there are atypical memory and cognitive findings in patients with MTLE with HS, and the higher the presurgical scores on verbal memory and naming tests, the higher the cognitive decline after surgery [59].

The issue of Wada test, and more recently functional MRI, for memory evaluation in presurgical investigation is complex and beyond the scope of this paper (for recent review see Bell et al. [8]).

## Hippocampal sclerosis as part of ‘dual pathology’

The term ‘dual pathology’ has been used in several different contexts in the past. In a general way, it describes two etiologically independent pathologies, such as, for example, HS and highly differentiated neoplasms or dysplastic or vascular lesions either in the temporal lobe or in extratemporal regions [37]. In daily clinical routine, this use of ‘dual pathology’ may be practicable; however, in a neurobiological context it may be nonspecific or may even proof wrong in the future, since ‘dual’ appearing pathologies can in fact be part of one spectrum.

The recent FCD classification by ILAE [26] proposed that the term dual pathology should refer “only to patients with HS, who have a second principal lesion affecting the brain (which may be located also outside the ipsilateral temporal lobe), that is, tumor, vascular malformation, glial scar, limbic/Rasmussen encephalitis or MCD (including

FCD type IIa/IIb)." In addition, cytoarchitectural abnormalities in the temporal lobe associated with HS should not be diagnosed as "Dual Pathology" but FCD type III [26]. It should be emphasized that the term 'type IIIa' refers to the ILAE classification for FCDs and not the HS classification. In this FCD classification, the FCDs type I and type II cover isolated FCDs, and the type III FCDs are those associated with other lesions [26].

Neuroimaging studies have shown that developmental lesions are more likely to be associated with HS than lesions acquired later in life, regardless of the location of the lesion, suggesting that a common pathogenic mechanism during pre or peri-natal development is more likely to cause concomitant HS and extra-hippocampal lesions, than is secondary epileptogenesis related to the extra-hippocampal lesion [41]. Results from a surgical series indicate that in patients with dual pathology, removal of both the lesion and the atrophic hippocampus is the best surgical approach and should be considered whenever possible [95].

In one MRI study, dual pathology was by far more common in patients with malformations of cortical development (MCD), porencephalic cysts, and reactive gliosis [37]. The findings of that study indicate that specific kinds of structural lesions, for example MCD, are more likely to be associated with hippocampal pathology, independent of the distance between the lesion and the hippocampus. In patients with other types of lesions, such as vascular malformation, dual pathology tended to be found when the lesion is in the vicinity of the hippocampus [37].

On histopathological studies, HS is frequently associated with other pathologies in the temporal lobe including highly differentiated often glioneuronal tumors as well as focal cortical dysplasias (FCD) [27]. Future studies will provide us with a better pathomechanistic understanding of the shared and diverging factors underlying respective coinciding pathology patterns.

A matter of intense debate has been the clinical outcome of patients with HS and FCDs in temporal lobe locations adjacent to the hippocampal formation. A recent taskforce of the ILAE diagnostic commission has, therefore, classified this particular combination as FCD type IIIa [26]. Intriguingly, the FCD type IIIa postsurgical outcome has been demonstrated as highly similar to that in patients with HS only [122]. Cortical abnormalities generally accepted to contribute to FCD type IIIa together with HS are present in only approximately 10 % of temporal lobe surgical specimens from HS patients [25]. Those comprise an intriguing abnormal band of small and clustered "granular" neurons present in the outer part of neocortical layer 2 [57, 124]. Characteristically, these alterations are accompanied by substantial neurodegeneration in layers 2 and 3 as well as gliotic changes (Fig. 4). Temporal lobe structural changes that accompany HS include circumscribed lentiform nodular heterotopias (Fig. 4), which are generally not detectable on MRI [105]. Lentiform nodular heterotopias should not be confused with heterotopic neurons that are typically present at the border between gray and white matter or located even deeper in the white matter. The epileptogenic potential of such neuropathological findings is still a matter of intense debate [3, 51, 105]. Recent data did not demonstrate a clear separation of temporal FCD type I and IIIa patients with respect to clinical aspects [54].

For the case of increased numbers of heterotopic neurons in white matter as the only abnormal finding in neuropathological specimens from epilepsy surgery the diagnosis of mild malformation of cortical development (mMCD type II) according to Palmini's classification system may well be considered [26, 111].

