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Short communication

Familial temporal lobe epilepsy due to focal cortical dysplasia type IIIa

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ABSTRACT

Purpose: Focal cortical dysplasia (FCD) represents a common cause of refractory epilepsy. It is considered a sporadic disorder, but its occasional familial occurrence suggests the involvement of genetic mechanisms.
Methods: Siblings with intractable epilepsy were referred for epilepsy surgery evaluation. Both patients were examined using video-EEG monitoring, MRI examination and PET imaging. They underwent left anteromedial temporal lobe resection.
Results: Electroclinical features pointed to left temporal lobe epilepsy and MRI examination revealed typical signs of left-sided hippocampal sclerosis and increased white matter signal intensity in the left temporal pole. PET examination confirmed interictal hypometabolism in the left temporal lobe. Histopathological examination of resected tissue demonstrated the presence FCD type IIIa, i.e. hippocampal sclerosis and focal cortical dysplasia in the left temporal pole.
Conclusion: We present a unique case of refractory mesial temporal lobe epilepsy in siblings, characterized by an identical clinical profile and histopathology of FCD type IIIa, who were successfully treated by epilepsy surgery. The presence of such a high concordance between the clinical and morphological data, together with the occurrence of epilepsy and febrile seizures in three generations of the family pedigree points towards a possible genetic nature of the observed FCD type IIIa.

1. Introduction

Focal cortical dysplasia (FCD) is characterized by disorganization and structural abnormalities of the cerebral cortex due to alterations in cell proliferation, differentiation and migration during cortical development [1]. The presence of FCD is associated with a high risk of intractable epilepsy in both children and adults. It was first described in detail by Taylor and colleagues in patients who underwent temporal lobectomy [2]. FCD located in the temporal lobe has been reported to be a common dual pathology in 50% of patients with hippocampal sclerosis (HS) [3]. The clinical significance of the strong association between FCD and HS led to the introduction of type IIIa FCD in the latest revision of the FCD classifications [4]. However, the causal relationship between FCD and HS remains unknown, as well as the etiopathogenesis and genetics of the FCDs. Neither identical FCD, nor FCD in combination with HS have been previously reported in related individuals. We herein describe an unusual and unique case of mesial temporal lobe epilepsy (MTLE) in siblings characterized by a nearly identical clinical course and histopathological findings of FCD Type IIIa.

2. Case reports

2.1. Case 1

A twenty-seven year old woman with a brother, grandmother and two cousins diagnosed with epilepsy (supplemental Fig. 1A). Her mother experienced febrile seizures (FS) in early childhood and has a normal brain MRI. Whether FS were simple or complex could not be determined from her personal history. The exact

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nature of epilepsy and seizure types in the grandmother and cousins is also not known.

The patient is from an uncomplicated pregnancy. Following her birth she developed pneumonia, which was treated with antibiotics. At 12 months of age, she developed complicated FS. At nine years of age, she experienced her first unprovoked seizure. From the onset, her seizures were refractory to medical treatment and were classified as complex partial. The seizures started with initial aura followed by early oral automatisms, right face clonic seizure, asymmetric tonic limb posturing (figure of four sign) and occasional secondary generalization. Due to intractability, the patient underwent presurgical evaluation. Video-EEG monitoring confirmed the seizure semiology described above. In scalp EEG, seizure onset was characterized by initial attenuation of background activity followed by rhythmic 5–6 Hz activity in the left sphenoidal (Sp1) and fronto-temporal (T3, F9) electrodes (supplemental Fig. 1C). Interictally, spikes and intermittent slow waves in the left anterior temporal region and left sphenoidal electrode were present (supplemental Fig. 1B). The MRI revealed typical signs of left-sided HS. Increased signal intensity in T2-weighted images and blurring of the grey-white matter junction were present in the white matter of the left temporal pole (Fig. 1A–C). FDG-PET showed left temporal lobe hypometabolism. The patient underwent left anteromedial temporal lobe resection at the age of 22 years. Histopathological examination demonstrated the presence of FCD type Ib in the left temporal pole and adjacent parahippocampal gyrus and HS, classified as FCD type IIIa (supplementary Fig. 2A–C). Following surgery, she became seizure free with persisting auras only (Engel 1B). One year following the surgery, she developed psychogenic non-epileptic seizures. The patient refused to be genetically tested for presence of *Scn1a* mutation.

2.2. Case 2

A brother of the women described in case 1, twenty-nine year old male from a pharmacologically supported pregnancy complicated by abnormal fetal position and clouded amniotic fluid. At 14 months of age, following a mild head trauma, a seizure with loss of consciousness and right-sided hemiclonus occurred. At 16 months of age, he experienced a complicated FS, which was followed by the development of spontaneous and recurrent seizures. Until the age of eight years, the seizures were fully controlled by antiepileptic drugs then medication was withdrawn.

