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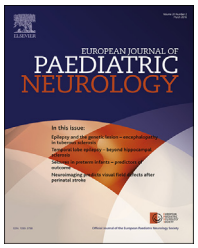

Original article

Childhood onset temporal lobe epilepsy: Beyond hippocampal sclerosis

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ABSTRACT

Objective: Hippocampal Sclerosis (HS) is widely recognized as a significant underlying cause of drug-resistant temporal lobe epilepsy (TLE) in adults. In contrast, HS is a rare finding in pediatric surgical series, and a higher incidence of HS associated with cortical dysplasia (i.e. FCD type IIIa according to the new ILAE classification) than in adult series has been reported. Data about the electro-clinical characteristics of this subgroup are scarce.
Methods: We studied 15 children and adolescents with drug-resistant TLE and HS who had anterior temporal lobe resection at our center with regard to electroclinical characteristics, MRI features and histopathology. Children in whom histopathology was consistent with Focal Cortical Dysplasia (FCD) type IIIa (n = 7) were compared with those who had HS only (n = 8).
Results: Clinical characteristics associated with this highly selective subset of patients with FCD type IIIa were: the presence of febrile seizures during infancy, a shorter duration of active epilepsy and a lower age at epilepsy surgery. In addition, there were non-significant trends towards more extended abnormalities on both EEG and neuroimaging. We were, however, not able to find group differences with respect to neuropathologic subtyping of the HS.
Conclusion: We present the first detailed description and comprehensive data analysis of children with FCD type IIIa. According to our results, this patient group seems to show a distinct clinical phenotype.

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1. Introduction

Hippocampal sclerosis (HS) is the most common underlying pathology of drug-resistant temporal lobe epilepsy (TLE) in adults.[1] In contrast, the pathologies most frequently seen in children and adolescents with intractable TLE are low-grade tumors (40%) followed by malformations of cortical development (30%). In contrast, HS is only found in about 22%.[2] Further, a higher incidence of HS associated with cortical dysplasia than in adult series has been reported in these patients (79% versus 17–30%), whereas isolated HS seems to be rare.[3,4] In addition, subtle changes such as increased deep white matter neurons, blurred grey-white matter border or unspecific alterations of the cortical lamination have been found in resected specimens.[5,6] The new classification system for Focal Cortical Dysplasia now subsumes clustering of neurons in layer two of the cortical ribbon or so-called "lentiform" neuronal heterotopias associated with HS under the category "FCD type IIIa".[7,5]

Resective epilepsy surgery has become an established treatment option for carefully selected individuals with drug-resistant TLE.[8] Precise presurgical delineation of the epileptogenic zone and complete resection – if necessary, of both mesial and adjacent neocortical structures – are crucial for an optimal outcome. However, both patient selection for epilepsy surgery and the calculation of potential risks and benefits in young patients with TLE remain a challenge for several reasons:

1) On the one hand, these lesions often escape visual MRI inspection, although subtle abnormalities in the adjacent temporal neocortex of children with chronic TLE have been found in histopathological specimens[3,9–11];
2) On the other hand, MRI may show alterations in the temporal pole not related to any histological findings.[12]
3) Detailed data about the electro-clinical characteristics of the new histological subtype FCD type IIIa are therefore needed, but still scarce.

We report detailed histological, MRI and electro-clinical data of children with TLE/HS who had resective epilepsy surgery at the Vienna pediatric epilepsy center. Special focus was set on the novel category of FCD type IIIa.

2. Patients and methods

All children with drug-resistant TLE, who underwent epilepsy surgery at our center, were reviewed provided that they had complete documented pre- and postsurgical data of at least 12 months (i.e. demographic data, video-EEG-monitoring including sphenoidal electrodes, clinical and neuropsychological examinations as well as modern neuroimaging). Seizure outcome was defined according to the ILAE proposal (Wieser et al.).

Clinical and video-EEG monitoring data was re-analyzed by experienced epileptologists (Martha Feucht, Gudrun Gröppel, Angelika Mühlebner, Anastasia Dressler).

2.1. Interictal EEG findings were categorized into three groups

- "temporo-mesial EEG": representing regional spikes in the sphenoidal electrodes.
- "extended temporal EEG": representing marked additional involvement of the temporo-lateral electrodes (Fig. 1A).
- "generalized EEG": representing cases with diffuse/generalized spikes.

2.2. Ictal EEG

All recorded seizures were reviewed. Due to the variation of recorded seizures and for statistical reasons analysis was limited to six seizures per patient.

The ictal EEG at seizure onset was divided into six different categories: rhythmic hemispheric delta, rhythmic theta mesial, rhythmic theta widespread, rhythmic hemispheric theta, isolated spiking sphenoidal electrodes and beta activity sphenoidal electrodes (Fig. 1B).

2.3. Neuroimaging

MRI examinations were performed on a 1.5 Tesla system with sequences as follows: axial FLAIR sequence of the entire brain (5 mm), paracoronal (perpendicular to the course of the hippocampus) turbo SE T2w sequence (2 mm), Inversion-recovery and FLAIR sequence (3 mm). MRI was reviewed with respect to presence of hippocampal atrophy/sclerosis, T1 hypointensity, T2 hyperintensity, changes in Fornix and Corpora mamillaria, blurring of the grey-white matter junction in the temporal pole, signal changes of the subcortical white matter, and pole atrophy (Fig. 2A and B). Images were initially reviewed by Gregor Kasprian and Daniela Prayer and afterwards re-evaluated by Maria Schmook blinded to the previous results and histological evaluation.

2.4. Type of surgery

Type of surgery (anterior temporo-polar resection vs. selective amygdalohippocampectomy) was based on the results of presurgical evaluation and discussed/agreed on in an experienced pediatric epilepsy surgery board (Martha Feucht, Thomas Czech and Daniela Prayer).

2.5. Histology

Histopathological specimens were carefully orientated, trimmed and sectioned in the plane and according to its axis. The specimens were routinely processed for histopathology. In addition to hematoxylin and eosin (HE) stainings immunohistochemistry was performed. We stained tissue sections with antibodies against neuronal nuclei (NeuN, Chemicon; 1:1000), microtubule associated protein 2 (MAP2, Chemicon, 1:500), glial fibrillary acid protein (GFAP, Dako, 1:3000), non-phosphorylated neurofilament (SMI32, Sternberger, 1:200).

Histopathological analysis was done blinded to MRI and clinical data by Johannes A. Hainfellner, Harald Stefanits and