Ipsilateral temporal atrophy with temporopolar gray/white matter blurring is visible on MRI in up to 70 % of HS patients [43, 106]. Intriguingly, recent data demonstrated patchy myelin loss in the temporal white matter as neuropathological substrate in contrast to dysplastic alterations [58].

## Presurgical evaluation of epilepsies with hippocampal sclerosis

Definition for medical intractability may vary among centers, but it usually includes failure to achieve seizure control with two or more AEDs with adequate dosage and posology [87]. The decision as to when one should refer patients for possible surgery has been problematic due to lack of knowledge about current evidence by some physicians [52, 53, 135]. Delaying surgery while running through a range of AED monotherapies and combination options may worsen the long-term prognosis [140]

Because of the psychosocial consequences of disabling epilepsy in adolescence and early adulthood, patients with MTLE should be referred to epilepsy centers as soon as it is apparent that seizure control cannot be achieved with first-line medications. Surgery is worth considering because the long-term postoperative prognosis is very good [103]. Patients with MTLE and unilateral HS are excellent candidates for surgical treatment, with a 60–80 % chance to become free of disabling seizures, which is clearly superior to continuing medical treatment for patients who failed two adequate AED trials [52, 135].

Traditionally, physicians, including many neurologists, consider epilepsy surgery the last treatment option for patients with partial epilepsy. The average duration of surgically treatable epilepsy among young and middle-aged adults referred for epilepsy surgery at major adult epilepsy centers is more than 20 years [127]. The poor long-term prognosis of intractable epilepsy with the increased overall

