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Electroencephalographic findings in patients with circumscribed thalamic lesions

Elene Tsoures[a], Jan Lewerenz[a], Elmar Pinkhardt[a], Albert C. Ludolph[a], Susanne Fauser[a,b,*]

[a] Department of Neurology, University Hospital Ulm, Oberer Eselsberg 45, 89081 Ulm, Germany
[b] Epilepsy Center Bethel, Mara Hospital, Maraweg 21, 33617 Bielefeld, Germany

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ABSTRACT

Introduction: Thalamo-cortical networks have mainly been studied in the generation of idiopathic (genetic) epilepsies. The purpose of this study was to analyze EEG patterns and the occurrence of focal (symptomatic) epileptic seizures in patients with acquired circumscribed thalamic lesions.

Patients and methods: Among 596 patients with thalamic lesions, we identified 47 patients in whom circumscribed thalamic lesions were detected by MRI and who underwent an EEG examination at the same stay at hospital. EEG findings were divided into normal findings, unspecific pathological changes and epileptiform discharges. The EEG findings were correlated to the localisation of the lesion within the thalamus and to the patients symptoms.

Results: In 32 patients (68%) pathological EEG findings were observed. They were heterogeneous and comprised regional and generalized slowing, triphasic waves, generalized periodic and regional epileptiform discharges. However, some characteristic findings were seen: Regional slowing was associated with ipsilateral thalamic lesions independent of the thalamic subarea, epileptiform discharges were related to lesions in the ipsilateral medial thalamus and periodic generalized discharges/triphasic waves with lesions in the anterior-ventromedial thalamus. Epileptic seizures were also more common in patients with medial thalamic lesions. Patients with regional epileptiform discharges responded to antiepileptic treatment whereas patients with triphasic waves and generalized periodic patterns did not. In some cases, it remained difficult to decide whether the thalamic lesion was the cause or consequence of epileptic activity.

Conclusion: Pathological EEG findings are common in patients with acute and chronic thalamic lesions. EEG patterns associated with circumscribed thalamic lesions were influenced by the affected thalamic subregion. As in idiopathic generalized epilepsy, also in symptomatic epilepsy, the medial thalamus revealed to play a role in the generation of epileptiform discharges. In the patients with generalized periodic discharges and acute lesions in the ventral-anterior-medial thalamus, however, EEG changes were more likely caused by a disinhibition of cortico-thalamic networks than by a status epilepticus and thus risks and benefits of an aggressive antiepileptic treatment must be thoroughly balanced.

1. Introduction

Since long thalamo-cortical networks have been intensely studied and discussed as a structural basis in the generation of absence epilepsies and other subtypes of idiopathic (genetic) generalized epilepsies (e.g. Berg et al., 2010; Gorji et al., 2011; Gloor 1968; Meeren et al., 2005). Data were mainly derived from rodent models of epilepsy (e.g. Luhmann et al., 1995; Lüttjohann et al., 2011; Meeren et al., 2002) but also from functional imaging in patients with idiopathic generalized epilepsy (Carney et al., 2010; Labate et al., 2005; Moeller et al., 2008).

The importance of thalamic lesions in the generation of focal (symptomatic) epilepsy, however, has not been widely explored. However, growing evidence suggests that early thalamic lesions may lead to sleep-potentiated epileptiform activity, in particular to continuous spike-wave during slow wave sleep (CSWS) (Fernández et al., 2012; Guzzetta et al., 2005; Losito et al., 2015). Small case series showed that patients with perinatally acquired unilateral thalamic lesions can present with a symptomatic epilepsy mimicking idiopathic generalized epilepsy with generalized tonic-clonic and myoclonic seizures and 2.5–3.0 Hz generalized spike wave and poly-spike-wave patterns in day-time EEG (Kelemen et al., 2006; Nguyen et al., 2006; Tezer and Saygi, 2009).

In addition, electrical stimulation of different thalamic nuclei (mainly the anterior nucleus of thalamus) modulates focal epilepsy and has recently been approved in the treatment of refractory focal epilepsy

* Corresponding author at: Epilepsy Center Bethel, Klinik Mara I, Maraweg 21, 33617, Bielefeld, Germany.
E-mail address: susanne.fauser@mara.de (S. Fauser).

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(Fisher et al., 2010; Salanova et al., 2015).

On the other hand, thalamic lesions in chronic and acute seizure disorders are rare. Three different patterns of thalamic lesions in patients with epilepsy were described: fluid attenuated inversion recovery (FLAIR) hyperintense pulvinar lesions as known from status epilepticus, linear defects in the medial and anterior thalamus, and extensive bilateral thalamus lesions in patients with syndromes caused by mitochondrial mutations (Tschampa et al., 2011). No systematic analyses are so far available with regard to the effect of thalamic lesions acquired at older age, on EEG findings and on their contribution to epileptogenesis

In this study, we systematically analyzed the EEG and MRI findings as well as the clinical presentation of patients with circumscribed thalamus pathologies, most of them acquired at older age. The results of our study may help to interpret EEG findings and clinical symptoms in patients with acute and chronic thalamus lesions. Moreover, it was of interest whether particular thalamic subregions were more prone to elicit pathological EEG findings or to contribute to epileptogenesis.

