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REVIEW

HIPPOCAMPAL SCLEROSIS

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Summary

Hippocampal sclerosis is one of the most common causes of focal epilepsy. At the same time, hippocampal sclerosis is the most common surgical substrate in focal pharmacoresistant epilepsies. The hippocampus has a specific anatomical structure consisting of a total of four sectors. In a physiological context, the hippocampus is essential in many neuropsychological processes, so hippocampal sclerosis (an entity recognized and associated with epilepsy as early as the 19th century) is very interesting in terms of research. The pathohistological pattern of hippocampal sclerosis is now very precisely represented, which helps uniform recognition. The causes of hippocampal sclerosis are not known, but so far, numerous factors have been identified that are associated with the occurrence of this pathological process. There is no doubt that excitotoxicity, along with changes in the redox system, is the most essential pathophysiological mechanism. Hippocampal sclerosis is clinically very recognizable. Epilepsy patients whose basis is hippocampal sclerosis have very typical epileptic seizures consisting of an epigastric aura followed by a focal epileptic seizure characterized by confusion of consciousness and oroalimentary automatisms. Today, thanks to modern neuroimaging (primarily magnetic resonance imaging), the detection of this pathological pattern is exact and unambiguous.

Keywords: hippocampal sclerosis, epilepsy, magnetic resonance imaging

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INTRODUCTION

Hippocampal sclerosis (HS) is recognized in modern epileptology as one of the most common causes of focal epilepsy (1). It is present in 10% of newly diagnosed focal epilepsies (2). One third of pathological findings in surgical series of pharmacoresistant epilepsy in adults belong to this etiological entity (3). On the other hand, the facts that the hippocampus has a physiological role in the formation of memory and that it probably possesses extraordinary neural plasticity in the central nervous system, which is shown by the presence of neurogenesis in the dentate gyrus (4), make HS, in addition to the "title" of the carrier of a specific epileptic syndrome also interesting in many ways as a research model. This is also why HS is a research model of pervasive study, both by epileptologists and other disciplines in neuroscience.

ANATOMY OF THE HIPPOCAMPUS

The name of this brain structure was given by the Venetian anatomist Aranzi (Julius Caesar Aranzi) in the 16th century due to its resemblance to a seahorse (lat. hippocampus from Greek ἵππος - horse and κάμπος - seahorse). In the 18th century, the Danish anatomist Winsløw (Jacob Winsløw) proposed the name "cornu Amomonis" - the horns of (the Egyptian god) Amon. This name remained for a sector of the hippocampus – CA1-4. Anatomically, the hippocampus is the folded edge of the cerebral cortex in the S-shape and is essentially a bilaminar structure, i.e., the hippocampus formation consisting of the "real" hippocampus and the dentate gyrus (both structures maintain a mutual relationship along the entire length). The hippocampus belongs to the limbic cortex (lat. limbus - border), as is the case with cingulate and olfactory cortex and amygdala. In the structural sense, it is a most straightforward cortical organization - the allocortex (or archeocortex). This brain structure is arched around the mesencephalon and is divided into three parts: the head (anterior segment), where the elevations (hippocampal digitations) can be seen; the body (middle segment); and the tail of the hippocampus (posterior segment) which gradually narrows and disappears below the splenium. The hippocampus has a very complex geography, and one of the consequences is that slices through the hippocampus can show different shapes depending on the angle and location of the slice.

Nevertheless, four fields of the "true" hippocampus are recorded in the coronary section (5): CA 1 – starts from the subiculum, and its pyramidal neurons are triangular, small, and scattered; CA 2 –- continues from CA 1 and consists of large, ovoid and densely packed neurons; CA 3 – continues from CA 2 and its neurons are similar but rarer and are characterized by the presence of unmyelinated mossy fibers originating from the dentate gyrus; CA 4 – right above the dentate gyrus and consists of sparsely distributed ovoid and large neurons and myelinated mossy fibers originating from the dentate gyrus. In the coronary section, the dentate gyrus is a narrow and dorsally concave lamina that envelops the CA 4 segment. In the histological sense, the "real" hippocampus has six layers (from outside to inside – alveus, stratum oriens, stratum pyramidale, stratum radiatum, stratum lacunosum, stratum moleculare), and the dentate gyrus has three layers (stratum granulosum, stratum moleculare and polymorphic layer).

