HIPPOCAMPAL SCLEROSIS – CAUSE OR CONSEQUENCE OF MESIAL TEMPORAL LOBE EPILEPSY IN CHILDREN?

Adriana Gabriela Albeanu[1], Sanda Magureanu[2], Dana Craiu[2], Lieven Lagae[3]

[1]Hiperdia Clinic, Brasov

[2]Department of Pediatric Neurology. "Al. Obregia" Clinical Hospital, Bucharest

[3]Department of Pediatric Neurology, University Hospitals KULeuven, Leuven, Belgium

ABSTRACT

Mesial temporal lobe epilepsy with hippocampal sclerosis is a well defined epileptic syndromic entity, especially in adults. In pediatric population, this syndrome has been less well studied, probable because of the particular electroclinical features of temporal seizures in children. This article reviews evidence for and against the causal relationship between hippocampal sclerosis and mesial temporal lobe epilepsy and offer some insights in the etiology and pathogenesis of hippocampal sclerosis.

Key words: hippocampal sclerosis, epilepsy, children

THE CONCEPT OF MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

The mesial temporal lobe epilepsy (MTLE) was described in detail as an entity consisting of seizures that are originated in limbic areas of the mesial temporal lobe, particularly in the hippocampus, amygdala and the parahyppocampal gyrus. The histopatological hallmark is hippocampal sclerosis (HS). It is the most common pathology identified in adult patients who require surgical intervention for epilepsy (1).

Thus, a subcommission of the International League Against Epilepsy, chaired by Heinz-Gregor Wieser, clearly defined MTLE with HS as a syndromic entity that is a subtype of the greater syndrome of MTLE. However, no consensus was reached, regarding some particular features of MTLE with HS, such as the progressive nature of HS, genetic predisposition and the variability of the "initial precipitating incidents" (IPI) during the history of the patient (febrile seizures – FS, hypoxia, trauma, intracranial infection) (2).

In its classical presentation, MTLE with HS is characterized by an association with febrile seizures or other insults during early life (usually under the age of 5 years) (2), the clinical picture consisted of mesiotemporal lobe seizures that are initially controlled by antiepileptic medication, but progressively become medically intractable (3). Also, interictal and ictal electroencephalography (EEG) abnormalities are localized around the anterior and basal temporal lobe regions, magnetic resonance imaging (MRI) demonstrated unilateral hippocampal atrophy and/or abnormal signal intensity and a normal contralateral hippocampus and functional neuroimaging data and neuropsychological tests which also point to the mesiotemporal structures (3).

THE NATURAL HISTORY OF MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

The natural history of a disorder is defined by the course from onset of the disorder without intervention until the disorder resolves or death ensues. Thus, little data exist about the natural history of MTLE with HS, because the majority of the infor-

Author for correspondence:
Adriana Gabriela Albeanu, MD, 0729018501, Hiperdia Clinic, Calea Bucuresti street, no 27A, Brasov, Romania
e-mail: adriana.albeanu@yahoo.com

mation derived from surgical series (4). The following features characterize the natural history of MTLE with HS: (1) history of IPI; (2) family history of MTLE; (3) the presence of a latent and silent period, even if there are insufficient data to sustain this two last features (5,2). In contrast, it was acknowledged that the clinical picture and the investigations, other than MRI, help to differentiate MTLE with HS from other forms of MTLE, underlining the importance of natural history in the clinical diagnosis of MTLE. Moreover, the type of IPI, especially the presence of FS, and the time at which an IPI occurs, are reportedly of high prognostic value, regarding the response to medical treatment and postsurgical seizure outcome (5,2,4).

It is very important to distinguish two different forms of MTLE with HS: one with onset in childhood and adolescence and one with onset in adults (5). Recent studies revealed that these two different forms are caused by a different set of etiologies (6,7).

We considered that the detailed description of the etiological and pathophysiological aspects of the MTLE with HS with onset in childhood and adolescence is very important because this can explain the multiple gaps that we have in our understanding of how HS develops. The major question still remains if temporal lobe seizures are the cause of HS or HS generate seizure activity in mesial temporal regions (8).

CAUSATIVE FACTORS OF MESIAL TEMPORAL LOBE EPILEPSY WITH HIPPOCAMPAL SCLEROSIS

The majority of studies from surgical series demonstrated the high incidence of IPI, represented by febrile seizures, cerebral trauma, hypoxia or intracranial infections in the personal histories of patients with MTLE with HS (2, 9, 10).

Between these IPI, the majority of controversies are around prolonged febrile seizures (FS). Beginning with Falconer et al. (11), the majority of retrospective studies revealed that up to half of the patients with MTLE – HS have a history of prolonged FS in early childhood (12). Moreover, the magnetic resonance imaging (MRI) studies had demonstrated specific abnormalities at the hippocampal level after complex FS, especially if the MRI was performed shortly after the seizures (13,14).