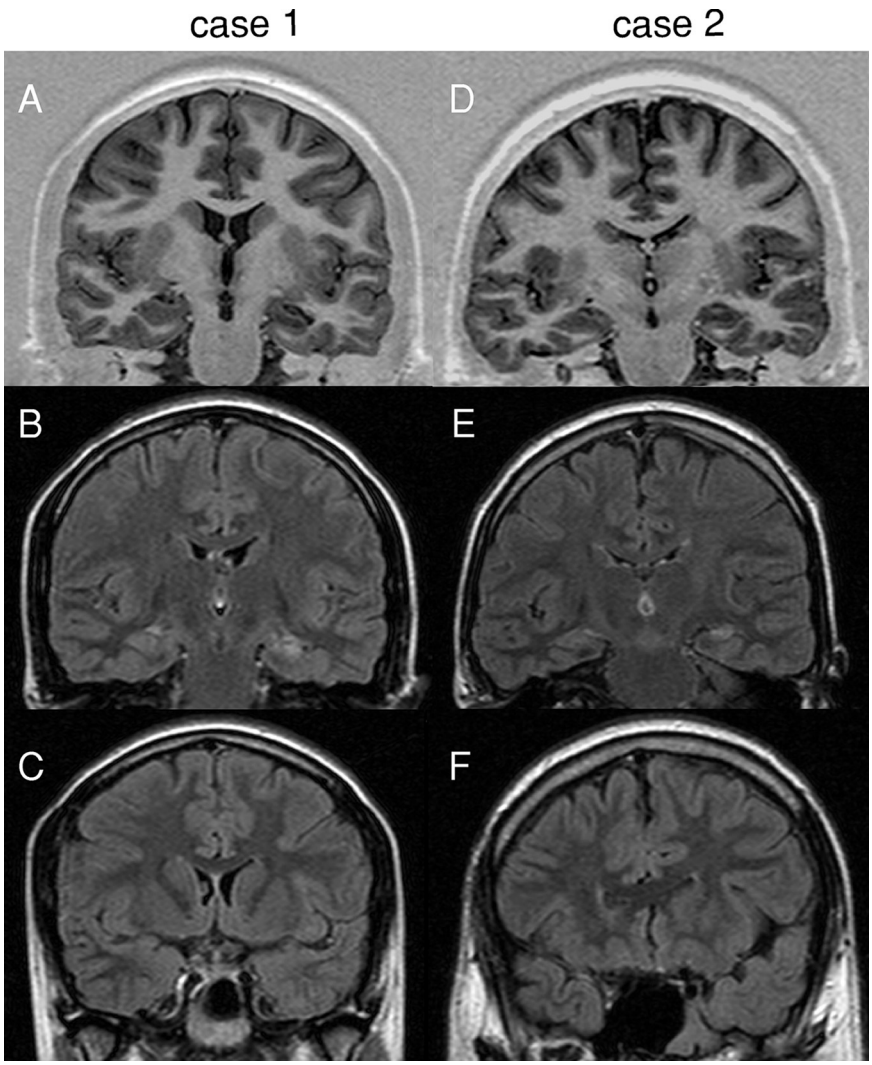

Fig. 1. MRI findings in siblings. (A, B) The sister's MRI was characterized by the presence of atrophy in T1-weighted images (A) and increased signal intensity in T2-weighted images (FLAIR) in the left hippocampus (B). (C) Increased signal intensity in T2-weighted images (FLAIR) in the left temporal pole. (D–F) The brother's MRI showed similar changes in the left hippocampus and also in the left temporal pole (F) (Department of Radiological Techniques, Motol University Hospital, Prague). MRI findings were confirmed by histopathological examination.

At the age of 10 years, seizures reoccurred and they were characterized by epigastric aura followed by oral automatisms, right face clonic seizure, right head version and asymmetric tonic seizure. Occasionally, he suffered from secondarily generalized tonic-clonic seizures. Ictal EEG was characterized by initial attenuation followed by rhythmic 5–6 Hz activity in the left sphenoidal electrode (Sp1) and fronto-temporal region (F7, T3; supplemental Fig. 1E). Interictal EEG demonstrated spikes and intermittent slow wave activity in the same region (supplemental Fig. 1 D). The MRI revealed a similar pathology to his sister (Fig. 1D–F) and left temporal lobe hypometabolism was identified by FDG-PET. The patient underwent anteromedial temporal lobe resection at the age of 25 years. FCD type IIIa was diagnosed by histopathological characterization (supplemental Fig. 2D–F). After the surgery, he became seizure free (Engel 1A). Genetic *Scn1a* testing was done through DNA sequencing and multiplex ligation-dependent probe amplification. None of the tests demonstrated any abnormality in the *Scn1a* gene.