HIPPOCAMPAL SCLEROSIS IN THE MIRROR OF TIME

The pathological change of the hippocampus in epilepsy was recognized in 1825 in a research by Camille Bouchet and Jean-Baptiste Cazauvielh who attempted to determine the cause of epilepsy (l'épilepsie) and madness (l'aliénation mentale), when they described a macroscopic abnormality of the hippocampus in 5 out of 31 post-mortem patients with epilepsy. In the description of "crazy epileptic number 10", the authors documented a clinical picture that correspond to the syndrome of mesial temporal lobe epilepsy (MTLE) where "a 31-year-old patient becomes restless before the attacks, which are accompanied by vomiting and stomach irritation... and at autopsy, there is a small mass of greyish, hard and resistant matter contained in the horn of Ammon on the left side" (6) **(Figure 1)**. However, Bushe and Cazauvieilh did not establish an interdependent relationship between epilepsy and sclerotic hippocampus. It was only in 1880 that Karl Wilhelm Sommer examined 90 autopsied patients with epilepsy and concluded that "there is no doubt that epileptic symptoms are often associated with

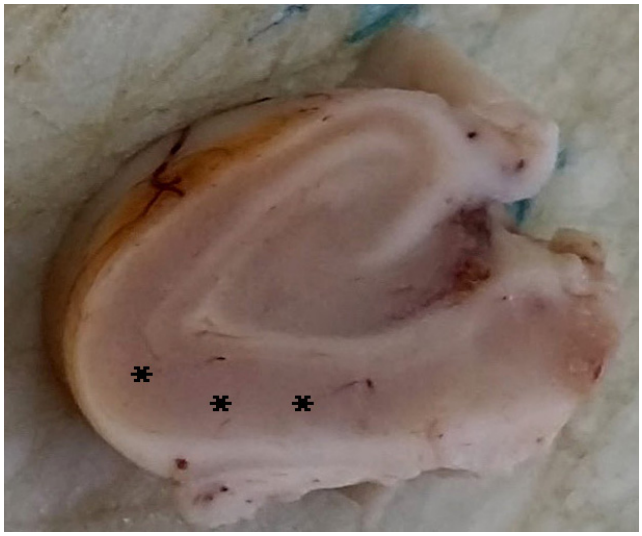

Figure 1. Macroscopical features of hippocampal sclerosis (type 2). * CA1 sector – absence of the clear boundaries between gray and white matter (sample from the patient with mesial temporal lobe epilepsy operated at the Clinic for Neurosurgery, University Clinical Center of Serbia).

diseases of the horn of Ammon and its surroundings." In a very detailed analysis, Sommer described the basic microscopic features of HS in the case of a 25-year-old patient with complex focal seizures - gliosis and a loss of pyramidal cells primarily in the CA1 sector, which was later called Sommer's sector (7) **(Figure 2)**. At the very end of the 19th century, Emil Bratz published a study of microscopic analysis of the hippocampus in patients with epilepsy where he concluded that there was a region between the hilus and Sommer's sector (in which the hippocampal pyramidal cells are very resistant and which is nowadays known as the CA2 sector) and that HS was not a consequence of vascular processes, but a pathological entity with a unique pathogenesis (8). These early understandings were confirmed in the new momentum of research epileptology, this time in the Anglo-Saxon area, in the works of Wilder Penfield and Jasper in the 1960s, and then in the literature that we know as modern. However, most of the observations published by Sommer or Bratz are challenging to reconcile with today's experiences. For example, as many as 60 out of 90 HS cases in Sommer's study were described as dementia patients. Of course, we should keep in mind that the perception Sommer had when anticonvulsant therapy was not available and when most patients with epilepsy died early in hospitals is hard to imagine nowadays.