Conversely of studies from tertiary surgical centers that demonstrated an increased incidence of FS in the history of patients with MTLE-HS, prospective and population-based retrospective studies showed that, only in rare cases, FS were followed by the development of HS (15). Indeed, Tarkka et al demonstrated that the occurrence of HS following even prolonged FS is an uncommon event (16).

In general, simple FS don't have any adverse effect on the brain. In contrast, complex FS have been associated with MTLE in the majority of studies (17). More recently, it was demonstrated that a history of simple FS can be associated with hippocampal abnormalities in adults that are not necessarily epileptogenic (18).

Different from complex FS, the presence of febrile status epilepticus (SE) indicates the major risk for development of subsequent hippocampal sclerosis (19). There are two hypotheses that explain the possible relationship between febrile SE and MTLE. The first one postulates that the febrile SE causes acute hippocampal injury that later evolves in HS and MTLE. The second one states that both febrile SE and MTLE are based of an already injured hippocampus or a genetic predisposition (20). From the beginning, these two possibilities are difficult to demonstrate firstly because the development of MTLE is a progressive process with a long duration after the initial febrile SE and secondly because is not possible to determine the existence of an occult brain injury or developmental abnormalities before the initial febrile SE (19).

A great number of studies used MRI data to explain the link between febrile SE and MTLE – HS. In the beginning there were some case series that showed T2 signal changes in the children hippocampi immediately after febrile SE (21). Prospective studies revealed preexisting hippocampal pathology and it was suggested that the rapid development of HS after febrile SE may be in fact an underlying developmental disorder or the result of a prior insult (22). After that, the longitudinal studies of Scott et al. also demonstrated changes of hippocampal volume immediately (hippocampal edema) and 6-8 months after febrile SE (hippocampal atrophy) (23,24).

Although the prior studies have not clearly shown the development of HS after febrile SE, Provenzale et al. demonstrated the existence of hyperintense hippocampal signal intensity on T2-weighted MR images immediately after febrile SE that was associated with subsequent hippocampal volume loss and persistent abnormal signal intensity on T2-weight images (25).

Other clinical studies (26) and some animal models (27) also suggested that preexisting brain

abnormalities may predispose to prolonged seizures. Subtle cortical dysplasia or others developmental hippocampal abnormalities may exist in patients with latter evidence of HS (26).

The FEBSTAT study, a large, prospective, multicentre clinical study that was investigated the risk factors and outcome in patients with febrile SE, indicates that the majority of patients have a focal onset of their SE (28). Moreover, this may reflect the possibility that FS has a focal limbic origin and these may be named secondarily generalized hippocampal seizures (29). Animal models sustained this theory, because the studies showed the appearance of "limbic seizures" at low and high dose of seizure precipitants and generalized motor seizures with secondary hippocampal damage (30).

Now, multiple evidence indicates that a genetic predisposition increases the susceptibility to both, prolonged seizures and seizure-induced hippocampal damage (13).Thus, the monozygotic twins studies revealed a risk of SE of 38% among the cotwins, if the other twin experienced SE (31).

It is known that the majority of febrile seizures exhibit complex genetic inheritance due to multiple gene and environmental factors. There are several chromosomal loci (FEB 1–10) that determined familial FS (32). Moreover, a mutation was identified in SCN1A gene at the FEB 3 locus in individuals that present afebrile seizures and subsequently develops MTLE (33). Mutations in SCN1A gene are frequently seen in generalized epilepsy with febrile seizures plus (GEFS+) (34). The "classic" phenotype of GEFS+ consists of FS that persists beyond six years of age, but only in rare cases, the TLE may be part of GEFS+ phenotype, with the implication of the SCN1B gene (35). There was only one report of a proband with persisting FS beyond six years of age that subsequently developed refractory MTLE with the MRI evidence of HS (36).

Another strong evidence in favor of the genetic background is also the existence of a familial form of MTLE (FMTLE). In fact, there are two different subtypes of FMTLE: a benign form of FMTLE without a history of FS and without HS on MRI and a form of FMTLE with MRI evidence of HS and/or FS in antecedents (37). Indeed, the majority of studies about FMTLE demonstrated a polygenic inheritance of this epileptic syndrome and a great intra and interfamilial variability (38, 39). The most important aspect remains the hippocampal atrophy that was seen in 88% of cases with refractory FMTLE and in only 65% of benign cases. However, the MRI evidence of HS was also observed in some family members who had a benign course of the disease and occasionally even in members with no history of epilepsy (40). Thus, it may be supposed that the HS in FMTLE does not develop as a consequence of repeated seizures, even if in sporadic refractory MTLE frequent seizures may cause progression of HS (26).

In the etiology of MTLE – HS may be implicated other IPI, different by FS and febrile SE, and these are trauma and intracranial infection, but their incidence is much lower then that of FS in studies of HS in children (41). Frequently, these IPI are the cause of prolonged and recurrent seizures, even SE that clearly predisposes to the development of HS (42). A case was described with bilateral HS after a non-paraneoplasic limbic encephalitis that was recognized as a precipitating factor of MTLE only in adults (43).

