Neurological Sciences
https://doi.org/10.1007/s10072-020-04782-y

BRIEF COMMUNICATION

Coffin-Siris syndrome and epilepsy

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Received: 14 March 2020 / Accepted: 26 September 2020

Abstract

Coffin-Siris syndrome is a rare genetic disorder defined by the presence of particular facial traits, congenital malformations, intellectual disability, and speech impairment. Epilepsy in Coffin-Siris syndrome has only occasionally been reported, and its features are poorly defined. We provide a detailed description of the clinical and instrumental findings of three patients with Coffin-Siris syndrome and epilepsy. The clinical diagnosis in our patients was confirmed by molecular analysis, which identified the presence of de novo mutations of ARID1B and SMARCB1 genes, in two patients and one patient, respectively. All the patients presented with epilepsy, with a mean age of seizure onset of 5.5 years. Seizures were brief and had a focal onset with secondary generalization. Electroencephalographic recording documented a unilateral, and less commonly bilateral, paroxysmal activity in the temporal, parietal, and occipital regions. Clinical response to anticonvulsive therapy was satisfactory, with a low rate of seizure recurrence. Our case series contributes to delineate the phenotype of Coffin-Siris syndrome. We wish this report could pave the way for further studies that will better define the prevalence and clinical manifestations of epilepsy in this rare syndrome.

Keywords Coffin-Siris · Epilepsy · Seizures · ARID1B · SMARCB1

Introduction

Coffin-Siris syndrome (CSS) is a disorder related to mutations of genes coding for BAF subunits. Rearrangements involving these genes are also responsible for a spectrum of phenotypes including Nicolaides-Baraitser syndrome (NBS). These syndromes share common features like particular facial traits, congenital malformations, intellectual disability, language impairment, and behavioral abnormalities [1, 2]. Moreover, CSS is characterized by hypoplasia or aplasia of the fifth fingernails and hypoplasia of the terminal phalanges, whereas NBS is associated with broad distal phalanges, progressive hair thinning out, and face coarseness with growth [1].

Epilepsy in CSS has occasionally been reported and its features are poorly defined [2–5]. We provide a description of the clinical and instrumental findings of three patients with CSS and epilepsy.

Case report

Patient 1 is a 7-year-old female with a p.Glu1756LysfsTer3 mutation of the *ARID1B* gene. Motor and language delay, failure to thrive, and hyperactive behavior were reported. At the age of 5 years, she presented with seizures both during wakefulness and sleep. Parents reported 4 episodes of generalized convulsive seizures without asymmetries, all interrupted by rectal diazepam. Brain magnetic resonance imaging (MRI) revealed gliotic scars in the retrotrigonal white matter, a thick corpus callosum, a wide cisterna magna, and hypoplasia of the cerebellar vermis and the right cerebellar hemisphere. With the suspicion of focal seizure onset, carbamazepine (CBZ) 18 mg/kg/day was started. One year after, she experienced another convulsive episode; since then, she has been seizure-free. The last electroencephalogram (EEG),

The work described has not been published before and it is not under consideration for publication anywhere else. Its publication has been approved by all co-authors, as well as by the responsible authorities at the institute where the work has been carried out.

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Published online: 02 October 2020

performed at the age of 7 years, showed a background rhythm of 7–8 Hz and spike-and-waves in the left central-frontal-temporal region.

Patient 2 is an 8-year-old female with a p.Ile876Tyrfs*66 mutation of the *ARID1B* gene. At the age of 11 months, axial hypotonia, joint laxity, and delayed neurodevelopmental milestones were observed. Her first seizure occurred at the age of 5.5 years: during drowsiness, she experienced vomiting followed by muscle hypotonia and loss of consciousness. Valproic acid (VPA) 25 mg/kg/day was started, with a good response: a single convulsive episode two years after was reported. However, due to the occurrence of episodes of loss of contact, lamotrigine (LTG) was started as an add-on therapy. Brain MRI was normal. The last EEG showed an 8–9-Hz symmetrical and reactive background rhythm; sleep figures were normally represented. The recording showed the presence, during sleep, of sequences of spikes and spike-and-waves in the right occipital and posterior-temporal region.

Patient 3 is an 8-year-old male with a p.Arg366Cys mutation of the *SMARCB1* gene. Speech impairment and intellectual disability were reported. At the age of 6.3 years, he experienced his first generalized seizure during sleep. CBZ (16 mg/kg/day) was started and later switched to VPA (22 mg/kg/day) that could exert an additional role as a mood stabilizer, from which the hyperactive patient could benefit. Since then, he has been seizure-free. Brain MRI was normal. The last EEG showed an 8–10-Hz symmetrical and reactive background rhythm with normal sleep figures. During sleep, spikes were recorded in the right parietal-occipital region and the right temporal region.

Discussion

CSS and NBS belong to a phenotypic spectrum related to mutations of a chromatin remodeling complex [6]. The presence of epilepsy has been reported in both of them; however, its prevalence and features have not been thoroughly investigated.

In a study about epilepsy in 13 subjects with either NBS or CSS, seizures occurred in all the patients. Among these, 11 were diagnosed with NBS and 2 with CSS, which was genetically proven in 1 patient only; both patients had brain MRI abnormalities. In the whole sample, seizures were commonly generalized and their mean age of onset was 17 months [5].

Epilepsy has also been described in one-third of patients harboring pathogenic variants of the *ARID1B* gene (6q25.3), one of the genes potentially responsible for CSS. The median age of onset of the seizures was 4 years and all the patients showed a good response to anticonvulsive therapy [7].

Epileptic seizures are also frequently reported in subjects with *SMARCB1* gene (22q11.23) mutations, which has also been described in association with CSS. In a study evaluating 13 subjects with mutations of this gene, central nervous system abnormalities were observed in 100% of the patients, whereas seizures were documented in 80% of them [8].

We describe the findings of three patients affected by CCS and epilepsy. The clinical diagnosis was confirmed through molecular analysis, which identified the presence of de novo mutations of the *ARID1B* and *SMARCB1* genes, in two patients and one patient, respectively. Proteins coded by these genes play a critical role in cell cycle regulation and crosstalk between signaling cascades. They are both expressed in the central nervous system, where they are involved in neuronal development. *ARID1B* deficiency has been associated with a decreased dendritic arborization and decreased the number of cortical GABAergic interneurons. We can speculate that the subsequent imbalance between excitatory and inhibitory synapses might contribute to epileptogenesis. *SMARCB1* is also involved in dendrite growth, and we hypothesize its mutations might be responsible for the development of abnormal neuronal circuits, potential substrate for seizure development.

The mean age of seizure onset was 5.5 years; seizures were brief and had a focal onset with secondary generalization. Electroencephalographic recording documented a unilateral, and less commonly bilateral, paroxysmal activity in the temporal, parietal and occipital regions. Brain MRI was normal in two patients, whereas in one of them, signs of perinatal suffering and brain malformations were documented. We believe there might be an association between seizures and CSS in our patients' series, although in one patient we cannot rule out the possibility that seizures are attributable to perinatal brain damage. Clinical response to anticonvulsive therapy including CBZ or VPA, alone or in association with LTG, was satisfactory, with a low rate of seizure recurrence.

Conclusions

Our case series contributes to delineate the phenotype of CSS, providing a detailed description of the seizure features, the electroencephalographic findings, and the response to anticonvulsive therapy in these patients. We wish this report could pave the way for further studies that will better define the prevalence and clinical manifestations of epilepsy in CSS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not appicable.

Informed consent Informed consent was obtained from the patient's parents.

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