3. Discussion

FCDs belong to a group of disorders known as malformations of cortical development. It is estimated that up to 40% of medically refractory epilepsy is caused by malformations of cortical development including FCDs [5]. Although FCDs represent a frequent cause of epilepsy, the pathological and etiological factors are poorly understood. It has been demonstrated that specific types of cortical malformations have a genetic origin due to mutations in genes controlling cell proliferation, neuronal migration and apoptosis [6]. The genetic cause of FCD could be explained by the occurrence of *de novo* gene mutation and/or a non-inherited multifactorial mechanism. A recently published study of familial cases of FCDs showed that the clinical profile, location, spatial extent and type of FCD often varied between affected family members pointing to the possibility of the double hit theory being responsible for such variations [7]. This theory assumes that the genetic polymorphism provides a susceptible background for environmental factors to alter pre- and postnatal cortical development. Morphological heterogeneity of FCDs can be explained by the existence of multiple pathogenic mechanisms and molecular pathways. For example, enhanced mTOR signalling has been shown to be a pathogenetic mechanism involved in FCD type IIb, tuberous sclerosis and hemimegaencephaly.

FCD type IIIa identified in the cases presented is characterized by the presence of cortical lamination abnormalities in the temporal lobe associated with HS. This type of FCD is often found in patients with refractory MTLE. It is well established that the presence of dysplastic tissue in the temporal neocortex plays a crucial role in mesial temporal lobe epileptogenesis, where even tissue with mild dysplastic features can possess a strong epileptogenic potential, sufficient to induce MTLE [8]. The causal relationship between FCD, HS and FS in the pathogenesis of MTLE has not yet been determined and several alternative theories have been proposed. Complicated FS are referred as one of the most frequent insults preceding the development of HS, but some studies have also reported complicated FS as a consequence of the pre-existing structural lesion of the hippocampus or temporal lobe neocortex [9]. Some authors proposed that early, frequent and intractable seizures originating from the hippocampus could interfere with the development of the neocortical temporal lobe [10] and thus lead to the development of FCD. The underlying pathology, such as, HS and/or cortical dysplasia, can generate seizures or lead to an increased susceptibility to FS that could augment already present structural lesions or play a crucial role in epileptogenesis. In our previous study, patients with FCD type IIIa were characterized by a more frequent absence of any initial precipitating insult in early childhood, when compared to patients with isolated HS. On the contrary, meningitis was much more frequently present in the history of patients with isolated HS and was not reported in patients with FCD type IIIa [3]. Familial MTLE with or without HS and FS was identified in several studies often with autosomal dominant inheritance, but with incomplete penetrance, suggesting an underlying genetic defect and involvement of genetic mechanisms in the development of hippocampal damage. MTLE has been described in several families with generalized epilepsy with FS plus (GEFS+) syndrome due to *Scn1b* gene mutations [11]. Recent genome-wide association study in large cohort of patients with MTLE has revealed that variations in and near *Scn1a* gene can increase the susceptibility to MTLE with HS and FS [12]. However, none of the published familial cases described the simultaneous presence of FCD and HS (FCD type IIIa). The co-occurrence of *Scn1a* gene mutations with malformations of cortical development (including FCD) was described in a small group of patients with Dravet syndrome spectrum [13]. Studies in *Scn1b*-null mice demonstrated that this gene product, voltage-gated sodium channel β1 subunit, plays a critical role in postnatal brain development [14]. Absence of any *Scn1a* mutation in the brother makes the possibility of its involvement in the pathogenesis of FCD type III highly unlikely. However, the pathogenesis may involve different genes. For example, loss of *Scn1b* function results in altered proliferation, migration and pathfinding of cells within the postnatally developing hippocampus and cerebellum, representing the morphological substrate of increased hippocampal excitability. The causal relationships between FCD, HS and FS in the pathogenesis of MTLE remains to be determined. A growing body of evidence and the results from the presented cases suggest that genetic mechanisms should be always considered when the pathogenesis of focal cortical dysplasia type IIIa is discussed.

Contributors

All authors contributed to this case-report. We would like to thank Dr. Petra Hedvicakova from Department of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University in Prague, Motol University Hospital for performing the genetic analysis.

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Competing interests

None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2015.07.014.

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