TEMPORAL LOBE EPILEPTOGENESIS AND THE DEVELOPMENT OF HIPPOCAMPAL SCLEROSIS

The general assumption is that refractory MTLE with HS is an acquired process after an IPI during early life, with a variable latent period until the appearance of clinical epilepsy (44). Early studies demonstrated that this initial "pre-epileptic" state and duration reflect the length of a slowly, progressively developing process of hippocampal epileptogenesis (45). After the initial injury, the brain is not immediately "epileptic" because a delayed secondary process is needed to mature. In contrast, the immediate result of the neuronal loss that characterizes the HS may be an epileptogenic network imbalance that determines even the latter seizures through a "kindling" mechanism (45, 46). It is not clear if the duration of the latent period is, in fact, a reflection of the duration of the epileptogenic process, because it is very difficult to study a molecular or structural process that necessitated up to 30 years to mature (45).

Many authors tried to answer to the multiple questions and this led to the search for molecular, cellular and network changes in human HS. The possible mechanisms of hippocampal epileptogenesis were categorized into three major groups: changes of synaptic properties (synaptic reorganization of the mossy fiber system), changes of inhibitory and excitatory neurotransmission and alterations of the intrinsic properties of neurons (1). Recently, it was demonstrated that in addition to the neuronal changes, glial activation plays a very important role in epileptogenesis (47). Moreover, astrogliosis is one of the major pathologic features of HS (2).

Due to difficulty encountered in studying human patients, a lot of experimental animal models were created in order to understand the epileptogenic process of HS. However, there have been many difficulties for the creation of an "ideal "animal model that involves the pathology and pathophysiology of the MTLE with HS (45).

The majority of the animal models were used to explain the relationship between the prolonged FS and the development of TLE (48). Initially, it was attempted to demonstrate the role of the predisposing factors (dysplasia, brain injury, ion channel mutations) in the host brain on limbic epileptogenesis. Indeed, in the presence of these predisposing factors, FS affects the brain differently, including the risk for subsequent epilepsy (49). In contrast, FS occurs even in normal children, who have no evidence of any of the predisposing factors. The majority of studies demonstrated that the duration of seizures was statistically correlated with the epileptogenesis (23, 24). Thus, a series of animal models were created to demonstrate that the duration of FS contribute to the initiation of the epileptogenic process and was found that the duration of the febrile SE – like seizures influenced the incidence and the severity of limbic epilepsy in rats (50).

Clinical studies failed to clarify the relationship between hippocampal cell loss and epileptogenesis after prolonged FS in humans. Two hypotheses have been advanced. The first one is that FS caused HS and the development of MTLE is a consequence of HS (25, 24, 22). The second one is that MTLE after FS may precede the development of HS and this is determined by the recurrent seizures (51,13). The animal model created to sustain one of these two hypothesis had revealed three important aspects: (1) functional alterations of neuronal properties and network imbalance might take place in the absence of progressive structural changes (neuronal loss, sprouting) and result in epilepsy; (2) HS in individuals with TLE and febrile SE in antecedents might be not a cause, but a consequence of epilepsy; (3) the acute increased of T2 relaxation time in children immediately after febrile SE might not indicated acute neuronal loss (49).

Other studies showed that inflammation might play an important role in hippocampal epileptogenesis after febrile SE. During FS, fever increases brain temperature, but also determine the release of inflammatory mediators, particularly interleukin-1β (IL-1β) within the brain (52). Some authors revealed even a polymorphism in the interleukin-1β gene in patients with TLE and HS (53). Another interesting aspect was that fever in a context of a specific viral etiology, human herpes virus 6 (HHV 6), increased the probability of generation of FS (54). Also, evidence of HHV6 infection has been found in resected tissue from individuals with HS (55).

Animal models tried to elucidate the theory that IL-1β can contribute to the epileptogenic process initiated by FS and it has revealed an interesting aspect, namely hippocampal IL-1β levels were higher only in rats that developed epilepsy after FS (50). It was also demonstrated that experimental febrile SE induces numerous molecular changes in the expression of specific genes such ion channels and endocannabinoid receptors in neurons from the mesiotemporal regions (56,57).

In summary, an initial brain insult, especially prolonged FS and febrile SE, produced brain changes that promote epilepsy, changes that take place at multiple levels, are induced by inflammatory mediators and are driven by transcriptional mechanisms. The elucidation of the epileptogenic mechanism will play an important role in prevention and successful therapeutic intervention in MTLE.

