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Hippocampal sclerosis and the syndrome of medial temporal lobe epilepsy

Craig Watson

Medial temporal lobe epilepsy due to hippocampal sclerosis is the most common epileptic syndrome and, if medically refractory, is a progressive disorder. Advances over the past decade allow this clinicopathological syndrome to be diagnosed *in vivo*. Many patients with hippocampal sclerosis become refractory to antiepileptic medications and are at risk of progressive hippocampal damage, cognitive deterioration and other disabling manifestations of refractory epilepsy. Fortunately, if hippocampal sclerosis is detected early and treated surgically, most patients with this syndrome can be rendered seizure-free, thus sparing them from further progression and disability.

Expert Rev. Neurotherapeutics 3(6), 821–828 (2003)

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KEYWORDS:
anterior temporal lobectomy, hippocampal sclerosis, medial temporal lobe epilepsy, medically refractory epilepsy, PET scanning, volumetric MRI

The International Classification of Epilepsies, Epileptic Syndromes and Related Seizure Disorders recognizes five symptomatic localization-related (i.e., focal, partial) epilepsies, one of which is temporal lobe epilepsy (TLE) [1]. Most epileptologists would subclassify TLE into two or three main syndromes with further subdivisions as shown in BOX 1 [2].

The syndrome of medial temporal lobe epilepsy (MTLE) is characterized by seizures originating in or primarily involving medial temporal lobe structures, such as the hippocampus, amygdala and parahippocampal gyrus [3]. The vast majority of patients with MTLE have hippocampal sclerosis (HS), although lesions adjacent to or involving medial temporal lobe structures can also produce seizures identical to those seen in patients with HS. The syndrome of lateral temporal lobe epilepsy (LTLE), which is characterized by seizures originating in the temporal lobe neocortex, is more difficult to define, perhaps due to the reciprocal connections between medial temporal lobe structures and the lateral temporal neocortex [2,4–6]. Recently, several familial temporal lobe epilepsy (FTLE) syndromes have been described, including benign and refractory syndromes and a heterogeneous group of syndromes with a variety of genetic and clinical features, some of which have been linked to specific chromosomes [7–26]. The subject of this review is MTLE associated with HS.

Epidemiology

TLE is the most common epileptic syndrome [3]. HS is the most common neuropathologic finding in patients with medically refractory TLE and occurs in 60 to 75% of patients treated surgically for medically refractory TLE [27–29]. Therefore, MTLE associated with HS is the single most frequent epileptic syndrome [3]. HS is characterized by neuronal cell loss and gliosis involving hippocampal sectors CA1 and CA3/CA4 with relative sparing of CA2, the subiculum and dentate gyrus, although in severe cases pathologic findings may be widespread (FIGURE 1) [27,29,30].

Etiology & pathogenesis

Despite intensive investigation for over a century, the precise cause of HS remains elusive. Three main hypotheses concerning the etiology and pathogenesis of HS have been advanced [12,31,32]. The first theory is that a prolonged febrile convulsion or other initial precipitating injury (IPI), such as meningitis, encephalitis, head trauma or birth injury, damages the hippocampus during a vulnerable period of time in development. The damaged

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hippocampus then matures into an epileptogenic lesion (i.e., HS) over time and the patient develops habitual seizures characteristic of MTLE. This view is supported by the fact that approximately 50 to 70% of patients with refractory HS have a history of prolonged febrile convulsions or other IPIs in early childhood; although, as has been highlighted, this association is not universal [12,31].

The second theory over the etiology of HS concerns early disordered development. This view holds that HS is a developmental lesion and is present before birth. In this scenario, the prolonged febrile convulsion is regarded as a consequence of the developmentally abnormal hippocampus rather than the cause of hippocampal damage [33,34]. This view is supported by the high incidence of other developmental lesions found in the temporal lobes of patients with HS [35–38].

