TEMPORAL LOBE EPILEPSY AND GRAND MAL SEIZURES

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PhD Thesis

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ABBREVATIONS

AI: asymmetry index

ABS: absolute value

APR: automatisms with preserved consciousness.

ARBS: ability to react before seizures

HS: hippocampal sclerosis

TLE: temporal lobe epilepsy

CPS: complex partial seizure

FS: febrile seizure

SGTCS: secondary generalised tonic-clonic seizure

SUDEP: sudden unexpected death in epilepsy

MTLE-HS: mesial temporal lobe epilepsy with hippocampal sclerosis

VNS: vagal nerve stimulation

INTRODUCTION

Temporal lobe epilepsy

The prevalence of epilepsy is 0,5- 1%. 60-70% of adult drug resistant epilepsy cases is temporal lobe epilepsy (TLE, Halász, 1997; Janszky et al, 2001). TLE begins in childhood or in young adulthood (Janszky et al, 2004a). In clinical practice, TLE is divided into two forms: mesial and neocortical (French et al, 1993; Ebner, 1994). The new classification of ILAE (International League Against Epilepsy) makes no such distinction, it uses exclusively mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) terminology as an independent epilepsy syndrome. (Berg et al, 2010)

The most frequent seizure type in TLE is the complex partial seizure which is characterised by unconsciousness, manual and oral automatisms. Neither loss of consciousness nor automatisms are mandatory elements of CPS. Automatisms can be of wide variety: squelch, chewing, explorating movement, rhythmic knocking, playing around with fingers, pedal, oral or ambulatory automatisms (Williamson et al, 1993; Wieser et al, 2004). Secondarily generalised tonic-clonic seizure may rarely occur in temporal lobe epilepsy. The interictal EEG often shows uni or bilateral fronto-temporal spike focus (Willamson et al, 1993).

Hippocampal damage, especially hippocampal sclerosis (HS) is the most common pathological abnormality in chronic epilepsy (Babb and Brown, 1987), which can be associated with memory loss due to affecting the mesiotemporal structure.

More than fifty percent of patients with mesial temporal lobe epilepsy with HS (MTLE-HS) had a history of febrile seizure (FS) in childhood (French et al, 1993; Wieser et al, 2004). It is not clear whether the HS is a consequence or the cause of afebrile or febrile seizure.

Drug resistant TLE can be treated by resective epilepsy surgery. The most frequently used surgical procedure is the anterior temporal lobectomy. 60-90% of patients who underwent resective epilepsy surgery will be seizure free in correct surgical indication. The two most important parts of presurgical evaluation are the high resolution MRI using epilepsy protocol and the video EEG monitoring lasting 2-5 days.

Further treatment option is the vagal nerve stimulation (VNS) or deep brain stimulation in the anterior nucleus of thalami (ANT DBS) if the resective epilepsy surgery cannot be performed or is not effective (Müller et al, 2010, Fischer et al, 2010). In Middle Europe, it was first applied at our centre (Bóné et al, 2012).

Generalised tonic-clonic seizure

Reviewing the literature of generalised tonic-clonic seizure (GTCS) there is only a few study deals high scientific fastidiousness. The study of Theodore at al (1994) investigating 120 GTCS of 47 patients is highlighted, which primarily focused on the length and course of the seizure.

GTCS is divided into seven phases: **1. phase:** *simplex partial seizure*. A **2. phase:** CPS or other focal, absence seizure. **3. phase** is defined as onset of generalization as the brief period between the antecedent seizure and remaining phases of GTCS. it was often characterised by versive head or body movement or by vocalisation. **4. phase** This is the *pretonic-clonic phase which is characterised by clonic jerking, often irregular and asymmetric, preceding the tonic phase.* It was termed by „per ictal myoclonic state" by Gastaut and Broughton. **5. phase** The tonic phase is the sustained contraction of all body muscles. Some clonic jerking usually accompanied the increased tone. **6. phase** In this phase of „tremulousness", recurrent decreases in muscle tone begin to interrupt the tonic phase and very-high-frequency clonic jerking begins. Gastaut and Broughton called it „vibratory" phase. The tonic phase, the tremulous phase, and the final (clonic) phase may blend together in a continuum. **7. phase** This a phase of clonic jerking, which is defined as beginning when the jerks can be timed and counted.