SOME PATHOLOGICAL FEATURES OF HIPPOCAMPAL SCLEROSIS

From a neuropathological point of view, HS is defined by the characteristic features: gliosis and neuronal loss. These are found in all hippocampal regions, but also in the subicular region, parahippocampal gyrus and infero-medial temporal cortex (1). The most affected hippocampal regions are CA1 and CA3, CA2 region and the dentat gyrus were spared. Another features associated with HS are also granule cell dispersion and mossy fiber sprouting. The synaptic reorganization is often presented and it is not limited to mossy fibers and granular layer of dentat gyrus (1). Frequently, the hippocampal pathology is associated with an extrahippocampal one, especially in the amygdala, where neuronal loss and gliosis affects the laterobasal nuclear complex (amygdala sclerosis). In the temporal lobe white matter, it is possible to have ectopic neurons and perivascular oligodendrocyte-like infiltrates (2).

Beginning with Sommer that realized the first detailed description of the HS in 1880, multiple others studies confirmed the histopathological characteristics of HS, but also demonstrated the exis-

tence of some atypical models of HS, associated abnormalities in others mesiotemporal structures, occult second dual pathology and bilateral HS (58).A classification was done for one of the most frequent patterns of HS: (1) *type 1a*, classical HS, (2) *type 1b*, severe HS, (3) *type 2*, CA1 sclerosis and (4) *type 3*, end folium sclerosis (59). With the help of this histopathological classification some clinicopathologic correlations with the postsurgical outcome were constructed. Thus, the duration of epilepsy and the frequency of seizures are not correlated with the histopathological type of HS, but this is correlated with the age of IPI appearance. An early age of IPI (IPI<3 years) is a predictor of a severe hippocampal pathology, whereas IPI at a later age are correlated with a less extensive hippocampal pathology (59). The data confirms the earlier hypothesis that the developing brain is more prone to epileptogenic neurotoxicity compared to more mature hippocampal neurons and network (60).

In a proportion of patients with HS, the intracranial depth electrode recording revealed that the epileptiform activity is a more widespread area involving both mesial and lateral temporal lobe regions (61). The neuroimaging and neuropathological studies well established that HS can be associated with a second temporal lobe epileptogenic pathology, like cortical dyslamination, ectopic white matter neurons and low grade glio-neuronal tumors (62). This was called "dual pathology" and it was demonstrated that, in this case, it is a less severe hippocampal neuronal loss (HS type 3) (59,63).The successful surgical removal of both lesions indicated that each one contributes to the genesis of seizures. Moreover, this association also raises the question of a common predisposing malformative process for both lesions (64).

In children, the majority of studies revealed a high incidence of the dual pathology comparative with adults, without making a clear difference between the associated cortical malformations (heterotopia vs. cortical dysplasia) (10,65). Recently, a group of pediatric patients with heterotopia associated with HS was described and it was showed that the relationship between HS and focal cortical dysplasia is more complex in pediatric population (66).

CASES PRESENTATION

We want to present two typical cases of children with MTLE with HS, one in which MTLE is a consequence of HS and another one in which MTLE is a cause for HS.

Case 1

The case of a 12 years old boy, right handed, without epilepsy in the family. After an inconclusive perinatal history and a normal psycho-motor development, he had two febrile seizures at the ages of 8 and 17 months. Epilepsy started at the age of 4 years with a prolonged left focal seizure. MRI performed at 2 weeks after this seizure revealed a right hippocampal edema. He experienced the second seizure after two months with short epigastric aura, staring, clonic movements of left arm, unresponsiveness. He continued to present rare seizures (1 seizure per year) on valproic acid monotheraphy for 2 years.

After that the seizure frequency increased despite the treatment with two antiepileptic drugs. The MRI revealed a right HS. The EEG showed right anterior temporal spikes as well as right temporal slowing. During long-term video-EEG monitoring, habitual seizures were recorded exclusively with right temporal seizure pattern on ictal EEG. Moreover, ictal and interictal SPECT and SISCOM analysis confirmed the right anterior temporal epileptic focus. The neuropsychological evaluation revealed a memory deficit for visual patterns that is compatible with a right mesio-temporal lesion.

At the age of 7 years and 6 month a right amygdalohippocampectomy was performed. In the first year after surgery, he experienced some epigastric aura, but after that he remained seizure free for five years.