Recently, the possibility of a genetic contribution to the etiology and pathogenesis of HS has emerged. Although it has long been recognized that febrile seizures tend to run in families, HS has not been considered to have strong genetic underpinnings, a concept supported by identical twin studies [12,39,40]. Although initial studies describing FTLE suggested that this was a benign disorder with no evidence of hippocampal abnormalities, subsequent studies have shown that some FTLE patients do have HS [7,8,10,11]. Other studies have shown genetic abnormalities in some patients with HS [13–15]. From this evidence, it appears likely that the causes of HS are multiple and multifactorial [12]. While in some patients a single cause or event may lead to the development of HS, other patients may require a sequence of events involving multiple factors to develop this clinical and pathological entity. One suspects that more factors contributing to the pathogenesis of HS will be discovered in the future.

Box 1. Classification of temporal lobe epilepsy.

A. Medial temporal lobe epilepsy: seizures originating in or primarily involving medial temporal lobe structures (i.e., hippocampus and amygdala)

1. Hippocampal sclerosis (~ 70% of patients with refractory temporal lobe epilepsy)

2. Lesional medial temporal lobe epilepsy

B. Lateral (neocortical) temporal lobe epilepsy: seizures originating elsewhere in the temporal lobe (i.e., in the temporal lobe neocortex)

1. Nonlesional lateral temporal lobe epilepsy (~10% of patients with temporal lobe epilepsy)

2. Lesional lateral temporal lobe epilepsy

C. Familial temporal lobe epilepsy

1. Benign familial temproal lobe epilepsy (some patients with hippocampal sclerosis)

2. Refractory familial temproal lobe epilepsy (most patients with hippocampal sclerosis)

3. Familial temproal lobe epilepsy with various genetic and clinical features

Clinical features

Clinical presentation & course

As previously mentioned, there is often a latent interval between an IPI, such as a prolonged febrile convulsion and the onset of habitual seizures typical of MTLE. Although the onset of habitual seizures typically begins towards the end of the first decade of life, the latent interval can be quite long in some instances. Initially, seizures may respond well to antiepileptic medications and the patients do well for a number of years. However, as time passes many patients become refractory to antiepileptic medications and ultimately develop a progressive course in terms of seizure frequency, neuropsychological outcome and progression of hippocampal atrophy.

Clinical seizure characteristics

The clinical manifestations of seizures originating in medial temporal lobe structures have been studied intensely in the past 10–15 years utilizing data obtained from video EEG monitoring. From these studies, several features characteristic of medial temporal lobe seizures have emerged. The common seizure types associated with MTLE are simple partial seizures (SPS) characterized by retention of consciousness and therefore often termed an aura, complex partial seizures (CPS) characterized by an impairment of awareness and responsiveness and secondarily generalized tonic–clonic seizures.

SPS or auras are very common in HS and may occur in as many as 90% of patients. They can occur in isolation, but often serve as a warning or first manifestation of a CPS. In patients with HS, the most common aura is a rising epigastric sensation often described as nausea, butterflies or a queasy feeling in the epigastrium, which rises into the chest (often termed an abdominal aura). The second most common SPS in MTLE is the unprovoked feeling of fear. It is not unusual for fear and an abdominal aura to be present simultaneously in an individual patient [41]. Other less common auras described by patients with HS include déjà vu, jamais vu, tachycardia and palpitations, olfactory and gustatory hallucinations, as well as feelings of depersonalization. In general, the mentioned SPS or auras are helpful in localizing seizure onset to medial temporal lobe structures but are less helpful in lateralizing the side of seizure onset [42].

The typical complex partial seizure in MTLE begins with an arrest of motor activity and development of a blank stare with impaired awareness and responsiveness. The seizure may not progress beyond this state but more often semipurposeful, involuntary, automatic motor behaviors (automatisms) develop. The most common type of automatism seen in MTLE is an oral–alimentary automatism consisting of lip smacking, chewing, swallowing, lip licking and/or tooth grinding activity. Other types of more complex automatic behavior

can develop, including picking, scratching, squeezing and fumbling with objects in the patients' environment. Other less common automatisms in MTLE include vocalization, spitting, wandering and other more elaborate motor behaviors.