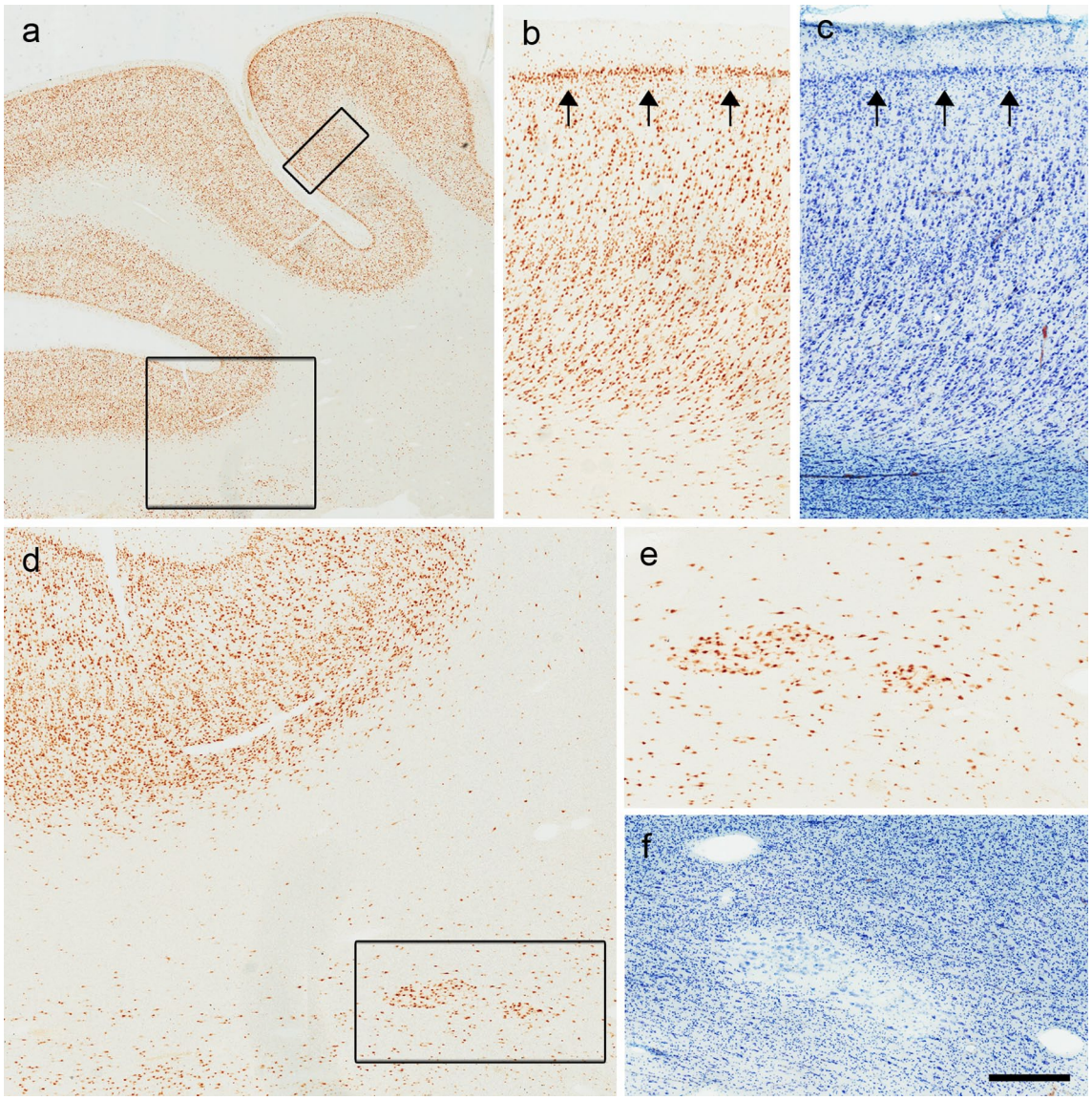


**Fig. 4** Photomicrographs from the anterior temporal lobe in a patient with HS type 1. **a** Low-power microphotograph of a NeuN immunostained section from the anterior temporal lobe; **b** high-power magnification of the *upper black box* region in **a**, showing the presence of dysplasia involving the interface between L II and III (*arrows*) and defined, since associated with HS, as "temporal lobe sclerosis"(Thom et al. [124]). **c** A similar finding is observed in the adjacent section thionin stained. Small "lentiform" heterotopias can also be found in the same section at low and medium magnification (*small box* in **a** and *large box* in **d**) and clearly detectable at high power in section processed for NeuN immunostaining (**e**) and thionin staining (**f**). *Scale bar* 2.3 mm (**a**); 440 μm (**b**, **c**); 670 μm (**d**); 335 μm (**e**, **f**)

morbidity and risk of sudden unexpected death in epilepsy (SUDEP) has been well documented [11, 44].

The presurgical evaluation should be made considering clinical factors, EEG, preoperative MRI, neuropsychological evaluation, and sometimes with additional functional imaging with either PET or SPECT as discussed above [136].

An important risk for surgery in MTLE to be considered is a postoperative decline in verbal memory following a dominant temporal lobectomy. The clear link between functional and anatomic integrity has led to the evaluation of hippocampal structure on MRI as a means of predicting postoperative memory decline. Patients at greatest risk for a decline in verbal memory following a dominant left temporal lobectomy are those with bilaterally symmetric severe MRI signs of HS. Patients at next greatest risk are those with MRI normal hippocampi (i.e., no atrophy) [35]. Patients with less risk for a postoperative verbal memory are those with significant unilateral left hippocampal atrophy [8].

## Clinical and surgical strategies

Medical treatment is based on the patient's response to AEDs, because some patients, especially those with familial MTLE, may have good seizure control with low doses of AEDs indicated for focal seizures. Factors related to a poor response to AED include a young age at onset, more seizures prior to the first medical visit, longer duration of disease, presence, type and extension of lesions on neuroimaging, psychiatric comorbidities, history of prolonged febrile seizures, and IPIs like severe head trauma [87–89]. However, early and adequate response to AED most likely reflects the complex interaction among the nature of epileptogenic pathology, genetic predisposition, and environment [19].

When seizures become refractory to medical treatment, they are unlikely to remit spontaneously. With long duration of uncontrolled seizures, increasing memory problems and other behavioral disturbances are usually reported. This sequence of events indicate that MTLE with HS may be a progressive condition [44].

The choice between anterior temporal lobectomy or a more selective approach usually depends on the experience and preference of the surgical teams. The major presumed benefit of selective amygdalohippocampectomy is the possible better neuropsychological outcomes due to the preservation of temporal structures associated with memory performance. Despite the large numbers of operated patients with MTLE, no convincing data exists that clearly demonstrates a superior neuropsychological outcome following selective resection of the mesial temporal structures. "Standard" cortico-amygdalo-hippocampectomy or "anterior temporal lobectomy" have the advantage of the removal of possible epileptic tissue located in the neocortical temporal cortex in a subgroup of MTLE-HS patients. The data available in the literature so far do not show consistent differences of outcomes between the two approaches [117].