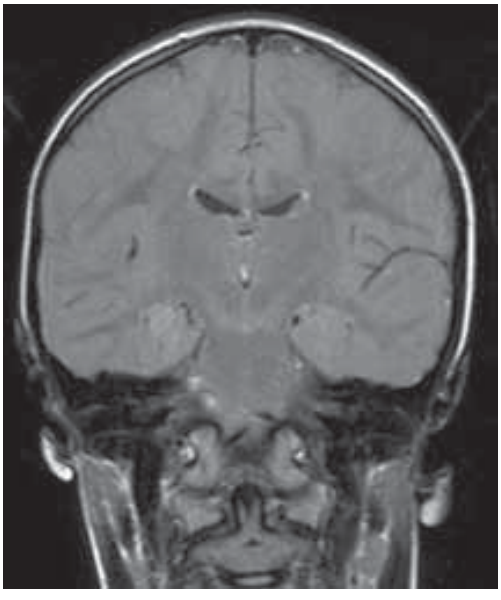

Figure 1. *Case 1 – presurgical MRI*

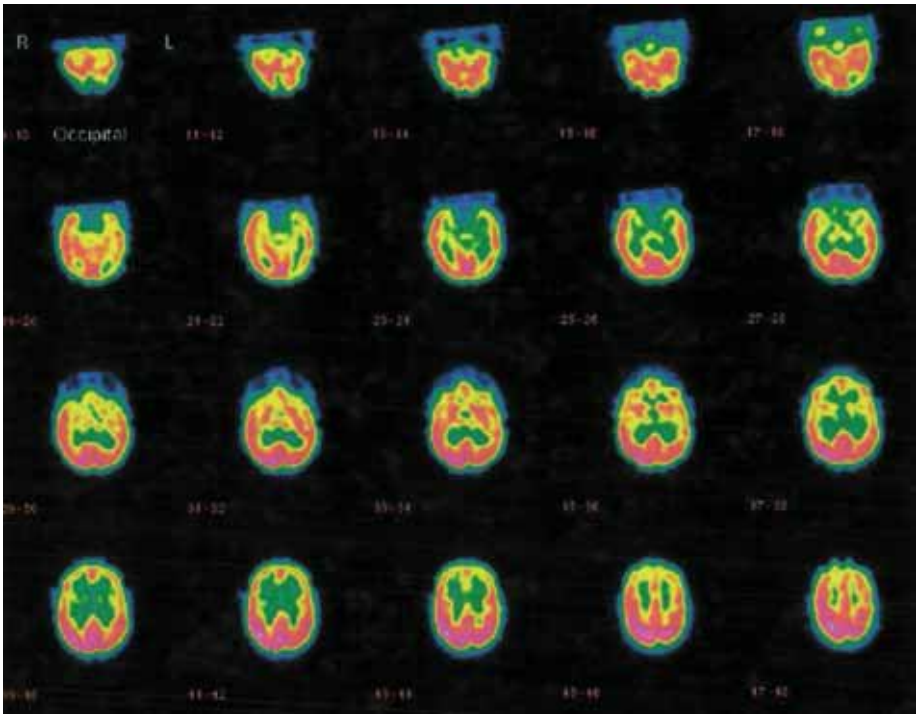

Figure 2. *Case 1 – ictal SPECT*

Case 2

The case of an 9 years old boy, right handed, with the family history positive for epilepsy. He presented a normal perinatal history, a normal psycho-motor development and no others significant events in his personal antecedents. He started to experience complex focal seizures at the age of 5 years. At this moment the MRI was normal. Soon after the onset, the seizures frequency increased and the child presented two types of seizures: short seizures with staring, unresponsiveness, vocalization and longue seizures with staring, pallor, oro-alimentary automatisms and right head deviation. At the age of 7 years the MRI revealed abnormal heterogeneous signal intensity in left anterior temporal pole (possible cortical dysplasia) and also a discreet HS. The interictal EEG showed a left anterior temporal focus and the long-term video-EEG monitoring recorded his habitual seizures and confirmed by ictal EEG the left anterior-temporal focus. Ictal, interictal SPECT and SISCOM demonstrated also the left anterior-temporal focus. The functional MRI showed left lateralization at the verbal fluency tasks. The neuropsychological evaluation revealed a QI 90 and material specific verbal memory deficit.