In the study of Theodore at al. the mean duration of GTCS (3-7. phases) was 62 second. Marked heterogeneity in GTCS phenomenology was present, only 27% of seizures included all five phases. The clinical phenomena suggest that multiple cortical and subcortical routes of spread may exist.

Generalised tonic-clonic seizure and temporal lobe epilepsy

The typical seizure type in TLE is the CPS which can be generalised. In this case we are speaking about secondarily generalised tonic-clonic seizure (SGTCS). The drug resistance and GTCS are the major risk factors for sudden death (SUDEP) and seizure-related fatal injuries. (Walczak et al, 2001).

SGTCS had a more pronounced impact on the postictal lowering heart rate variability (a potential predictor for sudden cardiac death) than CPS, which might explain why most SUDEP occurs after GTCS (Tóth et al, 2010).

It is important to screen patients suffering from TLE who are at risk for transition from CPS to SCTCS. It is unknown why some TLE patients have potentially life-threatening GTCS, while others have not.

To our knowledge, Rektor et al (2009) were the only ones who investigated the transition from focal-onset seizure to SGTCS, but they exclusively focused on electrophysiological findings. One of the unanswered questions is why some focal seizures propagate to SGTCS, while others do not.

The hippocampus and hippocampal abnormalities

Hippocampal damage and especially hippocampal sclerosis is the most common pathological abnormality in TLE.

Hippocampal sclerosis means neuron loss and secondarily astroglia proliferation. Is is clearly visible in high resolution MRI using epilepsy protocol: atrophy, T2 and FLAIR signal enhancement, T1 signal degradation, internal structure blurring, temporal horn dilatation, fornix and corpus mamillare atrophy (Barsi et al, 2000; Barsi,2001). The affected regions in HS are CA1, CA3 regions and endfolium (Diehl B. et al 2000; Babb and Brown, 1987).

The most often developmental abnormality is the isolated hippocampal malrotation (HIMAL), wich was first described by Péter Barsi (Barsi et al, 2000). It may not be the cause of epilepsy itself, but may indicate developmental abnormalities or damage of the affected hemispherium.

Temporal lobe epilepsy, febrile seizure and hippocampal abnormalities

A history of febrile seizures is frequent in mesial temporal lobe epilepsy. Febrile seizures occur in 2-5% of the population. There are two type of febrile seizures: simple and complex. Simple febrile seizures are shorter than 15 minutes and show no focal signs. Conversely, complex febrile seizures are longer than 15 minutes and can show focal origin. Febrile seizures can appear as status epilepticus in 5% of cases (Ahmad and Marsh, 2010).

70% of TLE patients with HS have febrile seizure in childhood. (French et al, 1993).

It is not clear whether the HS is a consequence or the cause of afebrile or febrile seizures (Cendes at al, 1993) and the relationship between **TLE, HS and febrile seizure is also unclear**. There are numerous studies investigating this relationship resulting in numerous theories

(1) One of these theories, the hippocampal damage is caused by FS and after this initial damage a synaptic reorganization takes place in the hippocampus, which progressively evolves into HS, and this latter is the final cause of epilepsy (Maher&McLachlan, 1995).

(2) It is possible that febrile seizure, HS and later consequence the TLE are independently created and developed, it is backed to same aetiology.

Kasperaviciute at al (2013) suggested that genetic predisposition is responsible for combined incidence of TLE, HS and febrile seizures. They found a mutation of SCN1A gen in the MTLE patient who had febrile seizure in childhood and it was not present after febrile seizure without epilepsy.

(3) In a third theory, a hippocampal abnormality (probably dysgenesis) generates FS, and FS causes HS in the already affected hippocampus. (Fernandez et al, 1998; Barsi et al, 2000).

(4) Fourth option: The pre-existing HS causes both FS and TLE. This theory is the most improbable (Davies et al, 1996; Bower et al, 2000).