In addition to these common automatic behaviors, a sequence of clinical manifestations with lateralizing features has been described in MTLE [3]. These signs include, nonforceful head turning towards the side of seizure onset early in the CPS, tonic or dystonic posturing of the contralateral upper and/or lower limbs, ipsilateral upper limb automatisms and forced contralateral head and eye deviation late in the seizure, often at the beginning of a secondarily generalized tonic–clonic phase of the seizure. Other manifestations of lateralizing value include ictal vomiting, which can be seen in nondominant or right medial temporal lobe seizures, unilateral eye blinking, which is usually ipsilateral to the side of seizure onset and speech arrest or aphasia in CPS originating from the dominant temporal lobe. Postictal aphasia also reliably lateralizes seizure onset to the dominant temporal lobe. Postictal anterograde or retrograde amnesia has also been reported in medial temporal lobe seizures in patients with HS, but has a less lateralizing value than many of the signs and symptoms previously mentioned.

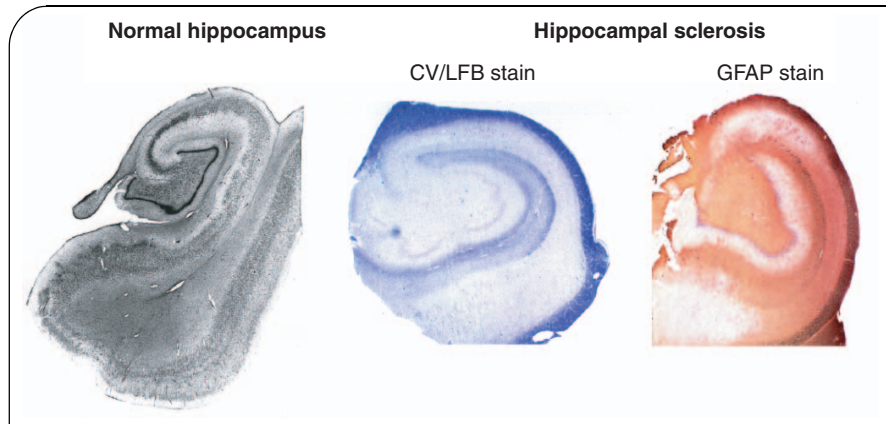

Figure 1. Coronal sections through the body of the hippocampus. Left panel: Normal hippocampus stained with CV. Middle panel: Hippocampus with marked HS stained with CV/LFB. Right panel: Hippocampus with marked HS stained with GFAP antigen to detect astrocytes (gliosis).
CV: Crystal violet; GFAP: Glial fibrillary acidic protein; HS: Hippocampal sclerosis; LFB: Luxol fast blue.

Diagnostic evaluation

Neurological examination

In patients with HS, the neurologic examination is usually normal, although a mild-to-moderate memory deficit may be demonstrable. More often, patients report difficulty with memory that often increases with the duration of their seizure disorder.

Electroencephalography

The typical interictal electroencephalography (EEG) findings in MTLE are unilateral or are independent bilateral spikes, spike and wave complexes, sharp waves and slow waves seen best with basal derivations, such as sphenoidal, anterior temporal or zygomatic electrodes. Prolonged video EEG monitoring may be necessary to demonstrate these interictal abnormalities, since routine EEG's in patients with HS are often normal or nonspecific.

During video EEG monitoring, the typical ictal EEG pattern begins with variable suppression of the background activity, followed by higher amplitude 5 to 7 Hz rhythmic sharp waves seen maximally in one sphenoidal electrode [3,33,43]. This activity may be seen at, or before, the clinical onset of the seizure or may appear within 30 s of a nonlocalizing ictal EEG onset [44]. Invasive intracranial depth or subdural electrodes are rarely required in the presurgical evaluation of patients with HS due to recent advances in neuroimaging modalities.