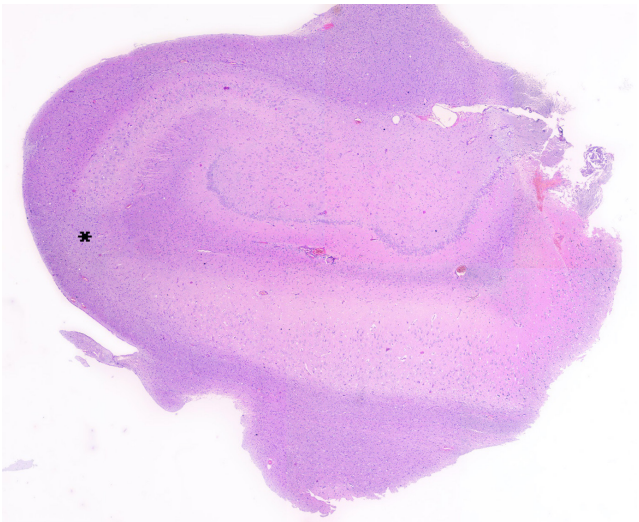

Figure 2. Microscopical features of hippocampal sclerosis (type 2). * CA1 sector – loss of the pyramidal cells (sample from the patient with mesial temporal lobe epilepsy operated at the Clinic for Neurosurgery, University Clinical Center of Serbia)

CAUSES OF HIPPOCAMPAL SCLEROSIS

When and how HS occurs, and which are the predisposing factors responsible for its occurrence are central issues in the current research efforts in epileptology. First of all, identifying susceptible individuals could lead to the application of prophylaxis in prevention of the onset or further progression of HS.

Generalized tonic-clonic seizures (GTCS) and status epilepticus (SE) are the earliest recognized causes of HS. In the same year when Sommer pathohistologically defined HS, Ludwig Pfleger described his 25 cases of macroscopically diagnosed HS. In one patient who died due to SE, he determined hemorrhagic lesions in the mesial temporal lobe as a result of "metabolic disorders" that occurred during the attack (9). Although in modern epileptology this causality has become generally accepted, in a study of postmortem samples of the hippocampus of patients with refractory epilepsy, it was shown that SE did not inevitably result in HS (in one patient, HS was not detected even after 30 episodes of ES) (10). Unfortunately, the characteristics that make patients with prolonged GTCS or SE more susceptible to developing HS are still unknown.

Significant brain insult or initial precipitating injury (IPI), such as, e.g., febrile convulsions, meningitis, or prolonged epileptic seizure, are often associated with HS (up to 50% in retrospective studies). The hypothesis supporting such observations argues that IPIs irreversibly damage (or change) the hippocampus, resulting in a process that finally leads to HS after a "latent period." The theoretical assumption that there is a "narrow age window" for this type of process (up to 4 or 5 years of age) in which the hippocampus is highly vulnerable is also significant. The effects of epileptic seizures in IPI are rather complex and include synaptogenesis, neurogenesis in the dentate gyrus, and neuronal loss (11). Direct evidence supporting this concept comes from neuroimaging studies which have shown that HS occurs after prolonged febrile convulsions. About 10% of children in whom febrile convulsions are >30 minutes have increased signal intensity on the T2 weighted MRI sequence in the hippocampus region, which later evolves into HS (11). However, it remains unknown why a systemic event, such as elevated body temperature, results in significant asymmetry (or exclusive unilaterality) in the involvement of the hippocampus, while this finding can be maintained throughout life. A partial explanation lies in the possible existence of subtle structural abnormalities of the hippocampus, shown in a neuroimaging study of blood relatives with familial aggregation of febrile convulsions, where a significant difference in hippocampal volume was determined (12). However, this observation's histological or genetic background has not been shown to date.

If accompanied by non-convulsive SE, brain injury can rarely result in HS (13). However, HS associated with vascular anomalies (e.g., cavernous angioma), severe malformations of cortical development, or low-grade tumors associated with epilepsy (dysembryoplastic neuroepithelial tumor - DNET or ganglioglioma) is far more significant and common. Moreover, it has been estimated that as many as 15% of patients with lesional epilepsy have associated hippocampal sclerosis (the so-called "dual pathology") (14). The hypothesis of this association suggests that seizures are first generated from the immediate vicinity of the lesion and then spread to the hippocampus. Long-term exposure of the hippo-

campus to discharges from the primary epileptic center leads secondarily to HS. This connection forms an inextricable epileptic network. This conclusion stems from the observation that in the case of surgical treatment in patients with "dual pathology," it is necessary to remove the hippocampus in addition to the lesion (15). There are, however, opinions that this rule excludes epilepsy of the "posterior quadrant," where the pathology of the hippocampus is temporally synchronous with the pathology of the occipitoparietal cortex (e.g., prenatal insult) because, in these patients, resection in the posterior part of the brain was sufficient to induce a complete remission (16). However, this study dealt with hippocampal atrophy without clear radiological signs of sclerosis.