AIMS

We were intended to answer the following questions:

1. Is there any association between febrile seizures and hippocampal damage without presence of epilepsy? Can simple febrile seizures cause hippocampal abnormalities? Are there any hippocampal abnormalities in healthy people 15-20 years after suffering a simple febrile seizure?
2. What clinical/neuroimaging features can be differentiated between TLE patients who regularly have SGTCS and those who do not?
3. Is there an association between secondarily generalised seizures and preceding seizure elements as well as clinical data?

METHODS

Methods in the case of first question

Advertisements on the notice boards at the various faculties of the University of Pécs invited the participation of healthy students/postgraduates who had suffered at least one FS in childhood, which they could prove by medical reports and who had no epilepsy. After their written informed consent had been given, an MRI investigation was planned.

Finally, the remaining 8 subjects with simple FS (FS+ subjects) were included. They were blindly paired with regard to age and sex with 8 control subjects (FS- subjects), who were also students or postgraduates and neither the subjects nor their parents were aware of any episode of febrile or afebrile seizures.

MRI examinations

- Visual inspection
- MRI Volumetry
- T2 relaxometry.

The MRI examinations were performed on a 1-Tesla Siemens Magnetom Harmony MRI machine (Siemens AG, Erlangen, Germany). We used the same MRI protocol in all subjects: T2-weighted axial, FLASH 3D T1-weighted, T2-weighted, FLAIR, and multi-contrast spin-echo sequences were made. The visual inspection was performed by a neuroradiologist (P.B.), who was blinded to the clinical data and was not present at the time of MRI examination.

For the MRI volumetry, the pictures were normalized by SPM-5 software in the standard MNI space (Friston et al., 1995). The volumetry was performed on the T1-weighted 3D FLASH images. For the automatic volumetry, IBASPM (Individual Brain Atlases using SPM) was used to determine the hippocampal volume *in vivo* (Fischl et al., 2004). The asymmetry between the volumes of the two hippocampi was characterized by the absolute value of the asymmetry index: ABS(AI) = ABS((lHV – rHV)/(lHV + rHV)) (l: left-sided, r: right-sided, HV: hippocampal volume, ABS: absolute value function, AI: asymmetry index).

For the T2 relaxometry, the equation of T2 relaxation ($I = I_0*\exp(-TE/T2)$) was fitted to each signal alteration according to TE, in order to obtain the T2 value of each voxel, thereby creating an individual T2 map for each subject. T1-weighted images were coregistered to the individual T2 maps by using SPM-5. With the IBASPM, individual brain atlases were created from the coregistered T1-weighted images, via fitting to each individual T2 image. In these individual atlases, the hippocampus was divided into three equal parts: anterior, middle and posterior parts. These individual atlases were applied to the individual T2 maps in order to calculate the mean T2 values of the parts of hippocampus in each subject.

Methods in the cases of 2nd and 3rd questions

In this retrospective study, we reviewed video-recordings and clinical data of 171 patients. The sample was comprised of patients who, due to drug resistance, had consecutively participated in our adult presurgical evaluation program where they had undergone ictal video-EEG recordings. All patients had a temporal lobectomy as a result of mesial or neocortical (lateral) TLE. When the patients were admitted to the presurgical unit, a history of the SGTCS was taken and the SGTCS frequency was ascertained by asking the patients (or in most cases their relatives) standard clinical protocol questions directly. Patients underwent continuous video-scalp EEG monitoring lasting more than 2 days. The electrodes were placed according to the 10-20 system. All patients had high-resolution MRI examinations made on 1.5 or 1.0 Tesla Siemens Magnetom MR machines (Siemens AG, Erlangen,Germany), using special protocol for detecting epileptogenic lesions. 1-3 seizures per patient were included. SGTCS in the patient history was defined if the patient had had more than one SGTCS on adequate antiepileptic medication. We selected clinical, EEG and MRI features, as well as seizure elements for the variables that were to be investigated for association with the presence of SGTCS: e.g. ability to react before seizures, pure ictal vocalisation.