Neuroimaging modalities

The advent of a variety of high-resolution imaging modalities in the past 20 years has had a significant impact on the diagnosis and management of patients with MTLE due to HS. Anatomical or structural imaging with high-resolution magnetic resonance imaging (MRI) modalities can readily detect hippocampal sclerosis in patients with MTLE. Functional imaging techniques, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are also valuable in the preoperative evaluation of patients with medically refractory MTLE due to HS [45].

The two principal MRI findings in HS are hippocampal atrophy and MRI signal changes indicative of increased tissue-free water [46–49]. A routine MRI scan can easily miss these findings, but HS is readily detected presurgically by using high-resolution MRI-based hippocampal volume measurement to document the hippocampal atrophy associated with the neuronal cell loss in HS and other appropriate sequences (T2-weighted and fluid attenuated inversion recovery [FLAIR] images) to detect the increased signal associated with gliosis [49–52].

The success of qualitative, visual analysis of MRI in detecting hippocampal sclerosis has varied widely in reported studies. The best results have been obtained using a combination of MRI criteria, such as increased signal intensity on T2-weighted or FLAIR images, decreased signal intensity on T1-weighted images, disruption of internal hippocampal architecture and hippocampal atrophy [45,53]. When these criteria are applied to thin (3–5 mm), coronal MR images, HS can be detected in 70 to 85% of cases.

To increase the sensitivity and specificity of MR imaging in the detection of HS, a variety of quantitative MRI techniques have been employed [46,49–51,54–60]. The most productive of these is the use of MRI-based volumetric measurements of the hippocampus to detect the volume loss characteristic of HS [46,49–51,54]. In utilizing this technique, HS can be detected in approximately 95% of cases. Several studies have demonstrated a close correlation between histologically determined cell loss and atrophy, as determined with hippocampal volume measurements [49,61–64]. The

Box 2. Manifestations of refractory epilepsy.

- Intractable seizures
- Excessive drug burden
- Neurobiochemical plasticity changes
- Cognitive deterioration
- Psychosocial dysfunction
- Dependent behavior
- Restricted lifestyle
- Unsatisfactory quality of life
- Increased mortality

Source: Brodie and Kwan. *Neurology* 58(Suppl. 5), S2–S8 (2002).

presence of unilateral HS, as determined by volumetric MRI and seizure control after anterior temporal lobectomy have also been demonstrated [65].

PET scanning with ^{18}F-fluorodeoxy-glucose (FDG-PET) in MTLE identifies areas of decreased glucose utilization (hypometabolism) involving the medial and lateral temporal cortices [66–68]. In addition, this area of hypometabolism may involve the ipsilateral thalamus and the frontal or parietal cortical areas ipsilateral to the epileptogenic temporal lobe [66–68]. Therefore, a rather wide area of hypometabolism can be present on FDG-PET scans in HS. PET studies using the benzodiazepine receptor antagonist Flumazenil (Anexate®, Hoffman-La Roche Inc., NY, USA) (FMZ-PET) have shown that patients with partial epilepsy, including MTLE, have significantly reduced binding in the epileptogenic focus and that the FMZ-PET abnormality is much more restricted than the FDG-PET area of hypometabolism [67–71]. Therefore, FMZ-PET appears to be a much more specific tracer for HS than FDG-PET [67,71].

Interictal SPECT scanning may show unilateral temporal hypoperfusion in MTLE, but the yield is much lower than interictal FDG- or FMZ-PET. However, when the SPECT tracer is injected during a seizure (ictal SPECT scanning), a characteristic pattern of hyperperfusion of the involved temporal lobe is seen. Therefore, ictal SPECT scanning is much more sensitive in the detection of HS than is interictal SPECT [72–74].