2. Patients and methods

2.1. Patients

Patients were retrospectively identified between January 2010 and August 2014 by means of a database for MRI results (PACS) of patients treated in the Department of Neurology of the University Hospital Ulm. 596 patients (obtaining a total of 1329 MRI scans) were identified by the search items “thalamus”, “thalamic ischemia”, “thalamic diffusion restriction”, and “thalamic bleeding” and variants of these words. The comparison with our EEG database resulted in 252 patients who underwent EEG examination and MRI scan during one and the same stay at hospital. Out of these, 47 patients presented with circumscribed lesions confined to the thalamus not affecting other regions. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was approved by the local institutional review board.

2.2. MRI

MRI was performed with a clinical 1.5 T scanner (TIM Symphony, Siemens Erlangen, Germany) according to the routine emergency MRI protocol comprising at least the following sequences: transversal T2-weighted turbo-spin-echo sequence with a slice thickness of 5 mm, a repetition time (TR) between 4000 and 5000 ms and a time to echo (TE) of about 120 ms, a coronal turbo inversion recovery sequence with a TR between 8000 and 9000 ms, a TE of about 82 ms, an inversion time of 2440 ms, a slice thickness of 3 mm, frequency-selective fat saturation, and an parallel imaging factor of 2 (GRAPPA), transversal T2*-weighted gradient echo sequence with TR between 900 and 1000 ms, a TE of 24 ms, and a slice thickness of 5 mm as well as the diffusion-weighted echo-planar imaging sequence, with a TR between 4000 and 6000 ms, a TE of 98 ms, a slice thickness between 3.5 and 5 mm and b-factors of 0 and 1000 mm^2/s.

The thalamic lesions were classified as ischemic, hemorrhagic and other pathologies and as acute or chronic lesions. Moreover, the localisation of the lesion within the thalamus was classified as dorsal, ventral, medial, lateral, anterior or posterior (including overlaps), and whether they were unilateral or bilateral. In addition, incidental findings such as e.g. subcortical white matter lesions were registered.

2.3. EEG

EEG was performed with the standard 10–20 system (21 electrodes) over 30 min using a digital EEG-acquisition and analysis system (Natus, Germany). Artifacts were detected by visual inspection. Frontal, central, temporal (including temporal anterior), parietal, and occipital regions were investigated in each participant.

EEG pathologies were divided into general and regional slowing, in regional epileptiform discharges and in periodic patterns such as generalized periodic discharges (GPDs). EEG localization of abnormal patterns was identified by the electrodes over which the slowing or the epileptiform discharges reached their maximum, i.e. highest amplitudes in referential derivations or phase inversion in bipolar derivations (Ebersole et al., 2014).

The EEG was independently interpreted by SF (experience of 16 years in epileptology and EEG interpretation, certified for EEG interpretation and epileptology by the DGKN and DGfE = Germany Society of Clinical Neurophysiology/for Epileptology) and by JL (experience of 4 years in epileptology and EEG interpretation, certified for EEG interpretation by the DGKN). In case of diverging conclusions the case was again discussed and a common consensus was found by both authors.

2.4. Clinical characteristics

Clinical characteristics were extracted from the medical charts. Of interest were the symptoms that led to hospitalization, the final diagnosis of the lesion, the occurrence of an epileptic seizure or the existence of epilepsy and whether there was an obvious causality between thalamic lesion and epileptic seizure(s).

2.5. Control group

Forty age- and gender-matched patients with subcortical white matter lesions were recruited from the same MRI database using the search items “small vessel disease”, “subcortical encephalopathy” and “subcortical white matter lesions”. Patients with thalamic lesions or other large coincidental pathologies were excluded. Small vessel disease was graded according to Fazekas et al., 1993. All patients obtained an EEG.

2.6. Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics 21.0 (IBM Corporation, Armonk, New York, USA). The Chi-Square test with continuity correction was used to compare:

1.) Occurrence of pathologic EEG findings in
   a) ischemic versus hemorrhagic lesions
   b) acute/subacute versus chronic thalamic lesions
   c) patients with thalamic lesions versus controls with small vessel disease only
2.) Occurrence of epileptic seizures in medial versus lateral thalamic lesions
3.) Occurrence of epileptiform discharges in medial versus lateral thalamic lesions

3. Results

3.1. Patients

Out of a total of 252 patients with thalamic lesions obtaining an EEG examination, only 47 patients (29 females, 18 males) fulfilled the inclusion criteria and had a lesion confined to the thalamic grey matter. The age at hospital admission ranged from 17 to 93 years, median 76 years.

3.2. MRI findings

3.2.1. Etiology and localization of the thalamic lesion

In 39 patients, the lesion was unilateral, in eight patients bilateral. Thirty-two patients were diagnosed with ischemia, 11 with hemorrhage, one with unspecific gliosis, one with a linear defect of unknown origin, and three with seizure-related diffusion restriction (one of the patients had both an ischemic and hemorrhagic lesion). Twenty-six patients suffered from acute/subacute thalamic lesions, in 21 the lesions were chronic. In patients with bilateral lesions, only one suffered from acute bilateral ischemic lesions caused simultaneously due to occlusion of an artery of Percheron. The other patients had ischemic and/or hemorrhagic lesions, which presumably originated at different times. The localization of the lesions within the thalamus is summarized in Supplementary Table S1.

3.2.2. Incidental findings in MRI

Apart from the thalamic lesion, three patients presented with no further cerebral pathologies. In the remaining patients (85%), MRI revealed minor (subcortical) incidental abnormalities like different degrees of small vessel disease (25% mild, 30% moderate, 45% severe),