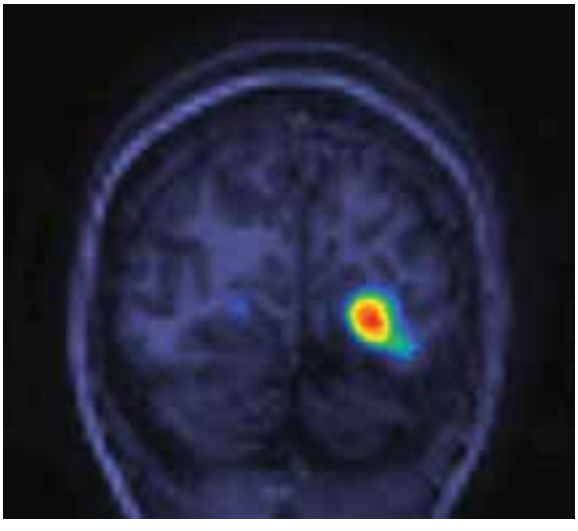

Figure 3*. Case 2 – presurgical MRI*

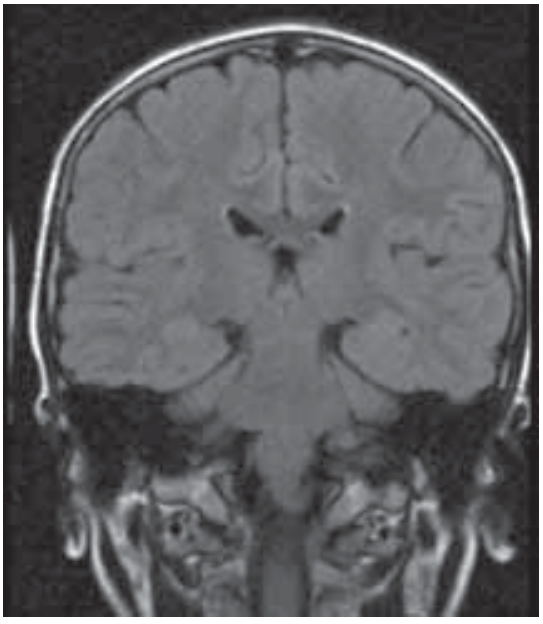

Figure 4. *Case 2 – presurgical f MRI*

Because the presurgical evaluation was compatible with the left anterior temporal focus, at the age of 8 years a left anterior temporal lobectomy and amygdalohippocampectomy were performed. The histopathological evaluation confirmed a microdysgenesis of temporal neocortex and endfolium sclerosis (type 3 HS). After surgery, the children presented only few auras for 1 year.

CONCLUSIONS

Since its discovery in the 19th century, much has been learned about hippocampal sclerosis, but despite many decades of basic and clinical research, there are still unanswered question about the causality between hippocampal sclerosis and mesial temporal lobe epilepsy. It is likely that the pathogenesis of hippocampal sclerosis is multifactorial and a genetic predisposition increases the individual's susceptibility to the development of HS. A better understanding of the epileptogenic process of HS will provide opportunities for discover new preventive and therapeutic strategies.

REFERENCES

1. **Mathern GW., Wilson CL., Beck H.** – Hippocampal sclerosis In: Engel J., Pedley TA. *Epilepsy: a Comprehensive Textbook*. Second edition. Lippincott Williams & Wilkins. 2008:120-137
2. **Wieser H.G.** – ILAE Commission on Neurosurgery of Epilepsy. Mesial temporal lobe epilepsy with hippocampal sclerosis. *Epilepsia.* 2004; 45:695-71
3. **Cendes F., Kahane P., Brodie M., et al.** – The mesio-temporal lobe epilepsy syndrome In Roger J., Dravet C., Genton P. et al. *Epileptic syndromes in infancy, childhood and adolescence*. Third edition. John Libbey & Co Ltd. 2002:513-530
4. **Berg A.T.** – The natural history of mesial temporal lobe epilepsy. *Curr Opin Neurol*. 2008. 21:173-178
5. **Rosenow F., Noachtar S.** – Mesial temporal lobe epilepsy: natural history and seizure semiology In Rosenow F., Ryvlin P., Lüders H. *The Mesial Temporal Lobe Epilepsies*. Editions John Libbey Eurotext. 2011:59-70
6. **Bocti C., Robitaille Y., Daidori P. et al.** – The pathological basis of temporal lobe epilepsy in childhood. *Neurology*. 2003.60:191-195
7. **Bien C.G., Urbach H., Schramm J., et al.** – Limbic encephalitis as a precipitating event in adult-onset temporal lobe epilepsy. *Neurology*. 2007.69:1236 -1244
8. **Fisher P.D., Sperber E.F., Moshé S.L.** – Hippocampal sclerosis revisited. *Brain Dev*. 1998.20:563-573
9. **Mohamed A., Wyllie E., Ruggieri P. et al.** – Temporal lobe epilepsy due to hippocampal sclerosis in pediatric candidates for epilepsy surgery. *Neurology*. 2001.56:1643-1649
10. **Smyth M.D., Limbrick Jr. D.D., Ojemann J.G., et al.** – Outcome following surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children: emphasis on mesial temporal sclerosis. *J Neurosurg.* 2007.106(3):205-210
11. **Falconer M.A., Serafetinides E.A., Corsellis J.A.** – Etiology and pathogenesis of temporal lobe epilepsy. *Arch Neurol.* 1964.10:233-248