Neuropsychological evaluation

Neuropsychological testing in patients with HS often demonstrates a material-specific memory deficit, in which patients with left-sided HS demonstrate a verbal memory deficit whereas those with right-sided HS may, in some cases, display a nonverbal or visual–spatial memory deficit. Neuropsychological evaluation during the intracarotid amobarbital (Wada) test demonstrates hemispheric dominance for language function, as well as the ability of the temporal lobe contralateral to the epileptogenic side to support memory function. During the Wada test, the reduced ability of the sclerotic hippocampus to support memory can be demonstrated when injection of amobarbital into the contralateral internal carotid artery results in a memory deficit. Many epilepsy centers are presently investigating the feasibility of replacing the Wada test with a noninvasive modality, the functional MRI (fMRI). To date, paradigms using fMRI to demonstrate language laterality have proven more robust than those to detect memory function.

Treatment & outcome

Current treatment options for patients with MTLE due to HS include antiepileptic drugs (AEDs), epilepsy surgery in the form of temporal lobectomy and vagus nerve stimulation (VNS). Most epileptologists begin medical treatment for HS with either carbamazepine or phenytoin and seizure control may be established for a number of years [75,76]. However, since most studies concerning AED efficacy do not separate patients with HS from those with other forms of partial epilepsy, little information is available concerning the long-term outcome of HS patients treated with either established or newer AEDs.

Two recent studies investigating the relationship between the cause of epilepsy and response to AED therapy shed some light on this issue. Semah and colleagues found that only 10% of their patients with HS were rendered seizure-free by AED therapy [77]. In a similarly designed study, Stephen and colleagues reported that 42% of their patients with HS were seizure-free on AED therapy [78]. The main difference between these two studies was that 70% of the patients treated by Stephen and colleagues were newly diagnosed and untreated when first seen, while only 8% of those treated by Semah and colleagues were untreated. Therefore, the patients of Semah and colleagues were in a more refractory group when entered into their study. These two studies, therefore, reflect the typical clinical course that patients with HS often follow (i.e., initial control of seizures by AEDs, ultimately giving way to medical intractability).

Surgical treatment of MTLE due to HS, on the other hand, is a much more efficacious therapy. Recent studies indicate that 80 to 90% of patients with this condition can be rendered seizure-free with anterior temporal lobectomy [79]. A recent randomized controlled trial of surgical versus medical treatment for TLE showed clear superiority of surgical therapy [80]. Anterior temporal lobectomy is generally safe and efficacious with the most significant adverse outcome being a 5 to 10% incidence of diminished verbal memory function.

The third treatment modality available at this time for patients with HS is VNS. However, to date, no studies have been performed testing the efficacy of VNS therapy in patients with MTLE due to HS.

Medically refractory medial temporal lobe epilepsy

Recent studies raise concerns that certain forms of partial epilepsy, including MTLE due to HS, may be associated with progressive damage to medial temporal lobe structures [81–92]. These studies, employing a variety of experimental and clinical methods, suggest that continuing seizures over time may result in progressive changes in hippocampal structure and function,

including a decline in neuropsychological functioning [91]. These studies found a longer duration of epilepsy, and an earlier age at onset or both, to be related to diminished hippocampal volumes, reduced N-acetyl aspartate/creatine, prolonged T2 relaxation times or increased severity of HS on pathological evaluation [82–88,91]. Using a longitudinal study design, the author recently showed that patients with intractable unilateral MTLE and HS showed a progressive volume loss in the hippocampus ipsilateral to the side of seizure onset [92].

A recent study by Kwan and Brodie demonstrated that patients with medically refractory epilepsy can be identified early on, utilizing a systematic and aggressive approach to medical treatment [93]. They and others, suggest that patients with refractory epilepsy should be managed aggressively and referred to comprehensive epilepsy centers for consideration of alternative treatments in order to prevent the disabling manifestations of chronic intractable epilepsy (BOX 2) [80,91–94]. Many patients with HS display these manifestations.