Recently, there has been research interest in the relative contribution of factors other than epileptic seizures (including genetic, environmental, and developmental factors) in the development of HS. Thus, the professional public was sporadically informed that there is a possible association of HS with genes encoding inflammatory cytokines (including interleukin 1β) or with the ApoE ε4 genotype (10). In addition, some research groups have reported that environmental factors may play a role in the development of HS, such as herpes virus infection (17). However, such results have not been consistently replicated in subsequent studies. In the most recent works, the research is concentrated on the association of HS with autoimmune encephalitis. In this context, the association of HS with autoimmune limbic encephalitis with antibodies to voltage-dependent potassium channels is best documented. Typically, these antibodies lead to acute or subacute encephalitis with enlargement of mesiotemporal structures with increased signal intensity on T2-weighted MRI. In the sequel, HS occurs in the same place (18). This suggests the importance of intensive early autoimmune encephalitis treatment.

The number of HS is decreasing in surgical series in most major surgical centers worldwide (19). The explanation of this observation is not uniform so far. One belief is that the number of smaller centers that have "taken over" the surgical treatment of cases with HS as "easily solved" has increased. Because of this, the number of patients with MTLE associated with HS in large surgical centers has decreased. However, the more likely hypothesis is that the number of operated patients with MTLE associated with HS is decreasing because the epidemiology of drug-resistant epilepsy is changing. More precisely, better treatment of risk factors for MTLE associated with HS, such as infections and complex febrile convulsions with anti-inflammatory drugs, is the essence of such observations. This belief is based on the observation that although the reduction in the number of cases of MTLE associated with HS is visible in all age categories, this phenomenon is particularly noticeable in the younger population.

Mechanisms of damage to hippocampal neurons

The question whether HS is a cause or effect of epileptic seizures seems to have been around for 100 years - without a good answer. Nevertheless (and not in order to absolve the research failure), it is fair to state that HS is a process that is far more complex than the simplistic consideration of simple neuronal loss. Insights into the mechanisms underlying hippocampal damage are mainly obtained from animal models of SE. These studies showed that although some degree of neural damage results from hypoxia, hypoglycemia, or hypotension, most nerve cell deterioration occurs independently of these factors (11). For now, it seems likely that excitotoxicity is stimulated by epileptic activity that mediates cell death through glutamate receptors.

Complementary and parallel examinations of changes in the human tissue of patients with MTLE associated with HS and in experimental animal models (the most commonly used kainate model) can provide more insight into the pathological process. There is enough evidence for the correctness of such conclusions, but one observation is particularly striking. In 1987, 14 people were poisoned by mussels containing the biotoxin domoic acid on the Prince Edward Islands in Canada. Domoic acid has an excitotoxic property similar to kainic acid owing to its structural similarity to glutamate. Neuropathological findings in those who died from poisoning showed necrosis and neuronal loss in the hippocampus and amygdalae (similar to the kainate model). In an 84-year-old man who had non-convulsive status epilepticus as part of the clinical picture of poisoning, MTLE developed after a "latent" period of one year. This patient died of pneumonia three years and three months after poisoning, and bilateral HS was found at autopsy (20).

In contrast to knowledge derived from human samples, which mainly reflect the late stages of epilepsy, animal models offer the potential to analyze cellular and structural changes through time dynamics. IPIs can significantly alter neurotransmitter receptors' and ion channels' expression and distribution in hippocampal neurons. It has been shown, especially in animal models, that acquired channelopathies significantly change the excitability of different neuronal hippocampal populations, such as, for example, altered expression of GABAA receptor subunits in the dentate gyrus (21). Some channelopathies can even render neurons susceptible to degeneration in selective populations. Deleting the calcium channel subunit, Cav3.2, prevents the loss of IPI-exposed neurons, as seen in HS (22). In addition, chemoanatomical studies show that "vulnerable" sectors of the hippocampus are rich in kainate (endfolium and sector CA3) and NMDA receptors (sector CA1) (21).