12. **Cersósimo R., Flesler S., Bartuluchi M., et al.** – Mesial temporal lobe epilepsy with hippocampal sclerosis: study of 42 children. *Seizure* 2011.20:131-137
13. **Shinnar S.** – Febrile seizures and mesial temporal sclerosis. *Epilepsy Curr.* 2003. 3:115-118
14. **Tanabe T., Hara K., Shimakawa S., et al.** – Hippocampal damage after prolonged febrile seizures: One case in a consecutive prospective series. *Epilepsia*. 2011. 52(4):837-840
15. **Berg A.T., Shinnar S., Levy S.R., et al.** – Childhood-onset epilepsy with and without preceding febrile seizures.*Neurology*. 1999.53:1742-1748
16. **Tarkka R., Paakko E., Phytinen J. et al.** – Febrile seizures and mesial temporal sclerosis: No association in a long-term follow-up study. *Neurology*. 2003.60(2):215-218
17. **Scantlebury M.H., Heida J.G.** – Febrile seizures and temporal epileptogenesis. *Epilepsy Res.* 2010. 89:27-33
18. **Auer T., Barsi P., Bone B. et al.** – History of simple febrile seizures is associated with hippocampal abnormalities in adults. *Epilepsia*. 2008. 49(9):1562-1569
19. **Ahmad S., Marsh E.D.** – Febrile status epilepticus: state of clinical and basic research. Semin Pediatr Neurol. 2010.17:150-154
20. **Cendes F.** – Febrile seizures and mesial temporal sclerosis. *Curr Opin Neurol*. 2004. 17:161-164
21. **Tien R.D., Felsberg G.J.** – The hippocampus in status epilepticus: Demonstration of signal intensity and morphologic changes with sequential fast spin-echo MR imaging. *Radiology.* 1995.194:249-256.
22. **VanLandingham K.E., Heinz E.R., Cavazos J.E.** – Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann Neurol*. 1998.43(4):413-426
23. **Scott R.C., Gadian D.G., King M.D., et al.** – Magnetic resonance imaging fi ndings within 5 days of status epilepticus in childhood. *Brain*. 2002.125:1951-1959
24. **Scott R.C., King M.D., Gadian D.G., et al.** – Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain*. 2003. 126:2551-2557
25. **Provenzale J.M., Barboriak D.P., VanLandingham K., et al.** – Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis. *Am J Roentgenol.* 2008.190(4):976-983
26. **Levis D.V.** – Losing neurons: Selective vulnerability and mesial temporal sclerosis. *Epilepsia*. 2005. 46: 39-44
27. **Germano I.M., Zhang Y.F., Sperber E.** – Neuronal migration disorders increase susceptibility to hyperthermia-induced seizures in developing rats. *Epilepsia*. 1996.37(9):902-910
28. **Shinnar S., Hesdorffer D.C., Nordli Jr. D.R., et al.** – Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. *Neurology*. 2008. 71:170-176
29. **Neville B.G., Gindner D.** – Febrile seizures are a syndrome of secondarily generalized hippocampal epilepsy. *Dev. Med. Child Neurol*. 2010.52:1151-1153
30. **Neville B.G., Gindner D.** – Febrile seizures - semiology in humans and animal models: evidence of focality and heterogeneity. *Brain Dev.* 2010.32:33-36
31. **Corey L.A., Pellock J.M., Boggs J.G.** – Evidence for a genetic predisposition for status epilepticus. *Neurology*. 1998.50:558-560