Expert opinion

MTLE due to HS represents a well-defined epileptic syndrome with known histopathology, clinical seizure semiology, clinical course, EEG and neuroimaging findings, response to medical and surgical therapy, and prognosis for the development of medically refractory epilepsy. Its pathogenesis and etiology are incompletely understood, but many features are emerging.

The best approach to this condition at this time is to aggressively pursue a definitive diagnosis in patients who appear to fit its clinical profile. This can easily be achieved with high-resolution MRI scanning and other studies. Once the diagnosis is established, aggressive medical therapy should ensue with new and established antiepileptic medications, as recently described by Brodie and Kwan [94].

If medications fail, the patient should be referred to a comprehensive epilepsy center for early consideration of alternative therapy, especially anterior temporal lobectomy. This therapy should be entertained early in the course of the disorder in order to halt seizures, prevent progression and forestall the manifestations of medically refractory epilepsy.

At this time, there is ample evidence that surgery is significantly more effective than AED therapy in controlling seizures in patients with intractable MTLE due to HS and that timely evaluation for temporal lobectomy is preferable to prolonged attempts at medical management [80]. Patients with MTLE due to HS suffer progressive hippocampal damage and neuropsychological decline and should be managed aggressively [91,92,94].

Five-year view

Over the next 5 years, one would expect significant advances in the diagnosis, understanding and treatment of patients with MTLE due to HS. These advances should come in the five areas mentioned, although many other areas may also emerge. I envision these five areas of advancement to include the fields of genetics, alternative surgical therapy, targeted antiepileptic drugs, antiepileptogenic interventions and improved early identification, and definitive therapy of medically refractory HS in order to avoid the disabling manifestations of medically refractory epilepsy.

The field of genetics will explode using microarray techniques to discover genetic involvement with pathogenesis and therapy, as well as the discovery of genes that directly contribute to the condition of HS. Genetic analysis will further aid in addressing the issues of FTLE versus sporadic HS and determine what overlaps are present and where the entities remain separate.

Current surgical therapy is evolving toward restricting the necessary volume of resection in hippocampal sclerosis. However, to date, the clear superiority of selective amygdalohippocampectomy over the traditional anterior temporal lobectomy has not been established. Other therapies, such as gamma knife treatment and deep brain stimulation are under study and may also play a role in the management of this intractable condition.

The pharmaceutical industry will undoubtedly utilize the knowledge gained through genetic research, as well as other molecular biology studies, to develop more targeted AEDs. This will allow drugs to attack the basic mechanisms involved in the pathogenesis of HS and in its evolution toward medical intractability [95].

Much work is underway to understand how interventions can be antiepileptogenic (i.e., block the development of epilepsy) as well as antiepileptic (i.e., simply blocking and controlling seizures) [95]. This is an especially important line of research in a condition, such as HS, which has now been shown to be a progressive condition.

All of these factors will allow the earlier identification and definitive treatment of conditions, such as HS. By intervening in this process early, one would hope that the disabling manifestations of refractory epilepsy will be avoided and our patients will return to productive and fulfilling lives.

Key issues

- Medial temporal lobe epilepsy (MTLE) due to hippocampal sclerosis (HS) represents a well-defined epileptic syndrome with known histopathology, clinical seizure semiology, clinical course, electroencephalography and neuroimaging findings, response to medical and surgical therapy, and prognosis for the development of medically refractory epilepsy. It is the single most frequent epileptic syndrome.
- Patients with MTLE due to HS suffer progressive hippocampal damage and neuropsychological decline.
- HS can be detected readily with high-resolution magnetic resonance imaging scanning and other studies.
- Once the diagnosis is established, aggressive medical therapy should ensue with new and established antiepileptic medications.
- If medications fail, surgical therapy should be entertained early in the course of the disorder in order to halt seizures, prevent progression and forestall the manifestations of medically refractory epilepsy.

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