In the context of inflammatory mechanisms (autoimmune encephalitis), significant heterogeneity of the cascade of pathophysiological events was also demonstrated.

In the cascade where the antigens are intracellular (anti-Hu, anti-GAD), the process is mediated by a cytotoxic T-lymphocyte reaction targeting hippocampal neurons. On the other hand, in the case of encephalitis with antibodies to the complex of voltage-dependent potassium channels expressed on the cell surface, the essence of the mechanism lies in the increase of the frequency of spontaneous depolarization of neurons.

A genetic predisposition to HS is suggested by the frequency of positive family history in patients with HS and the occurrence of familial MTLE associated with HS. Unfortunately, the specific gene in which the genetic abnormality would be directly and essentially related to the pathophysiological process has not been identified.

Although oxidative stress is undoubtedly at play in HS, it is unclear whether this disorder is a cause or effect in epileptogenesis. Our group was the first in the scientific community to show that the antioxidant system functions abnormally in the tissue of operated patients with MTLE associated with HS. More precisely, numerous enzymes of this process (catalase, glutathione peroxidase, glutathione reductase, manganese superoxide dismutase, and copper-zinc superoxide dismutase) show altered activity (23). In the context of our research efforts, the concentration of metals and electrolytes was also studied. It was found that the hippocampi of patients with epilepsy have reduced copper, manganese, and potassium values compared to controls (24). Moreover, it was found that metals (such as zinc, copper, or manganese) have a different distribution in the sectors of the hippocampus in patients with MTLE associated with HS compared to controls (25), which could indirectly indicate that metabolism metal has a specific role in the mechanism of epileptogenesis.

So far, only one thing is clear. HS is a multifactorial disorder; no single pathogenic factor is necessary or sufficient to generate this intriguing histopathological process.

Hippocampal sclerosis - more than one entity

Just as HS can have several recognized causes, the neuropathological concept is diverse. A new one replaced the earlier system of grading the severity of neuronal loss. In addition to the devastation of neurons, the pattern of nerve cell loss was also considered **(Table 1)** (26). The current classification correlates with the postoperative outcome and, to some extent, with the nature of the precipitating events. Unfortunately, although brain MRI can determine the severity of HS, currently, it cannot identify the pathohistological types of HS.

CLINICAL EXPRESSION OF HIPPOCAMPAL SCLEROSIS

Different causality, quite logically, can also cause different clinical pictures. There are three clinical entities in which HS is present. Without exception, the most important entity is the MTLE syndrome, in which HS is the central etiological substrate. In MTLE associated with HS, cell loss combined with synaptic reorganization in the hippocampus leads to electrophysiological changes that generate epileptic seizures with typical clinical phenomenology.

In a somewhat rarer epileptological entity-dual pathology, loss of hippocampal neurons occurs secondary to "kindling" by epileptic seizures originating from an epileptogenic lesion localized out of the hippocampus. In terms of the clinical manifestation of epileptic seizures, there are significant overlaps between patients with MTLE and those with dual pathology. Of course, the clinical picture of focal epilepsy primarily depends on the localization of the epileptic network. For this reason, MTLE has the most consistent clinical manifestation, while in the case of dual pathology, it also depends on extrahippocampal changes.

The third and rare clinical entity consists of elderly patients with HS, in whom epilepsy is not part of the clinical picture. In these patients, the crucial clinical presentation is cognitive impairment (so-called dementia with HS). Recent data indicate that this entity may represent part of the spectrum of tauopathy or even frontotemporal dementia (27).