32. **Bautista J.F.** – Genetics of mesial temporal lobe epilepsy and febrile seizures. In Rosenow F., Ryvlin P., Lüders H. *The Mesial Temporal Lobe Epilepsies*. Editions John Libbey Eurotext. 2011:37-41
33. **Mantegazza M., Gambardella A., Rusconi R., et al.** – Identification of an Na(v)1.1 sodium chanel (SCN1A) loss-of-function mutation associated with familial simple febrile seizures. *Proc Natl Acad Sci*. 2005. 102:18177-18182
34. **Singh R. Scheffer I.E., Crossland K. et al.** – Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. *Ann Neurol.* 1999. 45(1):75-81
35. **Scheffer I.E., Harkin L.A., Grinton B.E. et al.** – Temporal lobe epilepsy and GEFS+ phenotypes associated with SCN1B mutations. *Brain*. 2007.130:100-109
36. **Abou-Khalil B., Ge Q., Desai R., et al.** – Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation. *Neurology*. 2001.57:2265-2272
37. **Gambardelle A., Labate A., Giallonardo AT., et al.** – Familial mesial temporal lobe epilepsies: Clinical and genetic features. *Epilepsia*. 2009. 50:55-57
38. **Crompton D.E., Scheffer I.E., Taylor I., et al.** – Familial mesial temporal lobe epilepsy: a benign epilepsy syndrome showing complex inheritance. *Brain*. 2010.133:3221-3231
39. **Kobayashi E., Lopes-Cendes I., Guerreiro CA., et al.** – Seizures outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy. *Neurology*. 2001.56:166-172
40. **Kobayashi E., Li LM., Lopes-Cendes I.** – Magnetic resonance imaging evidence of hippocampal sclerosis in asymptomatic, first-degree relatives of patients with familial mesial temporal lobe epilepsy. *Arch Neurol*. 2002.59:1891-1894
41. **Ng Y., McGregor AL., Duane DC. et al.** – Childhood mesial temporal sclerosis. *J Child Neurol*. 2006.21(6):512-517
42. **Donaire A., Carreno M., Agudo R., et al.** – Presurgical evaluation in refractory epilepsy secondary to meningitis or encephalitis: bilateral memory deficits often preclude surgery. *Epileptic Disord*. 2007.9:127-133
43. **Kroll-Seger J., Bien C.G., Huppertz H.J.** – Non-paraneoplastic limbic encephalitis associated with antibodies to potassium channels leading to bilateral hippocampal sclerosis in a pre-pubertal girl. *Epileptic Disord*. 2009.11:54-59
44. **Velišek L., Moshé S.L.** – Temporal lobe epileptogenesis and epilepsy in the developing brain: bridging the gap between the laboratory and the clinic. Progression, but in what direction? *Epilepsia*. 2003.44:51-59
45. **Sloviter R.S.** – Hippocampal epileptogenesis in animal model of mesial temporal lobe epilepsy with hippocampal sclerosis: The importance of the " latent period" and other concepts. *Epilepsia*. 2008.49:85-92
46. **Bertram E.** – The relevance of kindling for human epilepsy. *Epilepsia*. 2007.48:67-74
47. **Aronica E., Zurolo E., Iyer A., et al.** – Upregulation of adenosine kinase in astrocytes in experimental and human temporal lobe epilepsy.*Epilepsia*. 2011.52:1645-1655
48. **Dube C., Richichi C., Bender RA., et al.** – Temporal lobe epilepsy after experimental prolonged febrile seizures: prospective analysis. *Brain*. 2006.129:911-922
49. **McClelland S., Dube C.M., Yang J., et al.** – Epileptogenesis after prolonged febrile seizures: mechanisms, biomarkers and therapeutic opportunities. *Neurosci Lett*. 2011.497:155-162.
50. **Dube C.M., Ravizza T., Hamamura M., et al.** – Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers.*J Neurosci*. 2010.30:7484-7494
51. **Mueller S.G., Laxer K.D., Cashdollar N., et al.** – Voxel-based Optimized Morphometry (VBM) of Gray and White Matter in Temporal Lobe Epilepsy (TLE) with and without Mesial Temporal Sclerosis. *Epilepsia*. 200647:900-907
52. **Vezzani A., Baram T.Z.** – New roles for interleukin-1 beta in the mechanisms of epilepsy. *Epilepsy Curr*. 2007.7:45-50
53. **Kanemoto K., Kawasaki J., Myamoto T. et al.** – Interleukin (IL)1beta, IL-1alpha, and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy. *Ann Neurol*. 2000.47(5):571-574
54. **Laina I., Syriopoulou V.P., Daikos G.L., et al.** – Febrile seizures and primary human herpesvirus 6 infection. *Pediatr Neurol*. 2010.42:28-31
55. **Karatas H., Gurer G., Pinar A., et al.** – Investigation of HSV-1, HSV-2, CMV, HHV-6 and HHV-8 DNA by real-time PCR in surgical resection materials of epilepsy patients with mesial temporal lobe sclerosis. *J Neurol Sci.* 2008.15:151-156
56. **Jung S., Warner LN., Pitsch J., et al.** – Rapid loss of dendritic HCN channel expression in hippocampal pyramidal neurons following status epilepticus. *J Neurosci*. 2011.31:14291-14295
57. **Wendt H., Soerensen J., Wotjak CT., et al.** – Targeting the endocannabinoid system in the amygdala kindling model of temporal lobe epilepsy in mice. *Epilepsia*. 2011. 52:62-65
58. **Thom M., Mathern G.W., Cross J.H., Bertram E.H.** – Mesial temporal lobe epilepsy: How do we improve surgical outcome? *Ann Neurol*. 2010.68:424-434
59. **Blumcke I., Pauli E., Clusmann H., et al.** – A new clinico-pathological classification system for mesial temporal sclerosis. *Acta Neuropathol*. 2007. 113:235-244
60. **Salanova V., Markand O., Worth R.** – Temporal lobe epilepsy: analysis of patients with dual pathology. *Acta Neurol Scand.* 2004. 109:126-131
61. **Bartolomei F., Chauvel P., Wendling F.** – Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. *Brain*. 2008.131:1818-1830
62. **Thom M., Eriksson S., Martinian L., et al.** – Temporal lobe sclerosis associated with hippocampal sclerosis in temporal lobe epilepsy: neuropathological features. *J Neuropathol Exp Neurol.* 2009. 68:928-938
63. **Blumcke I., Thom M., Aronica E., et al.** – The clinico-pathological spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostics Methods Commission.*Epilepsia*.2011.52:158-174
64. **Blumcke I.** – Mesial temporal lobe epilepsy: anatomy and neuropathology In Rosenow F., Ryvlin P., Lüders H. *The Mesial Temporal Lobe Epilepsies*. Editions John Libbey Eurotext. 2011: 25-36
65. **Bocti C., Robitaille Y., Daidori P. et al.** – The pathological basis of temporal lobe epilepsy in childhood. *Neurology*. 2003. 60:191-195
66. **Lopez HE., Fohlen M., Lelouch-Tubiana A. et al.** – Heterotopia associated with hippocampal sclerosis: an under-recognized cause of early onset epilepsy in children operated on for temporal lobe epilepsy. *Neuropediatrics*. 2010. 41:167-175