Conversely, we did not include those seizure elements that had a well-known direct association with SGTCS (sign of 4, mouth deviation, head version) because they would have provided redundant information and could not be put into multivariate statistical models

For statistical evaluation of categorical variables, Chi-square and Fisher’s exact tests were carried out. For evaluation of continuous variables, the Mann-Whitney test was

performed. Error probabilities of <0.05 were considered to be significant. For multivariate analysis, stepwise logistic regression was used. All statistics were performed by the SPSS 15.0 software package (SPSS Inc., Chicago, IL).

RESULTS

1. Is there any association between febrile seizures and hippocampal damage without presence of epilepsy? Can simple febrile seizures cause hippocampal abnormalities? Are there any hippocampal abnormalities in healthy patients 15-20 years after a simple febrile seizure?

Visual inspection

In 3 of the male subjects in the FS+ group, hippocampal abnormalities were apparent on visual inspection: 2 cases of mild left-sided HS, and 1 of mild right-sided HS and hippocampal dysgenesis on the left side. No FS+ women or FS- subject exhibited hippocampal abnormalities.

MRI volumetry

The mean volume of the left hippocampus was 2.39±0.6 cm^3 in the FS+ group and 3.01±0.8 cm^3 in the FS- group. The difference was not significant (p=0.21). The mean volume of the right hippocampus was 2.96±0.74 cm^3 in the FS+ group and 3.62±0.72 cm^3 in the FS- group, this difference showed a non-significant trend (p=0.093). The mean total volume of the two hippocampi was 5.36±1.33 cm^3 in the FS+ group and 6.63±1.46 cm^3 in the FS- group. This difference showed also a non-significant trend (p=0.069). As regards the volume asymmetry characterized by ABS(AI) values, there was no difference between the two groups: ABS(AI) was 0.11±0.005 in the FS+ *vs.* 0.11±0.007 in the FS- subjects.

Gender differences

Women. The mean volume of the left hippocampus was 2.5 ±0.78 cm^3 in the FS+ women and 2.32±0.18 cm^3 in the FS- women. The mean volume of the right hippocampus was 2.82±0.74 cm^3 in the FS+ women and 2.9±0.4 cm^3 in the FS- women. The mean total volume of the two hippocampi was 5.32±0.15 cm^3 in the FS+ women and 5.23±0.41 cm^3 in the FS- women. These small differences were not significant.

Men. The mean ages of the FS+ and the FS- men were identical (25.6±3.4 *vs.* 25.6±4.5, p=1.0). The mean volume of the left hippocampus was 2.34±0.6 cm^3 in the FS+ men and 3.43±0.9 cm^3 in the FS- men (p=0.08). The mean volume of the right hippocampus was 3.05±0.8 cm^3 in the FS+ men and 4.05±0.48 cm^3 in the FS- men (p=0.043). The mean total volume of the two hippocampi was 5.38±1.4 cm^3 in the FS+ men and 7.48±1.14 cm^3 in the FS- men (p=0.043).

There were no gender differences in the T2 relaxation time or ABS(AI), data not presented.

T2 relaxometry

The T2 values in the anterior part of the left hippocampus and in the middle part of the right hippocampus were elevated in the FS+ group

2. What clinical/neuroimaging features can be differentiated between TLE patients who regularly have SGTCS and those who do not?

If we consider the clinical data which were known before the video-EEG monitoring, only the presence of **hippocampal sclerosis** on the MRI showed a positive association with a history of SGTCS (Table 1). If we consider data obtained from video-EEG monitoring, then the presence of **pedal automatism and ictal speech** showed a negative association with a history of SGTCS, while the presence of SGTCS during the video-EEG revealed a positive association.

In order to find out which variables were independently associated with a history of SGTCS, we performed a stepwise logistic regression including those variables which showed significant associations with a history on SGTCS on bivariate tests (logically, we did not include the presence of SGTCS during the video-EEG). Logistic regression showed that all of these three variables (hippocampal sclerosis, p=0.02; pedal automatism, p=0.03; and ictal speech, p<0.001) *independently* associated with a history of SGTCS

3. Is there an association of secondarily generalized seizures *with preceding seizure elements and clinical data?*

This question was focused on the seizures and not on the patients. The presence of ARBS, oral and pedal automatisms, pure ictal vocalizations, ictal speech, and APR showed a negative association with a presence of SGTCS during video-EEG monitoring. At the same time, age, a history of SGTCS and sleep-onset seizures during the video-EEG provided evidence for a positive association with SGTCS during video-EEG monitoring.