The characteristic clinical syndrome of MTLE is mainly an expression of the fact that HS is a highly ep-

Table 1. The International League Against Epilepsy (ILAE) Classification of Hippocampal Sclerosis

Type 1	CA 1: > 80% cell loss CA 2: 30 - 50% cell loss CA 3: 30 - 90% cell loss CA 4: 40 - 90% cell loss The dentate gyrus (DG) is usually affected by 50–60% granule cell loss: 50 - 60%
Type 2	This type presents histopathologically with predominant neuronal loss in CA1, affecting almost 80% of pyramidal cells. All other sectors show mild cell loss barely visible by qualitative microscopic inspection, that is, in CA2 < 20%, in CA3 < 20%, and in CA4 < 25% of principal cells.
Type 3	This type 3 shows predominant cell loss in CA4 (approximately 50% cell loss) and the dentate gyrus (35% cell loss), whereas CA3 (<30%), CA2 (<25%), and CA1 (<20%) are only moderately affected
Type 4	Histopathologically do not show significant neuronal cell loss with only reactive gliosis

ileptogenic lesion that selectively affects one region of the brain, i.e., the hippocampus and immediate cortical structures. More specifically, no other epileptogenic lesion consistently affects a single anatomical region. The significant uniformity of the clinical manifestation of MTLE with HS was defined earlier (28), which allowed this syndrome to be viewed today as a paradigm of focal epilepsy. The typical clinical picture of MTLE with HS has several phases, some of which may be absent in individual patients: 1) febrile attacks in early childhood (<5 years) occur in up to 80% of patients. In a smaller percentage (about 30%), symptomatic epileptic seizures occur due to a CNS infection. Febrile attacks are atypical, i.e., complicated, with a duration longer than 30 minutes or occurring in a series of attacks in one febrile episode. Focal signs in atypical febrile attacks, such as Todd's paresis, are common but, unfortunately, rarely documented; 2) the latent period (in which antiepileptic therapy is often discontinued) until the onset of afebrile attacks lasts on average around 7.5 years (from 1 month to 31 years); 3) initial afebrile secondary GTCS rarely occur (28%) and are usually well controlled with lower doses of antiepileptic drugs. As a rule, after the cessation of such attacks, focal attacks occur in which full pharmacoresistance is manifested (almost 90%) (29). Secondary GTCS are rarely continuously present during the disease (12%), and even in about half of the patients, this type of attack will never occur; 4) initial afebrile focal seizures with typical semiology that occur after a latent period are refractory to high doses of antiepileptic drugs and occur in about 2/3 of patients. The average frequency of such attacks is about 13 per month.

Abdominal (epigastric) aura, which is one of the most typical initial clinical signs of epileptic seizures in MTLE syndrome associated with HS, is determined by electrical activation of the insula, not the hippocampus, which is best proven by registration from deep electrodes placed in both of these structures (Patrick Chauvel, personal communication). Electrical stimulation of the hippocampus with deep electrodes did not lead to any manifestation. Therefore, stimulation of the anteroinferior part of the insula consistently produced a specific sensation in the epigastrium region, which then had an ascending flow. Also, the very common affective, psychic aura of fear is most likely produced in the amygdala. The gustatory aura, in case of MTLE, is produced by an electrical discharge in the anterior or middle part of the insular cortex, where neurons sensitive to gustatory impulses are typically located (30).

On the other hand, the olfactory aura is produced by activation in the anteromedial temporal region (uncus, piriform cortex, or amygdala), proximal to the olfactory bulb in the orbitofrontal cortex or the region of the anterior insula. Apart from the mentioned auras, one of the most typical objective signs in the manifestation of epileptic attacks in MTLE are oroalimentary automatisms (OAA). They represent stereotypic actions involving the mouth, tongue, and throat and can mimic normal behaviors such as chewing, swallowing, or smacking. Data from deep electrode studies show that the appearance of OAA in attacks originating from the anterior and medial temporal lobes depends on their spread to insulo-opercular areas, especially their anterior part (e.g., anterior insula and frontal operculum). OAAs were not observed when the electrical spread was limited to the medial structures of the temporal lobe but became visible only after the spread involved the insulo-opercular regions bilaterally (31). The typical semiology of focal seizures in MTLE