## Predictors of treatment/surgical failures: are some of them pathology-related?

Classically, 60–70 % of AED-resistant MTLE-HS submitted to anterior temporal lobe resection or selective amygdalohippocampectomy become seizure-free after 2 years' follow-up [53, 135]. However, studies with long-term follow-up have demonstrated that only 50 % of patients remain free of seizures after ten years [49, 102]. In addition, a low percentage of MTLE-HS individuals submitted to surgery will be weaned off medications [53]. Thus, the "cure" of MTLE-HS following the removal of the temporal mesial structures happens in a low percentage of individuals and there is not yet a reliable predictor for complete postoperative seizure control without continuing AED therapy [45]. The risks of surgical complications are low and include superior quadrant visual field defects (~8 % for temporal lobectomies, and rare in selective resections), wound infections (~5 %), hemiparesis (~1 %), and atrophy of temporalis muscle (~2 %) [49].

A number of factors have been related to poor surgical outcome; however, there are heterogeneities in the studies and it is not possible to extrapolate these factors for individual patients. Some of these factors include history of secondary generalized seizures, ictal dystonia, longer duration of epilepsy, diffuse or poorly localized EEG, and high frequency of preoperative seizures [69, 70]. MRI lesions outside the hippocampus (dual pathology) or bilateral HS are classically associated with poorer seizure control after surgery [4, 38, 95]. This is in keeping with the association between poorer surgical outcome with functional and structural imaging evidence of a more extensive network of subtle and progressive epileptogenic damage [44, 76, 137, 139], as well as with the frequency and extension of EEG abnormalities [85, 118]. By contrast, larger extension of hippocampal and entorhinal cortex removal [28, 117], as well as resection of the area with PET hypometabolism [134] appears to correlate with better outcome.

There have been attempts to correlate patterns of histopathological hippocampal changes with postoperative outcome but without a clear consensus [24, 47, 48, 125]. The new proposal for an international consensus classification will help for better characterization of specific clinicopathological syndromes associated with HS and may help in improving our understanding of the factors related to good postsurgical seizure control [22]. Available data suggest that HS-ILAE type 1 is more often associated with a history of IPIs before the age of 5 years, as well as with earlier seizure onset and better postsurgical outcome [22]. Data for CA1 predominant HS-ILAE type 2 and CA4 predominant HS-ILAE type 3 are less robust, but appear to indicate a less favorable postoperative outcome [22].

It is possible that postoperative "de novo" epileptogenesis could be related to the etiology and pattern of the HS. The association between longer duration of epilepsy with poorer outcomes suggests that progression of brain damage related to ongoing seizures may trigger epileptogenesis distant to the original lesion; however, there is no conclusive evidence for that in humans. Further studies are necessary to understand better the mechanisms related to early and late postoperative seizure recurrence in patients with MTLE-HS.

## Summary and concluding remarks

HS has been recognized as the most commonly encountered pathological substrate of mesial temporal lobe epilepsy (MTLE). It is present in 60–70 % of patients with MTLE

who undergo surgery for treatment of medically refractory seizures. The recent classification system of the International League Against Epilepsy (ILAE) subdivides HS into 3 types and includes a term of "gliosis only, no-HS" [25]. HS ILAE type 1, which is the most frequent form, shows more than 80 % of neuronal cell loss in CA1 and 30–50 % of neuronal in CA2, 30–90 % in CA3, 40–90 % in CA4, and 50–60 % loss in the dentate gyrus granule cells. HS ILAE type 2 shows 80 % of neuronal loss in the CA1 sector and mild (<25 %) neuronal loss in all other subfields. HS ILAE type 3 is characterized by predominant neuronal cell loss (approximately 50 %) in CA4 as well as in the dentate gyrus, and <30 % of neuronal loss in other subfields. Hippocampal specimens with gliosis only (no-HS) are seen in approximately 20 % of MTLE patients in large surgical series.

HS is multifactorial and there is no individual pathogenic factor either necessary or sufficient to generate this intriguing histopathological condition. The variety of etiological factors underlying HS may explain the multitude of clinical presentations and different responses to clinical treatment: in one end of the spectrum, patients with good response to antiepileptic drug treatment, or even rare seizures in life, and in the other end of the spectrum patients who do not respond to medication and need surgical treatment. The success of surgery is not homogeneous for patients with HS, with approximately 2/3 having significant improvement or cessation of seizures and 1/3 with mild or no improvement. Another intriguing aspect of HS is that a significant number of patients who became seizure free after surgery relapse 5–10 years postoperatively, while others continue seizure free. The stratification of neuropathological patterns and better understanding of the pathogenesis of HS can help to answer these open questions.

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