In order to find out which variables were independently associated with the presence of SGTCS during the video-EEG, we performed a stepwise logistic regression including those variables which showed significant associations by bivariate tests (logically, we did not include the history of SGTCS). Logistic regression found that age (p=0.038 d), **ARBS** during video-EEG monitoring (p=0.007), **oral automatisms** (p=0.007), **pedal automatisms** (p=0.005**), pure ictal vocalizations** (p=0.015), and **APR** (p=0.027) were *independently* associated with the presence of SGTCS during video-EEG, while ictal speech and sleep-onset seizures were not.

DISCUSSION

Febrile seizure and hippocampal abnormalities

Our major findings are:

(1) Simple febrile seizures in childhood can be associated with hippocampal abnormalities (elevated T2 relaxation time and volume reduction) in healthy highly-educated adults who have never had afebrile seizures. A volume reduction has been demonstrated only in men. In male subjects with a history of FS, we found significantly smaller right-sided and total hippocampal volumes compared to the controls. Visual inspection of MRI pictures revealed abnormalities in 3 of the 5 men with a history of FS: all of them had mild HS, and one also hippocampal dysgenesis (HIMAL). No abnormalities were found in the women, but the number of women involved was too small to allow statistical conclusions. T2 relaxometry showed elevated T2 relaxation time in FS+ group. Both the hippocampal volume is decreased and T2 relaxation time is prolonged. These are suitable for the criteria of hippocampal sclerosis but the degree is smaller than in classic drug resistant MTLE-HS patient.

(2) The different hippocampal abnormalities are not necessarily associated with cognitive deficits. The all people in FS+ group and control people are student or postgraduate student independently MRI showed hippocampal abnormality.

FS occurs in 2-5% of the population and carries an increased risk of subsequent epilepsy with afebrile seizures, especially in cases of complex FS (Annagers et al., 1979; Annagers et al., 1987). Conversely, MTLE-HS occurs in <0.2% of the population (French et al., 1993; Wieser et al., 2004), and thus, only a minority of FS patients subsequently exhibit MTLE-HS. Most FS children who go on to develop epilepsy have simple FS (Nelson&Ellenberg; 1978). The short term and long term follow up studies – which experiments the role of febrile seizure of developing HS- exclusively focused on complex febrile seizure and it was performed in childhood.

In the present study, we investigated whether hippocampal abnormalities are observed in healthy people 15-20 years after a simple febrile seizure. These people had no cognitive impairment or epilepsy. In our healthy adult subjects with FS, the later

development of MTLE-HS in unlikely because only <8% of MTLE-HS cases begin in adulthood (Janszky et al 2004). Thus, our study has provided a strong argument that hippocampal abnormality associated with FS is not always accompanied by epilepsy.

We found a hippocampal abnormality and volume loss only in male FS patients. In TLE, the hippocampus seems to be more affected in men than in women (Briellmann et al., 2000). This may be due to gender differences in the nature of the seizures. Men have more serious and more frequently propagated seizures than women, or there may be a gender-specific vulnerability of the hippocampus to the seizures in men (Briellmann et al., 2000; Janszky et al., 2004).

The right-sided decrease in hippocampal volume in the FS subjects proved to be more pronounced than that on the left side. Another prospective study after our published study confirmed hippocampal sclerosis after FS is more frequent on the right side (Shinnar et al, 2012).

Based on our investigation it can be assumed a relationship between febrile seizure and hippocampal abnormality without rise to developing TLE. Hippocampal sclerosis can develop without causes epileptic seizure or cognitive disturbance. Based on our results we follow our investigation with iron sensitive MRI technique in healthy FS people and epileptic patients with hippocampal abnormalities.

Generalised tonic-clonic seizure in temporal lobe epilepsy

The major findings of our study are:

(1) The presence of *hippocampal sclerosis* on MRI showed a **positive association with a patient's history of SGTCS, while** *ictal speech* and *pedal automatism during video-EEG recordings* showed **a negative association with a patient's history of SGTCS**.