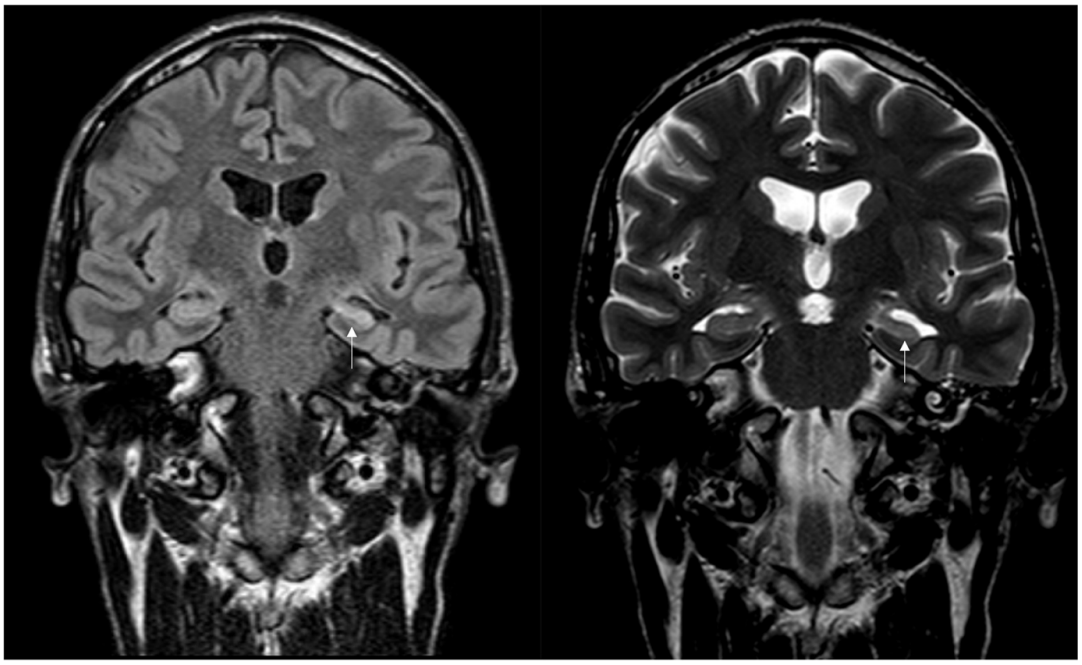

Figure 3. Brain MRI showing left hippocampal sclerosis (white arrow) on FLAIR and T2-weighed sequences on coronal slices.

associated with HS also includes a dystonic hand position (seen in almost all patients with this syndrome) (32, 33). It occurs contralateral to the epileptogenic zone and automatisms (usually hands and, less often, the legs) that are ipsilateral to the epileptogenic zone (34). Dystonia is defined as forced and prolonged, unnatural positioning of an arm or leg on one side of the body, either in flexion or extension, proximally or, more often, distally and usually with a rotatory component. Automatisms are characterized by stereotyped and purposeless involuntary movements more dominantly manifest distally. Although the lateralizing and localizing value of the described signs is only moderate if they occur individually, it is important to note that their combined manifestation - dystonia contralateral to the epileptic focus and automatism ipsilateral to the epileptic focus - is a reliable sign of MTLE associated with HS that carries a significant lateralization value (34).

DIAGNOSTIC METHODS

Magnetic resonance (MRI) enables the detection of HS in vivo, without which diagnosing the syndrome of MTLE associated with HS is unthinkable. Initial MRI examinations of patients with epilepsy during the early 80s did not detect HS. However, improvements in scanning techniques have enabled highly reliable detection of HS in the following years. This primarily refers to a special protocol for patients with MTLE. Such a protocol includes coronary sections perpendicular to the longitudinal axis of the hippocampus, the use of thin sections (e.g., 1 to 3 mm), and the application of IR (Inversion Recovery) and FLAIR (Fluid Attenuated Inversion Recovery) in addition to standard T1 and T2 sequences. MRI features of HS include hippocampal atrophy (from 90 to 95%), increased signal intensity on T2 and FLAIR sequences (80 to 85%), loss of internal structure with loss of hippocampal digitations predominantly seen on T2 sequences (60 to 95%) and signal reduction on T1 sequence (10 to 95%) **(Figure 3)** (35). Associated MRI features seen in HS are: 1) enlarged temporal horn of the lateral ventricle, 2) hypotrophy of the ipsilateral temporal lobe, 3) hypotrophy and increased T2 signal intensity in the amygdala, and 4) reduction of the gray and white matter demarcation of the temporal lobe (especially the temporal apex). In addition to qualitative analysis, HS can be detected by quantitative analysis, the so-called hippocampal volumetry. Although volumetrics can also be done by visual analysis, today, very advanced and precise software techniques exist (36). Positron emission tomography (PET) enables the examination of cerebral glucose metabolism in vivo. PET in patients with epilepsy mainly uses fluoro-2-deoxyglucose (FDG) as a ligand, and rarely 11C-flumazenil (FMZ), which binds to the central benzodiazepine receptor, is used. Brain MRI mainly limited the use of PET in patients with MTLE to rare cases in which HS was not recorded by MRI examination. FDG-PET shows multiregional hypometabolism of ipsilateral medial/lateral temporal lobe (90 to 95%), contralateral medial/lateral temporal lobe (10 to 40%), ipsilateral thalamus (60 to 80%), ipsilateral basal ganglia (40 to 50%), ipsilateral insula (40 to 60%), ipsilateral basal frontal lobe (20 to 30%), ipsilateral parietal lobe (20 to 30%), and ipsilateral occipital lobe (0 to 4%) (35). However, this proportion of hypometabolism regions in the brain is related to MTLE associated with HS and to "non-lesional" MTLE, MTLE associated with vascular changes or cortical organization disorder, or neocortical temporal lobe epilepsy. FMZ binds reduced to the hippocampus and, to a lesser extent, to the ipsilateral insula and thalamus. Areas of reduced FMZ binding on FMZ-PET are usually smaller than glucose hypometabolism detected on FDG-PET.

CONCLUSION

Current neurological science considers HS as both the cause and the consequence of epilepsy. It symbolizes much more than neuronal extinction restricted to the hippocampus. HS is the most frequently encountered cause of refractory temporal lobe epilepsy. MTLE due to HS is a surgically remediable focal epilepsy syndrome. HS is often associated with complicated febrile convulsions early in life, less commonly following non-febrile status epilepticus in infancy, but also as a consequence of CNS infections. The lower prevalence of HS in early childhood indicates that HS is part of a multistage/progressive condition (with an early initial injury followed by a long-lasting latent period prior to the development of chronic refractory epilepsy). Typical brain MRI features of a sclerotic hippocampus are a high signal on FLAIR and T2-weighted images, a low signal on T1-weighted images, and atrophy (volume loss). HS is characterized by neuronal death and alterations in neuronal connectivity and network behavior that underlie the development of chronic epilepsy and memory deficits.

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HIPOKAMPUSNA SKLEROZA

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Sažetak

Hipokampusna skleroza je jedna od najčešćih uzroka fokalne epilepsije. U isto vreme hipokampusna skleroza je i najčešći hirurški supstrat kod fokalnih farmakorezistentih epilepsija. Hipokampus poseduje specifičnu anatomsku strukturu koja se sastoji od ukupno četiri sektora. U fiziološkom konteksu hipokampus je veoma važan u nizu neuropsiholoških procesa, pa je hipokampusna skleroza (entitet koji je prepoznat i povezan sa epilepsijom još u XIX veku) veoma zanimljiva u istraživačkom smislu. Patohistološki obrazac hipokampusne skleroze danas je vrlo precizno predstavljen, što pomaže u uniformnom prepoznavanju. Uzroci hipokampusne skleroze nisu poznati ali su do sada prepoznati brojni faktori koji su udruženi sa nastankom ovog patološkog procesa. Nema nikakve sumnje da je ekscitotoksičnost ujedno sa izmenama u redoks sistemu najvažniji patofiziološki mehanizam. Hipokampusna skleroza je klinički veoma prepoznatljiva. Oboleli od epilepsije u čijoj je osnovi hipokampusna skleroza ima veoma tipične epileptične napade koji se sastoje od epigastrične aure iza koje sledi fokalni epileptični napad kojeg karakterišu pomućenje svesti i oroalimentarni automatizmi. Danas je zahvaljujući modernom neuroimidžingu (prvenstveno magnetnoj rezonanci) detekcija ovog patološkog obrasca veoma precizna i nedvosmislena.

Ključne reči: hipokampusna skleroza, epilepsija, magnetna rezonanca

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