(2) The *age* of patients showed a **positive** association with a presence of SGTCS during video-EEG monitoring, while *ARBS, oral automatisms, pedal automatisms, ictal vocalizations,* and *APR* showed a **negative** association with a presence of SGTCS during video-EEG monitoring.

The presence of *hippocampal sclerosis* on the MRI showed a positive association with a patient's history of SGTCS. Although we cannot fully explain this association, one of the theoretical explanations may be that generalized seizures cause a more pronounced

hippocampal injury than CPS or other focal seizures. There is early involvement of the hippocampus when a focal seizure shows a transition to SGTCS (Rektor et al., 2009).

We cannot fully explain the association of age with secondary generalization. Moreover, it was only true for generalization of seizures during video monitoring and not according to the patient's history. We can speculate that this association represents the progressive nature of drug-resistant TLE (Jokeit et al, 1999; Fuerst et al., 2003; Janszky et al., 2005).

There are no area which are thought to be unequivocally associated with pedal automatism, although there may some hypothesis that it represents a seizure spreads in the fronto-orbital areas (Swartz, 1994). Ictal speech automatism could be elicited by the electrical stimulation of the amygdala (Driver et al., 1965). Talairach et al (1973) suggested that oral automatisms during TLE seizures represent an involvement of the anterior cingulum. We found that these ictal automatisms (speech, pedal and oral) are associated with the absence of SGTCS, suggesting that amygdalar-orbitofrontal or cingular seizure spread infrequently evolves to SGTCS or may even inhibit the transition from focal seizures to SGTCS. Rektor et al (2009) found that during spread from focal to generalised seizures in TLE, the cingulate and fronto-orbital cortex showed slow activity on the stereo-EEG. They hypothesized that this slowing represents inhibition in these regions, findings that are in accordance with our results.

In the present study, the ARBS and the APR (independent of each other) showed a negative association with the secondary generalization. ARBS was associated with a more circumscribed region involved at seizure onset since we found that ARBS was associated with a lateralized seizure onset and a better outcome after TLE surgery. APR is a well-known sign for non-dominant TLE seizure (Ebner et al., 1995) but also indicates circumscribed seizure activity which strictly involves only one temporal lobe without seizure spread to the contralateral side (Park et al, 2001; Janszky et al., 2003).

It seems reasonable to take a clinical approach that avoids SGTCS in the monitoring unit because; due to the risk of injuries and SUDEP, it appears to be much more dangerous than focal seizures without secondary generalization. Moreover, through drug reduction, SGTCS can be artificially provoked and any complications caused by provoked seizures can be considered to be an iatrogenic event. Thus, it may be of high clinical value to assess the patomechanisms of the secondary generalization. In the presence of risk factors for SGTCS, we might become more cautious in reducing

drugs while monitoring presurgically. We could pay more attention to patients with a high risk for secondary generalization by avoiding potentially dangerous situations (for example when the video monitoring is paused). Detecting seizure elements that represent a high risk for secondary generalization (for example, high age, the absence of either oral automatism or ARBS) could help monitoring personnel be on alert for SGTCS that might require immediate medical intervention.

SUMMARY OF THE THESIS

1. We were the first who showed that simple febrile seizures in childhood may be associated with hippocampal abnormalities in adulthood without presence of epilepsy.

2. Hippocampal abnormalities are not always accompanied by cognitive disturbance affecting everyday life.

3. TLE patients with presence of hippocampal sclerosis on MRI showed frequent SGTCS. SGTCS are rarer in TLE patients who have CPS with automatisms. We propose that these results should be taken into consideration during video EEG monitoring: we can avoid grand mal seizure in the TLE patients who have a high risk for secondarily generalization and therefore we can prevent severe complications.

4. Complex partial seizures can evolve to secondary generalised tonic clonic seizures at a higher age. By contrast, in the presence of the ability to react before and during seizure, automatisms and ictal vocalisation, the secondarily generalisation is rare. This result confirms the hypothesis that in the process of secondarily generalisation, the frontoorbital cortex and cingulum may be inhibited. We may hypothesize that the type of the seizure spread at the beginning determines the later seizure spread.

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